Official Journal of the
Malaysian Medical Association

The Medical Journal of Malaysia

Reviews of Malaysian Research on Major Diseases (2000-2013)

Volume: 69

Supplement A

August 2014

ISSN 0300-5283 PP 2121/01/2013 (031329) MITA(P) 124/1/91

The Network of CRC

- *Vision : To become a leading clinical research institution in Asia*

- *Mission : To improve patients' health outcomes through ethical and quality clinical research*

No.	NETWORK	Contact No	No.	NETWORK	Contact No
1	CRC HOSPITAL TENGKU FAUZIAH PERLIS	04-9738000 ext 8413	16	CRC HOSPITAL SERDANG, SELANGOR	03-89475467 / 03-89455884
2	CRC HOSPITAL SULTANAH BAHIYAH KEDAH	04-7406227 / 28	17	CRC HOSPITAL KUALA LUMPUR	03-26155555 ext 1620 / 1114
3	CRC HOSPITAL SULTAN ABDUL HALIM SUNGAI PETANI, KEDAH	04-4457333	18	CRC HOSPITAL PUTRAJAYA	03-83124200 EXT. 4302/4202
4	CRC HOSPITAL PULAU PINANG	04-2225767 (T) / 5764	19	CRC HOSPITAL TUANKU JA'AFAR SEREMBAN, NEGERI SEMBILAN	06-7684000 EXT 5163 / 5255
5	CRC HOSPITAL SEBERANG JAYA	04-3827333 EXT. 511	20	CRC HOSPITAL MELAKA	06-2892195 / 06-2892182
6	CRC HOSPITAL RAJA PERMAISURI BAINUN IPOH, PERAK	05-2085138	21	CRC HOSPITAL SULTANAH AMINAH, JOHOR	07-2231666 EXT 2782
7	CRC HOSPITAL TAIPING, PERAK	05-8408066 / 05-8065187	22	CRC HOSPITAL SULTAN ISMAIL, JOHOR	07-3565155
8	CRC HOSPITAL SERI MANJUNG, PERAK	05-6896785 / 6691	23	CRC HOSPITAL PAKAR SULTANAH FATIMAH, JOHOR	06-9521901
9	CRC HOSPITAL RAJA PEREMPUAN ZAINAB II, KELANTAN	09-7452636	24	CRC HOSPITAL UMUM KUCHING, SARAWAK	082-276820 / 24
10	CRC HOSPITAL SULTANAH NUR ZAHIRAH, TERENGGANU	09-6212097	25	CRC HOSPITAL SIBU, SARAWAK	084-343333 EXT 6634
11	CRC HOSPITAL TENGKU AMPUAN AFZAN, PAHANG	09-5572922	26	CRC HOSPITAL MIRI, SARAWAK	085-420033 EXT. 157/174
12	CRC HOSPITAL SG.BULOH, SELANGOR	03-61454333 EXT. 5231	27	CRC HOSPITAL QUEEN ELIZABETH I, SABAH	088-517507
13	CRC HOSPITAL SELAYANG, SELANGOR	03-61263333	28	CRC HOSPITAL QUEEN ELIZABETH II, SABAH	088-324600 EXT. 2019
14	CRC HOSPITAL TENGKU AMPUAN RAHIMAH, KLANG SELANGOR	03-33756247	29	CRC HOSPITAL LIKAS, SABAH	088-522600 EXT. 2272
15	CRC HOSPITAL AMPANG, SELANGOR	03-42896559 / 6560	30	CRC HOSPITAL DUCHESS OF KENT, SABAH	089-248 600

MJM

Official Journal of the Malaysian Medical Association

Volume 69 Supplement A August 2014

EDITORIAL BOARD

PP 2121/01/2013 (031329) MCI (P) 124/1/91 ISSN 0300-5283

The Medical Journal of Malaysia is published six times a year
i.e. February, April, June, August, October and December.

Advertisement Rates:
Enquiries to be directed to the Secretariat.

Subscription Rates:
Price per copy is RM70.00 or RM300.00 per annum, for all subscribers.

Secretariat Address:
Malaysian Medical Association
4th Floor, MMA House, 124, Jalan Pahang, 53000 Kuala Lumpur.
P.O. Box S-20, 51700 Kuala Lumpur.
Tel: (03) 4042 0617, 4041 8972, 4041 1375 Fax: (03) 4041 8187
E-mail: info@mma.org.my / mjm@mma.org.my
Website: www.mma.org.my

Printed by: New Voyager Corporation Sdn. Bhd. (514424 U)
37 Jalan Gangsa SD 5/3D, Bandar Sri Damansara, 52200 Kuala Lumpur. Tel: 03-6273 2900 Fax: 03-6272 2380
Email: nvcomms@yahoo.com

CONTENT **Page**

Foreword by Director General of Health

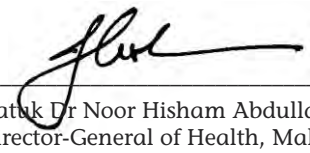
The Fédération Internationale de Football Association's 2014 World Cup saw unexpected teams beating favorites, and substitute players changing the course of games. Imagine how subdued and ordinary the games would have been if the underdogs did not rise to the occasion. They were given the opportunity to shine and they did not disappoint. Moving from the field of football to the field of medicine, how do we ensure that important research in the various therapeutic areas are given prominence and not rendered oblivious outside of the research team? Presenting our work in conferences, both local and international, is one form of spreading the word. But would the opportunity to present to perhaps several hundred people merit the cost incurred in attending? Even if it does, should we stop and be content that at least some of our colleagues are aware of our research. Indeed, this is hardly sufficient. Attending and presenting in conferences are crucial; as it encourages debate, interaction, and networking, but in order to create awareness of our work, we need a wider audience.

I may risk sounding like a broken record, but I cannot overemphasise the importance of "publish or perish", which is not only relevant for people in academia. Those of us in the Ministry of Health should also adopt this adage. If we can take it a step further, the word "perish" could be referring to the state of our medicine as well as our ability to offer best clinical care to our patients. This may sound harsh, but it is a reality we must accept. Tucking your research findings away will not benefit your colleagues, your institutions, and your country. Presenting to fellow clinicians may create a temporary buzz, but if those who heard you did not pass it on, the sizzle that you hoped to generate may just fizzle.

Another worrying trend is the lack of a historical record of the research work that we have published. The World Health Organization, for example, know little about the work we do as we do not publish much, and even when we do, these papers are not easily traced as they are rarely cited. It is ironic that we want the world to recognise our publications, but we ourselves rarely read and cite work of locals.

Without a proper compilation of our research, it is difficult to get the right perspective of the state of our healthcare. What are our strengths and weaknesses? What should be retained and what should be revolutionised?

Thus, I commend the initiative by the Clinical Research Centre in producing this Medical Journal of Malaysia supplement which consist of 12 review articles on the major illnesses, namely cancer, infectious diseases and mental health disorders. These review articles were based on articles published on Malaysian data from 2000 to 2013. It is no easy task to search, compile and review many years of publications. Here, I thank the initiatives of Prof Teng Cheong Lieng, an academic with a keen interest in improving the repository of local research and Assoc Prof Lim Kean Ghee, who possess a vast knowledge in various diseases. Both gentlemen have published books reviewing research in Malaysia. Their experience, together with the commitment and dedication of individual clinicians from the Ministry of Health, public and private universities who put in tremendous effort and time to review the articles in their respective fields, and the interest of the Medical Journal of Malaysia to publish this supplementary issue, comes this well-researched, comprehensive, open access publication, which I hope will be read and referred to. I also hope that such projects to bring to light our homegrown efforts flourish.



Datuk Dr Noor Hisham Abdullah
Director-General of Health, Malaysia

Foreword by Deputy Director General of Health

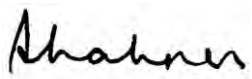
In the 1990s, a new disorder was coined as a result of the information revolution. Dr. David Lewis, a psychologist, described the weariness and stress that result from having to deal with excessive amounts of information as information fatigue syndrome. It also comes with its own set of symptoms; paralysis of the analytical capacity, the need to constantly search for more information, increased anxiety and sleeplessness, and increased self-doubt when making a decision. We will not dwell on whether the need for another syndrome is warranted, but it is true that we are bombarded with more information than we can digest. A simple search in PubMed can generate thousands of articles, which are bound to overwhelm any new researcher.

This is why systematic reviews are important. Not only does a systematic review sieve the high quality research evidence from the rest, the reviewer will also appraise and summarise the data generated in these articles. As professionals concerned about the delivery of healthcare, we should be reading systematic reviews to be aware of new data with clinical implications and the lack of data in our field of interest. As the data published in systematic reviews are meticulously analysed and succinctly written by healthcare specialists, we will have the assurance that what we read is the strongest summary of medical evidence.

In this Medical Journal of Malaysia supplement, we attempted to summarise research done in our country in several clinical areas. Although the methodology we employed is not entirely similar to how a systematic review is done, our objective is the same. We wanted to highlight the important findings of the best Malaysian articles that were published. The idea of doing a historic analysis of local data may not be novel, but it is crucial. How can we prepare for the future if we do not reflect on our past? Our foundation should be laid on the work of our predecessors. Our research should emulate the strengths of their studies, and if possible, elude the limitations they report. Knowing and understanding local research is not a mere exercise of patriotism. The important findings can and should be used to practice evidence-based medicine and to deliver better healthcare policies and strategies.

In addition, by knowing what we have done, we can discover what we need to do. These research gaps can perhaps be addressed by subspecialty trainees, medical doctors in post graduate training, allied health personnel as well as medical and nursing students as they do research that matters most to patients and healthcare system. In this way, their research ideas will not be redundant and resources will be concentrated in areas where we lack. This research stimulus may even give rise to one of our own as the next genius in medicine. The news of Thompson Reuters giving the distinctions of the world's top scientific minds to two Malaysian academicians from the engineering field and one from science and technology, should spur us on. They were chosen because of the high number of articles they published and how frequently their articles were cited.

In closing, I thank the various parties involved in this endeavour. I also encourage our clinicians to keep this as a reference for your practice, and if possible, be an author to review papers in your field. The authors in this supplement, all are passionate individuals, eager to share the progress of their chosen field of medicine.



Dr Shahnaz Murad
Deputy Director-General of Health (Research and Technical Support), Malaysia

Introducing a Collection of Reviews on Major Diseases in Malaysia

Lim Kean Ghee FRCS*, Lim Ai Wei MBBS, Goh Pik Pin FRCS****

* International Medical University Clinical School, Jalan Rasah, 70300 Seremban. ** Clinical Research Centre, Hospital Kuala Lumpur, Jalan Pahang, 50586, Kuala Lumpur

This collection of reviews of major diseases in Malaysia was initiated by the National Clinical Research Centre (NCRC) of the Ministry of Health (MOH).The aim was to examine what has been published on diseases that contribute most to disease burden in Malaysia, to highlight research findings that have significant clinical implication and to identify research gap. The Malaysian Burden of Disease Study[1] published in 2004 by Institute of Public Health, MOHshowed that, for cause-specific mortality, cardiovascular deaths (36%), consisting mainly of ischaemic heart disease and strokes, is the leading cause of deaths in Malaysia, followed by infectious diseases, chiefly septicaemia(12%), cancers(11%) and unintentional injury, contributed mainly by road accidents and falls (Table I).

When seen in the light of years lost to life (YLL), the same four categories still contributed most to Malaysia's disease burden, albeit their relative weight changes slightly. Unintentional violent deaths roseto become the secondhighest condition for YLL after cardiovascular diseases[1](Table II).

A third view of disease burden is from the perspective of years lived with disability(YLDs). Data collected in the year 2000 showed that mental disorders assumed a greater weight andbecame the leading cause contributing to most YLDs[1] (Table III).

The top five disease groups, based on their contribution to disease burden in YLL and YLDs, namely cardiovascular disease, infection, cancers, mental disorders and intentional and unintentional injury were selected for review.

The purpose of this review project is, firstly to compile essential findings from published articles from both published and unpublished clinical research on Malaysian data, to see what research findings can be translated into clinical practice and to identify research gap. It is hoped clinicians will translate important findings that are relevant to clinical practice. In addition we hope policy makers, health educators and public health officers will take note of findings that need action to prevent disease occurrence and improve standard of care. Secondly, these reviews will not only show what has been done but reveal gaps and unfinished research that may give investigators, such as postgraduate master and PhD students, research ideas to pursue. Individual papers are often like pieces of a jigsaw puzzle. A review will hopefully put the pieces together in a more coherent picture. Too often published work ends up lost on some shelf back in a library, or in the web-world today, lost is some unsearchable corner.

The structure and topics for reviews previously published in the book entitled 'A Review of Diseases in Malaysia'published in 2001[2] was used as a model for these reviews. This book which compiled reviews of articles published up to the year 2000 on all diseases in Malaysia is a reference for medical professionals for knowledge on diseases specific to Malaysia. This supplement contains reviews that carry forward from the year 2000. The major diseases in the top five disease groups were selected for review. The details of the method of literature search for these reviews are described in the following article in this supplement entitled. 'Bibliography of clinical research in Malaysia: methods and brief results'.

With the exponential growth of publications on diseases in Malaysia, numbering over 38,000 till date, the work of reviewing the literature is clearly beyond the capability of one person or even a few to do.Subject matter experts (SME) were sought and invited to participate in this task. We targeted clinicians and researchers who have experience and have published papers in the selected disease areas. They were requested to write a review on articles extracted from a bibliography prepared by Prof.TengCheong Lieng. We have, in this supplementary issue of journal 11 review articles on cancer (3 articles), infectious diseases (5 articles) and mental health (3 articles). In addition, we have the privilege of including a relevant update on Nipahencephalitis writtenby Tan Chong Tin and Sherrini Bazir Ahmad, not specifically written for this series.

Several findings from the reviews are worth highlighting here. In breast cancer, Malaysian women were found to have poor knowledge on risk factors, symptoms and early detection of breast cancer. That leads to late presentation, which carries a poorer prognosis. Public health education on screening methods such as breast self-examination (BSE), clinical breast examination (CBE) and screening mammography are important preventive measures that are not adequately exploited.For colorectal cancer, studies also revealed poor awareness of symptoms; risk factors and available measures for early detection of colorectal cancer among Malaysians compared to developed countries. Malaysians also perceive colorectal cancer as not such a severe disease compared to the population in our neighbouring countries. The late presentation and poorer prognosis for colorectal cancer adds up to over 1,000 lives lost annually. For cervical cancer, the mortality rate in Malaysia was more than twice as high as in developed countries. There is a need to examine why cervical cancer, potentially preventable and with good chances of early detection is still high in prevalence and mortality. There is lack of outcome research in cancer treatment. Research is needed to look into reasons for non-compliance to cancer treatment and delay in seeking treatment which currently has a big negative impact on prognosis of cancer.

Corresponding Author: keanghee_lim@imu.edu.my

Table I: Cause-specific Mortality in Malaysia 2000

	Total Deaths	%	Males	Females	M:F
Cardiovascular	39,812	36	21,705	18,107	1.2
Infectious Diseases (excludes respiratory infection)	13,607	12.3	7,657	5,832	1.31
Cancers	12,216	11.1	6,729	5,487	1.22
Unintentional injury	10,799	9.8	8,532	2,267	3.76
Respiratory diseases	8,882	8	5,532	3,350	1.65
Respiratory Infections	5,684	5.1	3,162	2,522	1.25
Digestive (includes oral)	5,335	4.8	3,343	1,956	1.71
Urogenital	3,421	3.1	1,781	1,640	1.09
Perinatal	2,575	2.3	1,441	1,134	1.27
Diabetes	2,261	2	857	1,404	0.61
Intentional injury	2,210	2	1,603	607	2.64
Congenital Abnormalities	1,545	1.4	840	705	1.19
Neurological	877	0.8	507	370	1.37
Mental Disorders	367	0.3	311	56	5.55
Skin	344	0.3	171	173	0.99
Maternal	231	0.2	-	231	--
Musculoskeletal	177	0.2	55	122	0.45
Nutritional	88	0.07	42	46	0.91
Sense Organs	13		6	7	
Total	110,442		64,552	45,889	1.41

Table II: Year of Life Lost (YLL) by Selected* Diseases in Malaysia in 2000

	Total(years)	%	%YLL: %Overall Deaths
Cardiovascular	497,668	28	0.77
Unintentional Violence	236,668	13.3	1.34
Infectious Diseases (excludes respiratory diseases)	222,833	12.5	1.01
Cancers	178,441	10	0.9
Respiratory	163,936	9.2	1.15
Respiratory Infections	77,646	4.4	0.86
Perinatal	77,303	4.4	1.91
Digestive	78,267	4.4	0.92
Urogenital	49,355	2.8	0.9
Intentional Violence	46,324	2.6	1.3
Congenital Abnormalities	45,407	2.5	1.79
Diabetes	31,069	1.7	0.85
Maternal	6,051	0.3	1.5
Total	1,710,968	96.1	1

*some categories with small numbers are excluded

Table III: Cause-specific Years Lived with Disability in Malaysia 2000

Condition	Total(years)	%
Mental Disorders	235,787	21.2
Sense Organs	159,500	14.3
Respiratory	90,292	8.1
Musculoskeletal	78,577	7.1
Diabetes	72,381	6.5
Cardiovascular	62,303	5.6
Neurological	54,398	4.9
Respiratory Infections	51,948	4.7
Congenital Abnormalities	46,566	4.2
Nutritional	42,801	3.9
Digestive (includes oral)	42,620	3.8
Perinatal	40,756	3.7
Infectious Diseases (excludes respiratory)	39,188	3.5
Unintentional injury	35,803	3.2
Skin	18,009	1.6
Blood	14,535	1.3
Urogenital	14,038	1.3
Cancers	7,783	0.7
Maternal	2,484	0.2
Intentional injury	1,003	0.09
Total	1,110,772	99.89

The review of HIV/AIDS noted that although in the early years, the disease was mostly confined within the circle of injecting drug users (IDU); it has since spread to every stratum of society. In 2010, 40% of new reported HIV cases were from heterosexual transmission, a dramatic increase from 27% in 2009.Data on management of HIV-HBV and HIV-HCV co-infections is lacking. There is also a need for more research on children living with HIV,onmarginalized-at-risk-populations (MARPs) such as transgenders, migrant workers and refugees.For tuberculosis (TB), studies showed a higher incidence of TB among patients with diabetes mellitus, smokers, HIV and immunosuppressed patients, health care workers and intravenous drug users. Screening of TBis currently conducted primarily on healthcare workers, TB contacts, prisoners and foreign workers. As the number of TB cases in the country has increased, concern has been raised concerning screening and treating latent TB among high risk groups within the population. As for malaria, the epidemiology of malaria has undergone significant change over the last decade, with *P.knowlesi*, a previously relatively unknown simian parasite rapidly becoming the most predominant malaria species thatinfect humans in Malaysia, especially in Sabah and Sarawak. The reasons for dramatic shifts from *P. Falciparum* to *P. Knowlesiinfection* in some localities in Malaysia remain to be elucidated. Collaboration between clinical, entomological, laboratory, public health and social science disciplines and agencies need to be strengthened.

For mental health research, understanding the pathway an individual with schizophreniatakes to receive health care is importantin order to reduce the duration of untreated illness. Depression is one of the common mental disorders worldwide and has become a leading cause of morbidity in Malaysia over the past decades.There is a lack of research in depression among men in Malaysia. Research on depression was using screening tools based on western cultures. Thereis a need to develop local screening tools based on our diverse culture and language and these tools need to be validated before being used in research or in clinical setting. We also need research onaccess to care and unmet needs in the care for people with depression. On drug abuse, secondary data analysis on data collected by the National Drug Agency is needed so as to demonstrate trend ontype of drugs used by abusers in Malaysia and to demonstrate the change from opioids to recreational drugs.

While reviewing the bibliography of published articles as well as unpublished grey literature, the authors expressed concern on the significant number of unpublished research projects by Malaysian investigators, especially dissertations and thesis bylocal postgraduate and PhD students. Concerted effort among university supervisors and MOH specialists is needed in helping postgraduate master students to do better quality research so that their research findings can be published. One such effort is identifying research gaps and listing research ideas in this supplement. There is a section on future research in the respective diseasesthat postgraduate students and subspecialty trainees can.

While doing the review, we observed that there has been significant duplication of research ideas and lack of collaboration between the Ministry of Health and medical universities. Barriers in inter-sectorial research collaboration need to be overcome and duplication of research minimised. We also propose that future research in all disease areas should focus on treatment outcome, including patient reported outcome and cost effectiveness of management and prognosis of disease, as well as basic science research in genetics of diseases.

In conclusion, clinical research has been made a national agenda as is mentioned in the 10th and 11th Malaysian Plan and also one of the 17 entry point's projects in the Healthcare National Key Economic Area in the Economic Transformation Program. Therefore to set strategic direction for clinical research is timely and important in order to achieve the country's goal of Vision 2020, towards a high income country. We hope this supplement issue of 10 review articles on major diseases in Malaysia will contribute towards this effort.Though we understand this is certainly an unfinished work as there remain many other diseases to be reviewed. We hope others will join in the endeavour to publish review articles so future researchers can benefit from them.

REFERENCES

1. Ahmad Faudzi Y, Amal Nasir M, Gurpeet K, M Azahadi O, Vos T, Rao VPC, Begg S. Malaysian Burden of Disease and Injury Study. Health Prioritization: Burden of Disease Approach. Institute for Public Health. Ministry of Health, Malaysia. 2004.
2. Lim KG. A Review of Diseases in Malaysia. 2nd Ed. 2001.
3. Teng CL,Zuhanariah MN, Ng CS, Goh CC.Bibliography of clinical research in Malaysia: methods and brief results. Med J Malaysia 2014; sA:4-7.

Bibliography of Clinical Research in Malaysia: Methods and Brief Results

Cheong Lieng Teng, MMed, Zuhanariah Mohd Nordin, MSc, Chun Sien NG, medical student, Cheng Chun Goh, medical student

International Medical University, Malaysia.

SUMMARY

This article describes the methodology of this bibliography. A search was conducted on the following: (1) bibliographic databases (PubMed, Scopus, and other databases) using search terms that maximize the retrieval of Malaysian publications; (2) Individual journal search of Malaysian health-related journals; (3) A targeted search of Google and Google Scholar; (4) Searching of Malaysian institutional repositories; (5) Searching of Ministry of Health and Clinical Research Centre website. The publication years were limited to 2000-2013. The citations were imported or manually entered into bibliographic software Refworks. After removing duplicates, and correcting data entry errors, PubMed's Medical Subject Headings (MeSH terms) were added. Clinical research is coded using the definition "patient-oriented-research or research conducted with human subjects (or on material of human origin) for which the investigator directly interacts with the human subjects at some point during the study." A bibliography of citations [n=2056] that fit the criteria of clinical research in Malaysia in selected topics within five domains was generated: Cancers [589], Cardiovascular diseases [432], Infections [795], Injuries [142], and Mental Health [582]. This is done by retrieving citations with the appropriate MESH terms, as follow: For cancers (Breast Neoplasms; Colorectal Neoplasms; Uterine Cervical Neoplasms), for cardiovascular diseases (Coronary Disease; Hypertension; Stroke), for infections (Dengue; Enterovirus Infections, HIV Infections; Malaria; Nipah Virus; Tuberculosis), for injuries (Accidents, Occupational; Accidents, Traffic; Child Abuse; Occupational Injuries), for mental health (Depression; Depressive Disorder; Depressive Disorder, Major; Drug Users; Psychotic Disorders; Suicide; Suicide, Attempted; Suicidal Ideation; Substance-Related Disorders).

[246 words]

INTRODUCTION

Research and publications in Malaysia up to the year 2000 has been documented in various bibliographic works[1-5]. A search of the PubMed using the text words "Malaya" and "Malaysia" retrieved 8850 items for the period 1950-1999. However, for the period 2000-2013, the number of items retrieved has increased dramatically to 17909 items [search date 22 August 2013]. PubMed is clearly a great place to look for Malaysian health sciences publications but it contains only a fraction of what is available. A search of the Scopus [all subject areas] using the text words "Malaya" and "Malaysia" retrieved 10425 items for the period 1960-1999. However, for the period 2000-2013, the number of items retrieved has increased dramatically to 30196 items [search date 22 August 2013]. Do note that, Scopus is a general database containing citations of all disciplines, so many articles in there are not health-related.

Searching for Malaysian research has improved with the electronic access of databases. However, comprehensive search of Malaysian health sciences literature continue to pose difficulty for a few reasons:

- There are at least 50 Malaysian journals containing health sciences literature; only a few of them are indexed in major databases (six in PubMed, three Web of Science and 11 in Scopus)[6,7].
- Inaccuracy of indexing of Malaysian works in the databases[6,7].
- Grey literatures (e.g. books, book chapters, reports, and monograph) are not indexed by databases.

This article describe search methods for "Bibliography of Clinical Research in Malaysia", a project funded by the Clinical Research Centre, Kuala Lumpur.

METHODS

A team of searchers (consisting of librarians, medical students and a clinician) conducted simultaneous search and import citations into a web-based bibliographic manager (Refworks, http://www.refworks.com). The type of citations retrieved consisted of the following:

1. Journal articles
2. Conference proceedings
3. Books and book chapters
4. Guidelines and reports
5. Theses and dissertations

Journal articles are searched at these databases and websites

1. PubMed (http://www.ncbi.nlm.nih.gov/pubmed/)
2. Scopus (http://www.scopus.com)
3. MyJurnal (http://www.myjurnal.my)
4. UKM Journal Repository (http://journalarticle.ukm.my/)
5. Publisher/journal websites

PubMed

PubMed is the free online database of life sciences journal articles offered by the National Library of Medicine, National Institutes of Health, United States. It currently host over 6000 journals containing over 23 millions citations from 1950s. At the moment, six Malaysian journals are indexed in this database.

Corresponding Author: cheonglieng_teng@imu.edu.my

Table I: List of Malaysian biomedical journals.

1. Annals of Dentistry. http://ejum.fsktm.um.edu.my/VolumeListing.aspx?JournalID=13
2. Archives of Orofacial Sciences. http://www.dental.usm.my/aos/
3. ASEAN Journal of Psychiatry. http://www.aseanjournalofpsychiatry.org/index.php/aseanjournalofpsychiatry/issue/archive
4. Asia Pacific Journal of Molecular Biology and Biotechnology. http://www.msmbb.org.my/apjhome.htm
5. ASM Science Journal. http://www.akademisains.gov.my/index.php?option=com_content&task=view&id=291&Itemid=328
6. Biomedical Imaging and Intervention Journal. http://www.biij.org/default.asp
7. Buletin Persatuan Genetik Malaysia. http://www.persatuangenetikmalaysia.com/index_files/bulletin.html
8. Education in Medicine Journal. http://saifulbahri.com/eimj/
9. FMS Malaysia [hand search]
10. International e-Journal of Science, Medicine & Education (IeJSME). http://web.imu.edu.my/ejournal/
11. International Journal of Public Health Research. http://journalarticle.ukm.my/view/divisions/J=5FIPHR/
12. Journal of Health Management. http://www.ihm.moh.gov.my/index.php/en/penerbitan/journal-of-health-management-ihm
13. IMR Quarterly Bulletin. http://vlibimr.moh.gov.my/eshop/eresources.php?p=p_27
14. International Medical Journal (IIUM). http://www.e-imj.com/
15. International Medical Research Journal (IMR) [hand search]
16. Journal of Nuclear and Related Technologies. http://www.nuklearmalaysia.org/index.php?id=14&mnu=14
17. Journal of Surgical Academia. http://jsurgacad.com/
18. Journal of the University of Malaya Medical Centre (JUMMEC). http://jummec.um.edu.my
19. Jurnal Anti-Dadah Kebangsaan (Malaysian Anti-Drugs Journal). http://www.adk.gov.my/web/guest/jurnal
20. Jurnal Kesihatan Masyarakat (Malaysian Journal of Community Health). http://journalarticle.ukm.my/view/divisions/J=5FKMM/
21. Kuala Lumpur Hospital Journal of Quality Improvement [hand search]
22. Malaysia Journal of Nursing. http://www.mjn.com.my/
23. Malaysian Family Physician (For the period 2000-2005, this journal is known as Family Physician). http://www.e-mfp.org/index.htm
24. Malaysian Journal of Analytical Sciences. http://www.ukm.my/mjas/
25. Malaysian Journal of Biochemistry and Molecular Biology. http://ejum.fsktm.um.edu.my/VolumeListing.aspx?JournalID=16
26. Malaysian Journal of Dermatology. http://www.dermatology.org.my/journal.htm
27. Malaysian Journal of Forensic Pathology and Science. www.forensiknet.com
28. Malaysian Journal of Health Sciences (Jurnal Sains Kesihatan Malaysia). http://ejournals.ukm.my/jskm
29. Malaysian Journal of Medical Sciences. http://www.mjms.usm.my/
30. Malaysian Journal of Medicine and Health Sciences. http://www.medic.upm.edu.my/index.php/en/journal
31. Malaysian Journal of Microbiology. http://web.usm.my/mjm/
32. Malaysian Journal of Microscopy. http://ibs.upm.edu.my/~aini/publications.htm
33. Malaysian Journal of Nutrition. http://nutriweb.org.my/publications/mjn0017_1/default.php
34. Malaysian Journal of Obstetrics and Gynaecology. http://www.ogsm.org.my/mjog.php
35. Malaysian Journal of Paediatrics and Child Health. http://www.mjpch.com/index.php/mjpch
36. Malaysian Journal of Pathology. http://www.mjpath.org.my/index.html
37. Malaysian Journal of Pharmacy. http://www.mps.org.my/index.cfm?&menuid=146
38. Malaysian Journal of Pharmaceutical Sciences. http://web.usm.my/mjps/home.html
39. Malaysian Journal of Psychiatry. http://www.mjpsychiatry.org/index.php/mjp
40. Malaysian Journal of Public Health Medicine. http://www.mjphm.org.my/mjphm/
41. Malaysian Orthopaedic Journal. http://www.morthoj.org/
42. Medical Journal of Malaysia. http://www.e-mjm.org/
43. Medicine & Health Reviews. http://mhr.uitm.edu.my/
44. Medicine & Health. http://www.ppukm.ukm.my/ukmmcjournal/
45. NCD Malaysia [hand search]
46. Neurology Asia. http://www.neurology-asia.org/
47. Neurology Journal of Southeast Asia. http://www.neurology-asia.org/
48. Pertanika Journal of Science & Technology. http://www.pertanika2.upm.edu.my/JST.php
49. Pertanika Journal of Social Sciences & Humanities. http://www.pertanika2.upm.edu.my/JSSH.php
50. Sains Malaysiana. http://www.ukm.my/jsm/
51. Sunway Academic Journal. http://sunway.edu.my/university/publications/academic-journal
52. Tropical Biomedicine. http://www.msptm.org/journal.html

BRIEF RESULTS

A total of 2056 publications fall within the above inclusion criteria. See Tables II and III for distribution of publications by year and topics. Of the 2056 publications, 1212 (58.9%) were retrieved from PubMed. Free full text is available for 1293 (62.9%) publications.

Table II: Number of citations by year

Year	All citations	Included
2000	932	58
2001	980	63
2002	948	71
2003	1102	74
2004	1275	111
2005	1595	103
2006	1708	118
2007	1681	145
2008	2153	179
2009	1911	147
2010	2213	199
2011	3039	275
2012	3415	237
2013	4308	272
All years	27260	2056

Table III: Number (in bracket) of included citations by domains and subtopics

Domain	Subtopic
Cancers (589)	Breast cancer (389)
	Cervical cancer (112)
	Colorectal cancer (97)
Infections (795)	Dengue (182)
	Enterovirus infection (50)
	HIV infection (294)
	Malaria (108)
	Tuberculosis (193)
Injuries (142)	Child abuse (41)
	Road traffic accidents (101)
Mental Health (582)	Depression (265)
	Drug abuse (157)
	Schizophrenia (164)

Note: The content of some citations cover more than one subtopic

The full lists of citations for all 13 subtopics are available in http://www.crc.gov.my/published-articles-on-malaysian-data/.

The following search string is used to query the PubMed for the period 2000-2013:
MALAYA **OR** MALAYSIA **OR** JOHOR **OR** JOHORE **OR** MELAKA **OR** MALACCA **OR** NEGERI SEMBILAN **OR** NEGRI SEMBILAN **OR** KELANTAN **OR** KUALA LUMPUR **OR** SELANGOR **OR** PERAK **OR** KEDAH **OR** PENANG **OR** PULAU PINANG **OR** PERLIS **OR** PAHANG **OR** SARAWAK **OR** SABAH **OR** TERENGGANU **OR** LABUAN **OR** PUTRAJAYA **OR** WILAYAH PERSEKUTUAN **OR** KANGAR **OR** ALOR SETAR **OR** IPOH **OR** SEREMBAN **OR** KUANTAN **OR** KOTA BHARU **OR** KUCHING **OR** KOTA KINABALU **OR** (MALAYA[AD] **OR** MALAYSIA[AD] **OR** JOHOR[AD] **OR** JOHORE[AD] **OR** MELAKA[AD] **OR** MALACCA[AD] **OR** NEGERI SEMBILAN[AD] **OR** NEGRI SEMBILAN[AD] **OR** KELANTAN[AD] **OR** KUALA LUMPUR[AD] OR SELANGOR[AD] **OR** PERAK[AD] **OR** KEDAH[AD] **OR** PENANG[AD] **OR** PULAU PINANG [AD] **OR** PERLIS[AD] **OR** PAHANG[AD] **OR** SARAWAK[AD] **OR** SABAH[AD] **OR** TERENGGANU[AD]) **OR** MALAYSIA[MH] **OR** (Malays J Pathol[TA] **OR** Med J Malaysia[TA] **OR** Malays J Nutr[TA] **OR** Malays J Med Sci[TA] **OR** Trop BioMed[TA] **OR** Biomed Imaging Interv J [TA])

[note: AD, TA, and MH are PubMed field tags that refer to address, journal title abbreviation and Medical Subject Headings, respectively]

The above search string retrieved 21291 citations

Scopus

Scopus is a subscription-based bibliographic database owned by Elsevier. It contains over 50 millions records from around 21000 journals. A search for "Malaysia" for the period 2000-2013 in the subject area of "Health Sciences" retrieved 9720 citations.

Other journal searches

Medical and health sciences journal listed in MyJurnal (a portal of 347 Malaysian journals, 38 are listed under "Medicine & Health Sciences") and UKM Journal Repository (a portal of 42 journals published by Universiti Kebangsaan Malaysia) are comprehensively searched. All together we conducted hand search and electronic search of 52 Malaysian journals published in the period 2000-2013 (see Table I).

Search for non-journal citations

For non-journal citations (e.g. theses and dissertations), we performed search using Google (http://google.com.my) and Google Scholar (http://scholar.google.com.my/). We queried the following databases and institutional repository, both local and international, for scholarly works containing health and medical information on Malaysia:

1. Open Access Theses and Dissertations. www.oatd.org
2. Directory of Open Access Repositories. http://www.opendoar.org/
3. Institute for Medical Research Library. www.imr.gov.my
4. Academy of Medicine Clinical Practice Guidelines. http://www.acadmed.org.my/index.cfm?&menuid=67
5. Ministry of Health Malaysia. www.moh.gov.my
6. International Islamic University Malaysia Repository. http://irep.iium.edu.my/
7. Malaysian Thesis Online. http://myto.upm.edu.my/myTO/myto.html
8. Universiti Kebangsaan Malaysia Institutional Repository. https://smk.ukm.my/erep/
9. Universiti Malaya Research Repository. http://eprints.um.edu.my/
10. Universiti Malaysia Sabah Institutional Repository. http://eprints.ums.edu.my/

11. Universiti Malaysia Sarawak Institutional Repository. http://ir.unimas.my/
12. Universiti Putra Malaysia Institutional Repository. http://psasir.upm.edu.my/
13. Universiti Sains Malaysia Institutional Repository. http://eprints.usm.my
14. Universiti Teknologi MARA Institutional Repository. http://eprints.uitm.edu.my/
15. Universiti Utara Malaysia Repository. http://repo.uum.edu.my/
16. University of Malaya Theses and Dissertations. http://www.diglib.um.edu.my/umtheses/#sthash.2gD1j0rp.dpbs

Data cleaning and coding

After removing duplicated items and non-Malaysian references, the keywords based on National Library of Medicine's Medical Subject Headings (MESH terms) were coded for each citation.

The inclusion criteria for the present "Bibliography of Clinical Research" has a limited scope (as requested by the funder):

1. Citations must be clinical research. The definition of clinical research by Glasser is adopted, i.e. patient-oriented-research or research conducted with human subjects (or on material of human origin) for which the investigator directly interacts with the human subjects at some point during the study[8].
2. Citations that fall within four domains and 13 subtopics (breast cancer, cervical cancer, child abuse, colorectal cancer, depression, drug abuse, enterovirus infection, HIV infection, malaria, road traffic accident, schizophrenia, ttuberculosis and dengue).
3. Citations that were published between 2000-2013.

RESULTS

A total of 1853 citations fall within the above inclusion criteria (see Tables II and III)

REFERENCES

1. Bibliomed - SM. Supplement. Tokyo: South East Asia Information Center, 1982
2. Bibliomed - SM2. 1980-1986. Tokyo: South East Asia Information Center, 1989
3. 100 Years of the Institute for Medical Research 1900-2000. Kuala Lumpur: Institute for Medical Research, 2000
4. Lim KG. A Review of Diseases in Malaysia. Kuala Lumpur: Pelanduk Publications, 1993.
5. Lim KG. A Review of Diseases in Malaysia, 2nd Edition. 2001
6. Teng CL. In Search Of Malaysia: PubMed, Google Scholar Or Scopus? IeJSME. 2008;2(2):5-8.
7. Teng CL. Visibility of journals of Asia-Pacific countries in PubMed, Web of Science and Scopus. APAME 2012, 31 Aug - 3 Sept 2012, Kuala Lumpur.
8. Glasser SP. Essentials of Clinical Research. Springer, 2008.

A Review of Breast Cancer Research in Malaysia

CH Yip, FRCS*, N Bhoo Pathy, MD, SH Teo, PhD*****

* Department of Surgery, Faculty of Medicine, 50603 Kuala Lumpur, ** Department of Social and Preventive Medicine, Faculty of Medicine, 50603 Kuala Lumpur, ***Cancer Research Initiatives Foundation (CARIF), Outpatient Centre, Subang Jaya Medical Centre, Subang, 47500 Selangor, Malaysia

SUMMARY

Four hundred and nineteen articles related to breast cancer were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. One hundred and fifty four articles were selected and reviewed on the basis of clinical relevance and future research implications. Overall, Malaysian women have poor survival from breast cancer and it is estimated that half of the deaths due to breast cancer could be prevented. Five-year survival in Malaysia was low and varies among different institutions even within the same disease stage, suggesting an inequity of access to optimal treatment or a lack of compliance to optimal treatment. Malaysian women have poor knowledge of the risk factors, symptoms and methods for early detection of breast cancer, leading to late presentation. Moreover, Malaysian women experience cancer fatalism, belief in alternative medicine, and lack of autonomy in decision making resulting in delays in seeking or avoidance of evidence-based medicine. There are ethnic differences in estrogen receptor status, HER2 overexpression and incidence of triple negative breast cancer which warrant further investigation. Malay women present with larger tumours and at later stages, and even after adjustment for these and other prognostic factors (stage, pathology and treatment), Malay women have a poorer survival. Although the factors responsible for these ethnic differences have not been elucidated, it is thought that pharmacogenomics, lifestyle factors (such as weight-gain, diet and exercise), and psychosocial factors (such as acceptance of 2nd or 3rd line chemotherapy) may be responsible for the difference in survival. Notably, survivorship studies show self-management programmes and exercise improve quality of life, highlighting the need to evaluate the psychosocial impact of breast cancer on Malaysian women, and to design culturally-, religiously- and linguistically-appropriate psycho-education programmes to help women cope with the disease and improve their quality of life. Research done in the Caucasian populations may not necessarily apply to local settings and it is important to embark on local studies particularly prevention, screening, diagnostic, prognostic, therapeutic and psychosocial research.

KEY WORDS: *breast cancer, Malaysia, review, genetics, screening, diagnosis, prognosis, treatment, outcome*

INTRODUCTION

Besides the articles searched through the database, we also conducted a literature review of articles indexed in PubMed from 1996 to 2014 on 30th April 2014 using the key words "breast cancer" "Malaysia" and reviewed 421 articles. Of these, 154 abstracts were considered relevant to clinical practice by the authors [a breast surgeon, a genetic epidemiologist and an epidemiologist] and full text articles were reviewed. The aim of this review article is to summarise what has already been published on breast cancer in Malaysia, to discuss the impact of the research findings to clinical practice, and to identify gaps in breast cancer research in Malaysia.

SECTION 1: REVIEW OF LITERATURE

INCIDENCE AND PRESENTATION OF BREAST CANCER

The National Cancer Registry (NCR) 2003-2005 reported an age-standardised rate (ASR) of 47.3 per 100 000. The incidence is highest in Chinese (59.9 per 100 000) followed by Indians (54.2 per 100 000) and Malays (34.9 per 100 000)[1]. The Penang Cancer Registry 2004-2008 reported an incidence of 48 per 100,000[2]. The International Agency for Research in Cancer (GLOBOCAN) 2012 estimated the ASR of breast cancer in Malaysia as 38.7 per 100,000 with 5410 new cases in 2012[3].

Malaysian women present at earlier age compared to women in Western countries. A collaborative study between two tertiary academic hospitals in Malaysia, and Singapore found that approximately 50% of women were diagnosed before the age of 50 years[4], whereas in most Western countries such as UK and Netherlands, 20% are diagnosed before age 50. Two factors account for the younger mean age at presentation in Malaysia. First, Malaysia has a younger demographic with median age of 26.1 years, compared with 39.8 years in United Kingdom[5]. Second, the current older population in Malaysia, experience lower-risk lifestyle factors (more children, more breast-feeding and lower urbanisation) and this cohort effect results in lower risk of post-menopausal breast cancer.

Malaysian women present at later stages compared to women in Western countries and Singapore[6-8] but presented at earlier stages compared to Indonesian women[9]. Presentation of breast cancer varies substantially not only among countries, but also within different settings in Malaysia. Table I summarises the stage at presentation, tumour size and age in different settings in Malaysia[2,8,10-13]. Delayed presentation remains very common[14] and a collaborative study in Malaysia, India and Hong Kong showed that inadequacies of health care infrastructures and standards, sociocultural barriers, economic realities, illiteracy, and the differences in the clinical and pathological attributes of this disease in Asian women compared with the rest of the world together result in significant proportion of late stage disease[15]. In Malaysia,

Corresponding Author: chenghar.yip@gmail.com

ethnicity, education level, socio-economic status and access to treatment centres in urban areas were found to be important factors influencing stage at presentation. By combining the hospital-based breast cancer databases in University Malaya Medical Centre (UMMC) and National University Hospital Singapore (NUHS) [5264 patients], it was found that the Malay ethnicity was significantly associated with larger tumours at presentation and later stages at presentation, compared to the Chinese and to a certain extent, the Indians[16]. Late stage at presentation of breast cancer had been attributed to a strong belief in traditional medicine, the negative perception of the disease, poverty and poor education, coupled with fear and denial[17]. In Sabah, patients who presented with advanced disease were also poor, non-educated and from rural areas[13].

LIFESTYLE AND GENETIC RISK FACTORS TO BREAST CANCER

A number of lifestyle and genetic factors cause an increased risk of breast cancer and these have been shown to increase risk of breast cancer in Malaysian women. Table II summarises results from case control studies involving Malaysian women[18-29]. Well-known risk factors such as nulliparity, family history, not breastfeeding and use of oral contraceptives are observed to be associated with an increased risk of breast cancer in Malaysian women, but other risk factors are not significantly associated (e.g. age at menarche and first childbirth). However, these studies are retrospective and may be underpowered to find statistically significant results. To date, no study has examined breast mammographic density and the extent to which ethnic-differences in breast mammographic density is associated with risk of breast cancer.

Genetic predisposition also play a role in the aetiology of breast cancer. Approximately 15% of breast cancer patients report family history of breast and ovarian cancer, and the most significant genetic predisposition genes identified are BRCA1 and BRCA2. Cohort studies have shown the prevalence of BRCA1 and BRCA2 among breast cancer patients of 2.7% and 5.4% respectively, which is consistent with other Asian ethnic groups 30-31. Large genomic rearrangements (LGRs) constitute 8% of BRCA1 and 4% of BRCA2 mutations, and a number of novel rearrangements have been reported, suggesting that comprehensive BRCA testing should include detection of LGRs[32,33].

Two algorithms to predict the presence of mutations, Manchester Scoring System and BOADICEA, were evaluated and found that the predictive power of these two models were significantly better for BRCA1 than BRCA2, and that the overall sensitivity, specificity and positive predictive value was lower in this population than previously reported in the Caucasian population[34]. Notably, breast cancers associated with BRCA1 mutations are more likely to be triple negative for estrogen, progesterone and HER2 receptors, and of higher grade; BRCA2 associated breast cancers were similar to non BRCA associated breast cancers[35]. These pathological characteristics are predictive of BRCA1 mutation status - twenty-eight percent of women with breast cancers negative for the estrogen, progesterone and HER2 receptors diagnosed younger than 35 years old were found to be BRCA1 carriers, while only 9.9% of women with non-TNBC and younger than 35 years were BRCA1 carriers. Addition of TNBC and PTEN status improved the sensitivity of the Manchester Scoring System[36].

Genetic counselling and genetic testing were accepted by 82% of women at high risk for hereditary breast and ovarian cancer (HBOC) syndromes. However, only 78% of carriers informed their families, and 11% of relatives came forward for predictive testing even when genetic counselling and testing were offered free[37]. Early experience of the genetic testing and risk management clinic for high risk breast and ovarian cancer families in UMMC showed that only 63.5% of eligible women chose to attend this clinic, 24% chose to have risk reducing mastectomy (RRM) while the rest chose breast surveillance. Sixty-three percent chose to have risk reducing salphingo-oophorectomy[38].

Of the high risk women who did not have germline BRCA mutations, four mutations in TP53 (5%) suggested that TP53 screening should be considered in women with early onset breast cancer (<35 years old)[39]. PALB2 mutations were also reported and screening with nine PALB2 mutations found two novel truncating mutations and ten missense mutations, and one additional PALB2 mutation indicating a low prevalence of PALB2 mutations[40]. A truncating mutation (1100delc) in the cell cycle checkpoint kinase -2 gene (CHEK2), a common moderate penetrance allele found in Caucasians, was not found in any of the cohort of 668 breast cancer patients, suggesting that screening for this allele should not be routinely conducted in Malaysia[41]. Other genes or genetic loci associated with breast cancer have also been reported including the human leukocyte antigen (HLA) types[42], and other loci of lower penetrance[43].

SCREENING AND EARLY DETECTION

One of the main determinants of survival from breast cancer is early detection, which in turn is dependent on disease awareness and uptake of screening (both opportunistic and population-based screening). However, breast cancer awareness is poor in Malaysian women and very few eligible women attend regular mammography screening. Table III summarises results of cross-sectional studies, utilising surveys and self-administered questionnaires, that have been carried out in the Malaysian community to assess knowledge of breast cancer and screening methods i.e. breast self-examination (BSE), clinical breast examination (CBE) and screening mammography[44-61]. Notably, even among high-risk women, a cross-sectional study of 131 women with a family history of breast cancer showed that 71% had poor knowledge about the risk factors for breast cancer[62] and women with a family history of breast cancer probably did not recognise their increased risk to cancer and so presented with same stage of disease as women with no family history of breast cancer[63]. Many studies have shown that symptom recognition remains an important public health issue in Malaysia, highlighting the pressing need to continue to educate women, their significant others, and primary health care workers[64].

To date, the only reported outreach programme, which was conducted over a 4-year period in Sarawak, showed that training health staff in hospital and rural clinics to improve their skills in early cancer detection, and raising public awareness through pamphlets, posters and sensitisation by health staff, resulted in a reduction in the proportion of stage 3 and stage 4 breast cancer from 60% in 1994 to 35% in 1998[65].

DIAGNOSIS AND PATHOLOGY

Mammography, ultrasounds, MRI and bone scans

Radiology is pivotal in the screening and diagnosis of breast cancer. The majority of mammography services have transitioned from screen-film to digital, but quality assurance continues to be an important challenge in Malaysia. A survey carried out by the Malaysian College of Radiology on 50 mammography units showed that although 86% passed the image quality test, only 12.5% complied with the ACR

(American College of Radiology) recommended view-box luminance[66]. Overall diagnosis was comparable between screen film mammography (SFM), computed radiography mammography (CRM) and full field digital mammography (FFDM), but FFDM improves the quality of mammography services by providing better workflow time and archiving system[67], and improving the detection of microcalcifications[68].

Breast mammographic density is higher in Asian women and may affect the sensitivity of mammographic screening. The majority of Malaysian women had dense breasts (59%) and age and parity were inversely related to breast density[69]. A number of dietary factors have been associated with mammographic density, but these require further validation[70]. There is currently no commonly accepted standards for quantifying breast mammographic density in Malaysia. However, a semi-automated technique for quantitative assessment of breast density from digitised mammograms correlated well with the Tabar pattern, with a kappa coefficient of 0.63[71], suggesting that both methods may be clinically useful.

Ultrasound is a useful adjunct to mammography in the assessment of breast lumps. To differentiate between benign and malignant lesions, conventional ultrasound has a sensitivity and specificity of 97%, and 61.4% alone, and 100% and 93% when combined with ultrasound elastography[72]. The validity of ultrasound in the assessment of a palpable mass found that ultrasound had a sensitivity of 100%, specificity of 85.7%, and accuracy of 81.3% for distinguishing a malignant mass from a benign mass in another study[73].

Magnetic resonance imaging of the breast is a relatively new diagnostic tool in Malaysia and should not be used for routine screening. A prospective study of SV (1)H MRS following dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) showed that there was good correlation between tCho peaks and malignancy[74]. The sensitivity of DCE-MRI alone in differentiating between malignant and benign breast lesions was 100% with a specificity of 66.7%[75].

Staging with bone scans are recommended in women with locally advanced or metastatic breast cancer, but the role in early Stage 1 and 2 breast cancer is equivocal. Notably, no patient with clinical Stage 0 or Stage 1, 4% with Stage 2, 9.5% with Stage 3 and 63% with Stage 4 disease had a positive bone scan, showing that there is little justification to perform a bone scan in early breast cancer[76].

Pathology

Diagnosis of breast cancer depends on team work between the radiologist, surgeon and pathologist. The three methods of biopsy are fine needle biopsy, core needle biopsy and excisional biopsy. The choice of diagnostic method depends on the expertise which is available. Fine needle aspiration cytology was the most common method of diagnosis (63.8% of cases) in UMMC followed by core needle biopsy and excisional biopsy[77]. For non-palpable breast lesions, a study of 38 cases in Hospital Kuala Lumpur showed that 26.3% of excisional biopsies after mammographic localisation with a hookwire were malignant[78], compared to 32.3% in 57 patients in UMMC[79]. For palpable breast masses, fine needle aspiration cytology on 676 palpable breast masses showed a sensitivity of 91.7%, specificity of 91.7%, with a false negative rate of 11%[80]. If the cytological suspicious / equivocal category was considered as test positive, the sensitivity of FNAC was further increased to 97.4% and the specificity to 92%[81].

Cytology tumour typing was accurate in 94.8%, cytology grading was accurate in 71% and evaluation of ER status in 92.5%[82]. Typical cytological pictures were described for invasive lobular83 as well as for mucinous carcinoma[84].

Breast cancer is a heterogenous disease and pathological assessment of the tumour is important for prognosis and treatment. Size, grade, lymph node status, ER PR and cerbB2 assessment should be done routinely and are essential for accurate decision making on treatment.

Breast specimens undergo shrinkage after fixation, losing more than a third of their original closest free margin, while the tumour itself does not shrink substantially[85]. Infiltrating ductal carcinoma was the commonest histology in all women, where it accounts for 74.6% of women diagnosed > 50 years old and 65.2% of women diagnosed <50 years old[86].

Table IV summarises the studies on molecular markers from various institutions in Malaysia[13, 87-93]. There are several notable points: first, the proportion of ER positive breast cancer has increased over time, probably due to the rapid urbanisation and changes in parity and breast feeding over time. Second, Malay women were more likely to be ER negative, probably because the cohort comprises women diagnosed at an earlier age of onset[87]. Finally, there is wide variation in proportion of HER2-positive and triple-negative breast cancer (TNBC) in the Malaysian population, which could be due to interlaboratory differences in quality assurance and standardisation of testing for the three molecular markers.

Consistent with studies in Caucasian populations, triple negative breast cancer is more likely to be associated with young age of diagnosis, high grade, dysregulation of TP53, high expression of EGFR, CK5/6 and c-KIT, and high Ki67 proliferation index[89,92]. Overexpression of HER2 was significantly associated with high tumour grade, PR negativity and lymphovascular invasion[88]. Tumours which are negative for the estrogen receptor but positive for progesterone receptor was found in 4.6% of cases and occurs at a younger age group with intermediate histopathological characteristics compared to the ER+PR+ and ER-PR- tumours, suggesting that it is likely to be a distinct entity and not a biological artifact[94], but this has not been replicated in other studies. A study in Sarawak on 1034 cases of female breast cancer suggest that there may be ethnic differences in the risk to different subtypes of breast cancer. Overall, the study reported 48% luminal A (ER+ PR+ HER2-) breast cancer, 12% triple positive (ER+PR+HER2+), 29% TNBC and 11% HER2 overexpressing subtypes (ER-PR-HER2+). The indigenous population had the highest incidence (37%) of TNBC compared to Chinese (23%) and Malays (33%), and this remain significant after adjusting for other variables including age. HER2 overexpression was more frequent among the Malays (29%) compared to Chinese (22%) and the indigenous population (21%)[93].

One study suggested that overexpression of p53, which was observed in 55.3% of tumours, may be a prognostic factor. With a median follow-up of 4 years, the median overall survival of tumours with wild type compared to p53 negative tumours was 3 years compared with 3.8 years while for disease-free survival, it was 2.5 years compared to 3.3 years[95]. However, the data was not adjusted to intrinsic subtypes of breast cancer or for treatment differences. Two other biomarkers which have been tested are PTEN and CA153. PTEN loss occurred in 48.3% of TNBC, and was significantly associated with younger age at diagnosis. Independent predictors of PTEN loss were late stage at presentation, cytokeratin 5/6 positivity and IGFBP2

expression. PTEN loss and high levels of IGFBP2 expression were associated with poorer survival, but neither of these trends were significant[96]. Elevated levels of CA153 was associated with a poorer survival, suggesting its potential role as a prognostic biomarker[97].

TREATMENT

Where possible, breast cancer patients should be treated by a multidisplinary team. Surgery remains the mainstay of breast cancer treatment, with chemotherapy, radiotherapy and hormone therapy as adjunctive therapy. Newer agents such as targeted therapy is also part of the armamentarium of treatment strategies.

Surgery

Over the past 10 years, there has been an increase in the number of general surgeons who subspecialise in breast surgery in Malaysia and improvements in surgery have been made. Conventional technology to use diathermy to cut and coagulate blood vessels compared with ultracision showed that the use of ultracision was able to reduce the amount of drainage annd number of drain days, hence allowing earlier discharge of patients[98]. Another randomised controlled trial comparing preemptive local infiltration with ropivacaine (PLA) with postoperative wound infiltration with ropivacaine (POW) found no difference in post-operative pain between the two groups[99].

Axillary lymph node status is the most important prognostic factor in breast cancer. Therefore, some form of axillary dissection is needed for accurate assessment of the axilla. Given that only 24 out of 53 (45.3%) with positive axillary nodes were palpable, surgeons should be aware that clinical and intraoperative assessment of the axilla is inaccurate and all patients require at least a Level 1-2 dissection[100]. However, this does not apply to small T1 tumours, where axillary dissection will result in over-treatment of up to 75% of cases, and therefore, a sentinel node biopsy is justified[101]. Multivariable analyses show that the predictors of lymph node metastases were lymphovascular invasion and tumour size. The degree of tumour free margins after surgery is also crucial in deciding subsequent management[85].

In metastatic breast cancer, mastectomy was previously not thought to improve survival. However, a study showed that breast surgery was associated with a 28% lower risk of death after adjustment for patient and tumour characteristics, metastatic profile and treatment[102].

Given that the majority of Malaysian women still present at late stage, mastectomy is an essential but disfiguring operation. Immediate reconstruction can help women feel whole again and reduce the negative impact on body image, but access, cost and fear of additional surgery remain significant barriers to reconstructive surgery. Only a third of patients undergoing mastectomy were offered immediate reconstruction[103].

Chemotherapy

Chemotherapy has been shown to improve survival in women with breast cancer in the adjuvant setting, but a major concern to patients is that their immune system may be compromised with chemotherapy. Anthracyclines are the most widely used anticancer agents for breast cancer and a study comparing the effect of FEC (5-fluorouracil, epirubicin, cyclophosphamide) and FAC (5-fluorouracil, adriamycin, cyclophosphamide) found no significant difference in the numbers of immune cells, percentages of lymphocytes subsets, Th/Cytotoxic-T-lymphocyte (Th/CTL) ratio, engulfment and killing abilities of polymorphonuclear cells (PMNs)[104], suggesting that the immune system is not a major target of epirubicin-chemotherapy. Three other side effects which are major concerns to patients are hypercalcemia, neutropenia and preservation of fertility. Hypercalcemia can occur in cancer patients with and without bone metastases and in a study of 1,023 breast cancer patients, 174 patients (17%) had increased calcium levels. Chemotherapy decreases calcium levels in breast cancer cases with hypercalcemia at cancer diagnosis, probably by reducing Parathyroid Hormone-Related Peptide (PTHrP) levels[105]. Neutropenia is a common side effect of chemotherapy, but with adjuvant taxane based chemotherapy for early breast cancer, febrile neutropenia was reported in 10% of cases and no treatment-related deaths were reported[106]. Chemotherapy-induced ovarian failure occured in 57% of women <35 years, 95% at 35-45 years and 97.9% at >50 years, but notably, this was reversible in 50% of women >35 years old[107].

Locally advanced breast cancer (LABC) is a common presentation in Malaysia, but may present clinical challenges in management of patients. Overall, neo-adjuvant chemotherapy gave a complete pathological response of 5.9-9.4%[108-109]. However, 17.6 - 25.1% of women defaulted part of the treatment, or did not receive optimal treatment, highlighting the importance of psychosocial support and counselling for this group of patients[108-109].

Pharmacogenomics

Although studies in other populations describe ethnic differences in pharmacogenomics, there have been few systematic studies on ethnic-differences in pharmacogenomic responses to chemotherapy in Malaysia.

One study showed ethnic differences in CYP3A4 and CYP2D6, which may in part explain the differences in antiemetic effects of granisetron and 5-HT receptor antagonist (e.g. tropisetron and dolasetron) respectively[110].

A retrospective study suggests that patients who were CYP2D6 IM (intermediate metabolisers) and homozygous CC genotype of C3435T have statistically significant higher risks of recurrence and shorter times to recurrence when treated with tamoxifen[111], but this needs to be validated through prospective studies.

Traditional and complementary medicine

Traditional and complementary medicine are often used by Malaysian women with breast cancer, with one study of 116 Malay women describing uptake of 64% and another study reporting 51%. The most common medicines in Malay women were dietary supplements, followed by praying and Malay traditional medicine[112]. In Sabah, where women were found to present late, ~20% of patients opted for traditional alternatives and defaulted treatment[13]. Women who defaulted treatment were significantly more likely to be non-Chinese[113].

To date, few traditional or complementary medicines have been robustly tested through randomised controlled trials. A study on Withania somnifera (Ashwagandha), an Indian traditional medication, in women undergoing either chemotherapy with oral Withana somnifera or chemotherapy alone, showed that patients in the control arm had a significantly higher fatigue score and poorer quality of life than the intervention arm[114]. Tocotrienols have potent antiproliferative and proapoptotic effects in vitro, but a double-blind, placebo-controlled pilot trial comparing adjuvant tocotrienol therapy in combination with tamoxifen with tamoxifen alone for five years in women with ER positive early breast cancer showed no effect on breast cancer specific survival[115].

OUTCOMES

Overall Survival

Survival from breast cancer has improved in the past 3 decades. The largest Malaysian population based study of 10,000 breast cancer patients diagnosed between Jan 2000 and Dec 2005 identified from the Health Informatics Centre, Ministry of Health Malaysia, the National Cancer Registry and the National Mortality Registry found that the 5-year overall survival rate was 49%[116]. However, overall 5-year survival of breast cancer patients in UMMC improved from 58% to 76% for patients diagnosed in 1993-1997 compared to 1998-2002 (11). The most likely explanation is the establishment of oncology services in the hospital in 1998. Survival analysis showed that stage, lymph node status, negativity for the estrogen receptor, tumour size and grade were the most important prognostic factors[117-118]. Notably, whereas several studies in Western settings had reported that lymph node ratio (LNR, i.e. the ratio of the number of positive nodes to the total number of nodes excised) was superior to the absolute number of nodes involved (pN stage), this did not improve prognostication in a Malaysian population[119]. Another prognostic factor is locoregional recurrence after mastectomy for breast cancer, which may predict distant recurrence and mortality. The overall post-mastectomy local recurrence rate was 16.4% and isolated local recurrence rate was 8.0% (42 of 522 patients). Race, age, size, stage, margin involvement, lymph node involvement, grade, lymphovascular invasion and ER status were associated with ipsilateral local recurrence (ILR)[120]. A number of studies have examined the prognostic value of new biomarkers but these studies have been limited by ascertainment bias, as patients were more likely to receive additional testing (e.g. HER2 testing) if they are at intermediate or high risk[121]. Investigating the prognostic value of new biomarkers in breast cancer using only patients with available biomarker status from hospital cancer registries may lead to invalid results. Compared with patients perceived as having low mortality risk, patients with high mortality risk were significantly less likely to be tested for HER2 status, whereas those with intermediate risk were more likely to be tested[121].

However, although survival is improving in Malaysia, overall survival continues to lag behind that of our neighbouring countries, particularly Singapore. A combined analysis of 5,264 patients treated in UMMC and National University Hospital Singapore (NUHS), showed 5-year overall survival of 82.5% in Stage 0 to Stage II breast cancer patients, and 30.2% in Stage III and IV patients (4). Malay women had significantly higher risk of all-cause mortality, independent of age, stage, tumour characteristics and treatment, compared to Indian and Chinese ethnicity in this and another Malaysian study [Indian: 10.0%, Chinese: 71.6%, Malay: 18.4%][16,122], but in another study, delayed time from diagnosis to treatment in Malay compared to Chinese women did not result in significant impact on survival[123].The combined Malaysia-Singapore database also showed that overall survival of breast cancer patients from Malaysia is much lower than that of Singaporean patients[8,12]. Table V summarises the 5-year survival data from different Malaysian institutions[8,11-12,116]. It is noteworthy that the survival in UMMC at each stage of diagnosis is better than that of Hospital Kuala Lumpur, suggesting that disparities in survival could arise from differences in compliance to treatment.

Notably, a limitation of the majority of studies conducted so far have been that they are single-institution-based studies that may not accurately provide an overall picture of presentation, management, and outcome of breast cancer in Malaysia. Recently, a multicentre retrospective observational study showed that the performance results, while acceptable for a middle income country, was below the 95% or higher adherence rates routinely reported by centres in developed countries[124]. Further multi-centre studies, such as the National Cancer Patient Registry-Breast cancer (NCPR-BC), would be useful for evaluating clinical management in Malaysia[125].

Another manifestation of the disparity in survival is in the over-optimistic prediction of survival from prognostic models. Prognostic models, such as Adjuvant! Online, which have been developed in Caucasian populations to guide decision making for adjuvant therapy in early breast cancers, has been found to significantly over-estimated the 10-year survival (70.3% predicted compared to 63.6% observed, difference of 6.7%)[126], thus highlighting the need to address the disparities in care.

Two groups of patients may have poorer survival, namely the elderly and pregnant women. Although there is limited information on the outcomes of elderly breast cancer patients, this group of patients tend to be undertreated and have poorer survival because of competing co-morbidities. Of one hundred and thirty six women with breast cancer aged 70 and older studied, the relapse free, cause specific survival and cumulative overall 5-year survival were 79.7%, 73.3% and 51.9% respectively[127]. Patients who develop breast cancer whilst pregnant were rare and they require a multidisciplinary approach involving an obstetrician, surgeon and oncologist. Experience with six patients in UMMC revealed that five patients refused any treatment during pregnancy and the outcome was poor, with all patients dying between 14 months and 52 months[128].

Biomarkers

To date, four pathological biomarkers have been evaluated in the Malaysian population for its prognostic value, namely HER2, TP53, PTEN and CA153. Consistent with studies in other populations, HER2 (cerbB-2 onco-protein) overexpression was associated with a shorter recurrence free survival and overall survival[129]. One study suggested that overexpression of p53, which was observed in 55.3% of tumours, may be a prognostic factor. With a median follow-up of 4 years, the median overall survival of tumours with wild type compared to p53 negative tumours was 3 years compared with 3.8 years while disease free survival was 2.5 years compared to 3.3 years[95]. However, the data was not adjusted to intrinsic subtypes of breast cancer or for treatment differences. Two other biomarkers which have been tested are PTEN and CA153. PTEN loss occurred in 48.3% of TNBC, and was significantly associated with younger age at diagnosis. Independent predictors of PTEN loss were late stage at presentation, cytokeratin 5/6 positivity and IGFBP2 expression. PTEN loss and high levels of IGFBP2 expression were associated with poorer survival, but neither of these trends was significant[96]. Elevated levels of CA153 was associated with a poorer survival, suggesting its potential role as a prognostic biomarker[97].

SURVIVORSHIP AND PSYCHOSOCIAL ISSUES

Physical and psychological impact of breast cancer diagnosis

With optimal treatment, survival from breast cancer is very good, with 5-year survival of over 80% reported from USA. However, breast cancer survivors may experience long-term side effects of treatment such as early menopause, infertility, and sexual function, and psychological issues such as fear of recurrence, sexuality and body image. Without appropriate social support, these physical and psychological issues can result in poor quality of life. Indeed, 17.6% of care givers of

breast cancer patients were diagnosed to have depressive disorders and this was associated with ethnicity, duration of caregiving, the patients' functional status, and the caregiver's education level 130. One solution for breast cancer patients is a 4-week patient self- management programme for breast cancer, which has been shown to improve the quality of life of breast cancer patients by enabling them to better manage the numerous medical emotional and role tasks[131], with the benefits experienced even after two years[132]. A shorter term solution of a one-month group psycho-education programme also improved well-being and reduced the proportion of depressed individuals from 23.5% to 2.9%[133]. Other avenues for support comes from the family and from survivor support groups. Family and support group interventions for survivorship strategies such as managing emotions, health, lifestyle and dietary practice are important[134-135].

To date, few studies have evaluated the psychosocial impact of a diagnosis of breast cancer and effects of treatment in the developing world and in Malaysia. In a study in Kelantan, the quality of life (QOL) of newly diagnosed breast cancer patients was satisfactory in both Malay and Chinese women, but Malay women had a lower QOL due to high general, as well as breast-specific, symptoms[136]. Three themes were found in a study of the live-in experiences of 20 of breast cancer patients (Chinese-10, Malays-10): uncertainty, transition from health to illness, and fatalism[137]. Several psychological tools developed in Caucasian countries to measure the coping mechanisms and psychosocial parameters in patients have been validated in Malaysia, including the COPE scale[138], the Malay version of the Breast Module (BR23)[139], the Malay version of the Breast Impact of Treatment Scale (MVBITS)[140], and the Malay version of the Hospital Anxiety and Depression Scale (HADS)[141].

Coping with treatment side effects

Few Malaysian studies have reported how Malaysian breast cancer patients cope with treatment-related side effects. One study used the validated questionnaire, Morrow Assessment of Nausea and Vomiting (MANE) and Osoba Nausea and Emesis Module (ONEM) to assess the impact of chemotherapy induced nausea and vomiting (CINV) on QOL and found that delayed CINV (3-5 days after chemotherapy) had a greater impact on QOL compared to acute CINV[142].

Lifestyle effects on survivorship

Some changes in lifestyles may improve survival. The majority of Malaysian breast cancer patients (72 of 116 women) considered diet as a contributing factor to breast cancer and 67 women changed their dietary habits, by increasing the consumption of fruits, vegetables, fish, low fat milk and soy products, and reducing red meat, seafood, noodles and poultry[143]. In other populations, weight loss after breast cancer and exercise have been linked to better outcomes. In Malaysia, 40% of women with breast cancer were overweight or obese, and significant weight gain was observed from time of diagnosis to study entry[144]. Women with more than 10% weight gain had the lowest servings of fruits and vegetables and the highest servings of dairy products[145]. Despite the many documented benefits of physical activity, the majority of survivors were not physically active, citing lack of time as the main barrier[146].

Many Malaysian women report the use of complementary and alternative medicine (CAM) to improve survivorship, despite scarce evidence of efficacy. Uptake of CAM was reported in 51-64% of women, to increase the body's ability to perform daily activities, enhance immune function and improve emotional well-being[112,147]. An in-depth interview with 11 Malaysian cancer survivors found that they sought CAM because of recommendation from family and friends, perceived benefit and compatibility, healer's credibility, reservations with western medicine and system delays[148].

Addressing reasons for delay in presentation and default in treatment

Given that some Malaysian breast cancer patients continue to delay in presentation and default treatment, a priority for Malaysian researchers has been the identification of the reasons for delay and the development of interventions to reduce delay and default. A qualitative study in the East Coast of Malaysia, where 72.6% of women delayed presentation for >3 months, found that the reasons for delay were poor awareness of breast cancer, fear of cancer consequences, belief in CAM, sanction by others, other priorities, denial of disease, the 'wait and see' attitude, and weaknesses in the health care system[149]. Other factors associated with delay were use of traditional medicine, breast ulcer, palpable axillary lymph nodes, false negative diagnostic test, non-cancer interpretation and negative attitude towards treatment[150]. A study in Hospital Kuala Lumpur, where 31.1% of women delayed presentation for >3 months, found that women who were divorced or widowed, or women who never performed BSE were more likely to delay[151]. Overall, six themes were identified in a qualitative study on the health seeking trajectories of' Malaysian women. First, women considered traditional- versus hospital-based treatment. Next, their experience with symptoms, with the healthcare system were important. Fourth, their psychological status were critical. Fifth, their interaction with a role model was pivotal and finally, their fear of removing the breast guided their decisions[152]. Four main operational constructs in delayed presentation were knowledge of disease and disease outcomes, knowledge of treatment and treatment outcomes, psychological and physical resources and support and finally, roles in decision making. Deconstructing why women present with advanced breast cancer and resist treatment provide clarity of the issues and opportunities for intervention[153].

One such intervention could be providing educational material for making decisions. Decision making experiences of women with breast cancer were explored through a qualitative study and identified four phases in the decision-making process: discovery (pre-diagnosis); confirmatory ('receiving bad news'); deliberation; and decision (making a decision) with the final treatment decision influenced mainly by women's own experiences, knowledge and understanding[154]. This should provide the basis for the formulation of decision aids adapted for use in the Malaysian population.

Another intervention is providing culturally-sensitive information for Malaysian patients. A comparison of the informational needs of women newly diagnosed with breast cancer in Malaysia compared to the UK showed that for Malaysian women, information about the likelihood of cure, sexual attractiveness and spread of disease were the most important information needs while sexual attractiveness ranked lower compared to in women in UK[155]. Breast cancer patients undergoing chemotherapy had high levels of informational needs and there were difference between what the patient needs and the nurse's perception of patient's needs[156].

Returning to work

Key barriers to return to work were physical-psychological after-effects of treatment, fear of potential environmental hazard, high physical job demand, intrusive negative thoughts and overprotective family. On the other hand, the key facilitators

were social support, employer support, and the need for financial independence[157].

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Risk factors for breast cancer in the local population were similar to published data i.e. nulliparity, family history, lack of breast feeding, oral contraceptive pill, obesity, and physical activity. Of these, it is expected that there will be a surge in the number of breast cancer cases in the not too distant future, in view that obesity rates are increasing at an alarming rate in Malaysia. Malaysian women are becoming "Westernised' in terms of changes in their reproductive risk factors, which starts with the earlier attainment of menarche, women opting to postpone marriage and pregnancies to a later age and having less number of children. Dietary changes may also play a role in the expected rise in the incidence of breast cancer.

Breast cancer associated with genetic mutations constitute a small percentage, between 5-10% of breast cancers. Nonetheless, they form an important group especially with increasing awareness about family history as a risk for breast cancer. The prevalence of BRCA1 and BRCA2, as well as less well known mutations such as TP53, PALB2 and CHEK2 in Malaysian women with breast cancer is reported, together with the clinical and pathological features. The results of the initial studies led to the establishment of a high risk management clinic, and early results of genetic testing and counselling revealed societal and cultural barriers to testing and preventative therapy. As Malaysia moves towards being a developed nation, development of facilities for genetic counselling, testing and preventative therapy are required.

Malaysian women, especially Malay women, present with late stages of the disease. Generally, there is a lack of breast awareness with a low uptake of breast self- examination, clinical breast examination and mammographic screening. These three methods appear to complement each other. Based on existing evidence, the Ministry of Health and NGOs will need to design community education programmes on modification of risk factors for breast cancer, signs and symptoms of breast cancer, and methods to detect breast cancer early.

Diagnostic radiology is important in the evaluation of a breast symptom. Screen film mammogram and digital mammogram are equally good in diagnosing breast cancer, although Full Film Digital Mammography (FFDM) seems to be superior in detecting microcalcifications and the quality of mammography by improving workflow. There are still a number of hospitals that are providing screen film mammography, which is cheaper and replacing all units with FFDM is probably not necessary. Ultrasound is a useful adjunct to mammography especially in younger women and combination of ultrasound elastography with conventional ultrasound is better in differentiating benign from malignant breast lumps, and may reduce the number of benign biopsies. MRI is also useful to differentiate malignant from benign breast lumps. Mammographic breast density is related to ethnicity, parity, age and diet, and is important because it reduces the sensitivity of mammography as well as increase risk to breast cancer. It is important that there is a standardisation of radiological breast reporting, and that density is reported as well, although there is no agreed method of reporting breast density.

Fine Needle Aspiration Cytology (FNAC) is the cheapest and quickest method of obtaining a diagnosis of breast cancer but requires the services of an experienced cytopathologist. In good hands, FNAC is able to determine the histological type, grade and ER status of the cancer. ER PR and HER2 are important in the management of breast cancer as it will classify breast cancer into four distinct subtypes i.e. Luminal A, Luminal B, Triple negative breast cancer, and HER2 overexpressing, with different prognostic implications. Other markers such as p53 have been assessed but their role is not as well-defined. While there is not much variation in the ER positive rate, TNBC and HER2 positive rates appear to vary widely in different local studies. However, some of these studies involve very small numbers of patients, and there may be interlaboratory variation in standardisation and reporting. It is important to develop and implement guidelines on collection of samples, laboratory standardisation and reporting of breast cancer.

Research on management of breast cancer is limited with only a significant study showing that mastectomy can improve survival in metastatic breast cancer; however, this is a retrospective study and a prospective study to confirm the findings is needed before becoming standard of care. CYP2D6 polymorphisms may play a role in tamoxifen resistance; however, the study was in a small number of women, and current guidelines do not require the evaluation of CYP2D6 polymorphisms before starting tamoxifen.

Survival analysis in different hospitals in Malaysia also show that there appear to be a great variation in survival rates among different hospitals in Malaysia, as well as between the three ethnic groups, with Malays having the poorest survival independent of pathological features, age and treatment. What is striking is that in HKL, the 5-year overall survival for Stage 1 and Stage 2 breast cancer was 58% and 53%, which is very low, when Stage 1 breast cancer in other studies have a survival of more than 90%. However, details of treatment were not available in the study from HKL, making it difficult to disentangle the impact of management patterns on survival. The two main determinants of survival are early detection and access to optimal treatment. Since the survival by stage differs so widely in different settings, access to optimal treatment may be an issue in some hospitals.

Breast cancer survivorship is a neglected area in Malaysia, and certainly the implementation of a sort of self-management/ psycho-education programme and education on lifestyle changes particularly weight control and exercise is needed. There is a need for psycho-oncologists to evaluate the psychosocial impact of breast cancer on women, and to design psycho-education programmes to help women cope with the disease and to improve quality of life. Women with breast cancer have multiple unmet needs that need to be addressed, whether in terms of education or support. Health care professionals need to work together to determine how best to support and improve quality of life. The reasons for delayed presentation has also been well studied. While some of the delays are due to patient delay, health care system delays contribute to this as well. Doctors also need to be educated on the symptomatology of breast cancer, and have better communication skills in breaking bad news. Poor decision making skills was also a reason for delay.

SECTION 3: FUTURE RESEARCH DIRECTION

Further research is required on the different presentation of breast cancer with different outcomes in the three ethnic groups in Malaysia, (summarised in Table VI) particularly on why

Malays have a poorer survival which is independent of pathology, stage and treatment. A hypothesis would be different lifestyles after completion of treatment for breast cancer and perhaps different pharmacogenomics in response to chemotherapy and hormone therapy.

It is generally accepted that breast cancer risk factors, which have mainly been studied in Western populations are similar worldwide. However, the presence of gene-environment or gene-gene interactions may alter their importance as causal factors across populations. Also, risk assessment models developed in the West such as the Gail Model has not been validated in Malaysia, and perhaps a large study can be done to determine if this model works in Malaysian women, and if not, then another model specific to the local population can be developed. Since risk factors is known to differ according to subtypes of breast cancer, a large study looking at risk factors, particularly the reproductive risk factors in different subtypes of breast cancer are warranted.

Breast cancer genetic research is expensive and not many centres have enough research money or even expertise to carry out this type of research. Future research should focus on identifying mutations specific to Asians that are neither BRCA1 nor BRCA2, and this is currently ongoing with the UM-CARIF group and need to be strengthened. Collaboration within the Asian region is also important since more patients will be needed to identify any novel mutations. Qualitative research into barriers to testing and preventative surgery need to be carried out.

Intervention studies are required to determine the appropriate early detection method which is not only effective but also economically feasible in Malaysia. Based on findings from Sarawak, it is felt that a well-designed randomised controlled trial, for example on CBE, with downstaging of breast cancer as a short-term outcome, and reduction of breast cancer mortality as a long-term outcome within a defined population would be more impactful than conducting a series of small questionnaire studies focussing on knowledge. Local information on the efficacy of screening is also lacking. Opportunistic mammogram screening programmes are available in government and private hospitals. There are no published results on the efficacy of opportunistic mammography screening in the local population.

The quality of breast imaging reporting depends more on the radiologist than technology, and future research on quality assurance of the radiology reporting is indicated. There are no local studies on the sensitivity and specificity of diagnostic mammography in the diagnosis of breast cancer. The study on validity of ultrasound was very small, in 70 patients of whom only eight had cancer. The role of MRI in the local setting, where breast density is higher than in western settings needs more study.

Breast density is an area of research that is fairly new, and local institutions are embarking on various aspects of breast density research. Not only lifestyle and genetic determinants of breast density are being studied but also the accurate methods of determining breast density. Results of these studies will add to the information about breast density and the risk of breast cancer.

The majority of breast cancer pathology research focuses on the associations of pathological variables with clinical characteristics, and may not be applicable to the clinical outcome. Since the distribution of the four subtypes of breast cancer (based on immunohistochemistry assessment of ER, PR and HER2) seem to vary considerably from one study to another i.e. in different labs, it may be due to problems with quality assurance and standardisation of reporting. Future research in the area of quality control and standardisation of testing, and perhaps quantification of ER and PR and its relationship to response to treatment may have more impact on patient management. Identification of new prognostic markers will require the availability of tissue samples with corresponding clinical data and outcomes, which are available in some centres.

There are not many controversial issues in the surgical treatment of breast cancer. However there have been no large local studies on breast conserving surgery versus mastectomy, or on the performance of sentinel lymph node biopsy in the local population. Well-designed clinical trials on different chemotherapy regimes are lacking, and studies tend to involve very small numbers. There is a need to establish multicentred trials on chemotherapy and hormone therapy, as well as a need for investigator initiated trials, particularly in natural products, and traditional products that are commonly used locally. The outcomes in these trials should not be only focussed on treatment effectiveness, but also on adverse effects, and patient-orientated outcomes such as quality of life. Pharmacogenomics is an emerging field and the multiethnic population in Malaysia would be ideal for studying genetic polymorphisms affecting pharmacodynamics, and pharmacokinetics.

We should also aim to get a sufficient number of our multi-ethnic patients enrolled in large scale international clinical trials, to enable appropriate conclusions to be made on the effectiveness of new anticancer therapies in Asians.

Future research would be to determine which of the lifestyle variables would contribute to improved survival from breast cancer. A prospective breast cancer cohort study is currently ongoing in UMMC (MyBCC study). This study looks at the quality of life, nutrition and weight changes, return to work, physical activity and its relationship to recurrence and survival. Similar studies should also be conducted in other settings such as rural regions as lifestyle might be different. Studies on the prevalence of long-term side effects of treatment such as premature menopause, menopausal symptoms, osteoporosis, infertility, sexuality, lymphoedema, fatigue, chronic pain and upper limb dysfunction is lacking, and cognitive deficits are areas for future research.

Future research would also be to determine what interventions would work in improving quality of life and ensuring that women do not delay treatment. A national study on delay in treatment is underway in UM, as well as a collaborative study with international research group to identify reasons for delay. There is a need for research on decision making processes in women with breast cancer as this is one of the areas identified as a reason for delay.

Breast cancer prediction rules including diagnostic, and prognostic rules which may be very useful in aiding clinical practices are increasingly shown to be 'setting specific'. The rules must therefore be validated in Malaysian women before implementing them in clinical care. In instances when they are not found to be accurate, it may even be necessary to build new 'Malaysian-specific' prediction models using a large cohort of Malaysian breast cancer patients.

The NCPR therefore will need to be strengthened, and eventually be used as a research resource like the SEER (Surveillance Epidemiology and End Results) database in USA. Finally it is important to remember that research done in the western counties may not apply to local settings and hence it is important to embark on local studies in all domains of research in breast cancer[158].

Table I: Stage at presentation of breast cancer in different institutions in Malaysia

Author (ref)	Institution	No	Stage 0 (%)	Stage 1 (%)	Stage 2 (%)	Stage 3 (%)	Stage 4 (%)	Size of tumour (cm,‡)	Mean Age
Penang Cancer Registry 2004-2008(2)	Penang	1091	NA	23.5	46.1	17.3	13.1	NA	NA
Hisham *et al* 2003(10)	HKL 1998-2001	774	NA	40		60		5.4	50
Taib *et al* 2011 (11)	UMMC 1993-97	423	NA	17.3	48.7	17.5	16.6	4.5	49
	UMMC 1998-2002	965	NA	21.5	48.8	17.7	12	4.4	49
Leong *et al* 2007 (13)	Queen Elizabeth Hosp KK	186	4.8	12.9	30.1	36.6	15.6	NA	51
Ibrahim *et al* 2012 (12)	HKL 2005-09	868	NA	14.6	43.8	25.6	16.0	5.0	NA
Saxena *et al* 2012 (8)	UMMC 1993-2007	3321	2.9	21.6	42.4	22.3	10.8	3	50
	NUH Singapore 1993-2007*	2141	10	24.7	42.9	24.4	7.9	2.2	50

‡ Mean tumour size is presented except the study by Saxena which presented median
*Singapore data for comparison

Table II: Risk factors for breast cancer

Author (Ref)	Controls (n)	Cases (n)	Recruitment	Factors that reduce risk	Factors that increase risk	Factors that are not significant
Matalqah *et al* (18)	150	150	Penang General Hospital	Low fat diet, education >11 years, breast feeding, being employed	Family history, benign breast disease, menstrual irregularity, use of oral contraceptive (OCP)	
Razif *et al* (19)	216	216	HKL and UKMMC	Higher number of life births	Family history	Age at first child birth and menarche not significant
Norsa'adah *et al* (20)	147	147	Kelantan		Nulliparity, overweight, family history, use of OCP	
Hejar *et al* (21)	89	85	Chinese, HKL and UMMC	Breast feeding		
Kamarudin *et al* (22)	203	203	HKL	Exercise, low fat diet, longer duration of breast-feeding		
Rejali (23)	62	62	Malaysian hospital	Higher intake of selenium	Nulliparity, exposure to cigarette smoke, use of OCP	
Shahar *et al* (24)	70	138	Klang Valley	Higher intake of selenium	Abdominal obesity, physical inactivity, low serum adiponectin	
Sulaiman *et al* (25)	382	382	Kuala Lumpur			Total fat and fat subtypes not associated
Suzana *et al* (26)	64	127	Klang Valley	Higher intake of selenium, vit A, vit E		
Sharhar *et al* (27)	57	139	Klang Valley		Poor antioxidant status and oxidative stress measured by higher levels of malondialdehyde (MDA)	
Shahril *et al* (28)	382	382	Kuala Lumpur	Higher Healthy Eating Index-2005 (HEI-2005) score		
Ho *et al* (29)	37 pre-menopausal 68 post-menopausal	36 pre-menopausal 66 post-menopausal	Kuala Lumpur		Higher serum progesterone and testosterone levels in postmenopausal women	

Table III: Breast awareness studies in Malaysia

Author (ref)	No	Recruitment	Age	Findings
Al-Dubai 2011 (44)	250	Random, Shah Alam	Mean age 28 years old	Did not know symptoms and signs of breast cancer Poor awareness of mammography
Kanaga *et al* 2010 (45)	125	Urban and rural areas	19-60 years old	Awareness of breast cancer and screening procedures increase with higher education and urban living
Abdul Hadi *et al* 2010 (46)	384	Penang	19-60 years old	Serious knowledge deficits about breast cancer and unaware of screening guidelines, ethnicity, education and employment status were significantly related to knowledge
Dunn *et al* 2011 (47)	816	Data from the Malaysian Non communicable Disease Surveillance-1	Above 40 years old	Malay women less likely than Chinese and Indian women to undergo mammography, but were more likely to undergo BSE. Education level and urban residence positively associated with each screening method among Chinese women but not among Malay women
Al-Dubai 2012 (48)	222	Urban area, Shah Alam	Mean age 28.5 years	55% of women practise BSE. Women >45 yrs, Malay, married and higher education level were more likely to practise BSE
Akhtari-Zavare *et al* 2013 (49)	252	Female undergraduates UPM	Mean age 22 years old	37% practise breast self examination (BSE), motivation and self-efficacy higher in those who practise BSE
Al-Naggar 2011 (50)	251	Female undergraduates MSU	Majority >20 yrs	55% practised BSE, barriers to BSE were lack of knowledge, not having symptoms and being afraid of being diagnosed with breast cancer
Al-Naggar *et al* 2012 (51)	250	Random sampling, mainly urban	Mean age 34.7 yrs	47.2% practise BSE, and race, marital status, residency, belief that breast cancer can be detected early, belief that early detection improves the chance of survival, and family history significantly influenced the practice of BSE
Rosmawati *et al* 2010 (52)	86	Suburban area in Trengganu	Mean age 40 yrs old	Proportions of women with good scores for knowledge, attitude and practice for BSE was 38.4%, 73.3% and 7% respectively. Not knowing the correct method for BSE, lack of knowledge about signs and symptoms of breast cancer, lack of support from friends and family were related to poor practices
Dahlui *et al* 2013 (53)	959	Rural areas,	NA	Knowledge about breast cancer and screening varied by ethnicity, location and type of support received. Women below 50 years old, of Malay ethnicity and who had secondary education scored better than those who were older, of Chinese ethnicity and had primary education. The uptake of BSE was 59%, CBE 61% and mammography screening was 6.8%
Dahlui *et al* 2011 (54)	718	Female staff, UM	35 years and above	41% practised BSE regularly, 47% had undergone CBE and 23% had had a mammogram. Those who had CBE were more likely to do BSE, while of the 19% who felt a breast lump on BSE, 87% went on to have a CBE
Dunn *et al* 2010 (55)	816	Data from the Malaysian Non communicable Disease Surveillance-1	Above 40 yrs old	Women who perform BSE were more likely to have undergone mammography screening in all ethnicities, suggesting that previous work on the efficacy of BSE in developed countries may not apply to nations with limited resources
Dahlui *et al* 2012 (56)	381	Suburban district Selangor	20-60 yrs old	58.5% of women practised BSE, uptake of mammogram was only 14.6%. Significant predictors of BSE were good knowledge of breast cancer, being married and attending CBE, while predictors of CBE was being married, good knowledge of breast cancer and good social support
Al-Naggar *et al* 2012 (57)	200	Shah Alam	65.5% under 50 years old	Only 15% of women had a mammogram. Barriers to mammographic screening were lack of time, lack of knowledge, not knowing where to go for a mammogram, and fear of the result
Rosmawati *et al* 2010 (58)	86	Suburban area in Trengganu	45.5 yrs	Only 10.5% had a mammogram done, and knowledge pertaining to mammographic screening was poor
Parsa *et al* 2010 (59)	425	Female teachers	Mean age 37 yrs	Only 13.6 % ever had a mammogram while 25% ever had a CBE. Having a perceived susceptibility for breast cancer, regular CBE's were predictors for having a mammogram
Chan *et al* 2011 (60)	Case control comparing 27 women who defaulted mammography appointments with 73 controls	Ipoh GH	NA	Women from lower socioeconomic groups and rural areas were more likely to default their mammogram appointment
Abdullah *et al* 2011 (61)	534	Female staff UMMC	40 years and above	20% of personnel did not undertake mammography screening although there is no cost incurred and the procedure is fully accessible to them. Barriers are negative perception of the procedure, low confidence with radiologist/radiographers in detecting abnormality; lack of coping skills in dealing with expected results and pain during procedure

Table IV: Molecular markers in breast cancer

Author (Ref)	Institution	No	Period	ER positive rate, %	HER2 positive rate, %	Triple negative breast cancer, %
Yip *et al* 2011 (87)	UMMC	279 1041 1757	1994-98 1999-2003 2004-2008	54.5 56.4 58.4	- - -	- - -
Tan *et al* 2009 (88, 89)	UMMC	996	2005-2007	-	30.3	17.0
Leong *et al* 2007 (13)	Sabah	186	2005-2006	59.1	-	-
Teoh *et al* 2011 (90)	Penang	NA	2005-2006	55.8	24	15
Chng *et al* 2012 (91)	HUSM, Kota Baru	94	2006-2010	53.2	24.5	22.3
Kanapathy *et al* 2012 (92)	Private hospital KL	340	2002-2006	-	37.2%	12.4
Devi *et al* (93)	Sarawak	1034	2003-	57	23	29

Table V: Outcomes - 5 year survival

Author (ref)	Institution	No	Overall 5 year survival, %	Stage 1, % (95% CI)	Stage 2, % (95% CI)	Stage 3, % (95% CI)	Stage 4, % (95% CI)
Taib *et al* 2011 (11)	UMMC 1993-97 UMMC 1998-2002	423 965	58.4 (54-63) 75.7 (73-79)	81.7 95.2	72.4 87.5	39.9 55.6	12.8 18.7
Ibrahim *et al* 2012 (12)	HKL 2005-09	868	43.5	58 (54.2-61.8)	52.7 (50.2-55.1)	39 (35.8-42.6)	19.8 (17-22.7)
Abdullah *et al* 2013 (116)	Data from Health Informatics, NCR, National Registration Dept 2000-2005	10 230	49.4 (NA)	NA	NA	NA	NA
Saxena *et al* (8)	UMMC 1993-2007	3320	69 (67-71.1)	93 (91.9-94.1)	79 (77.8-80.3)	52 (49.4-54.6)	12 (6.8-17.1)
	NUH Singapore 1993-2007*	2141	80 (79-80.9)	98 (97-99)	85 (83.7-86.3)	66 (62.5-69.6)	23 (16.6-29.5)

*Singapore data for comparison

Table VI: Molecular markers in breast cancer

Author	Time period	Institution	Presentation and survival	Malays	Chinese	Indians
Taib *et al* (112)	1993-1997	UMMC	No	85	261	67
			Prevalence (%)	21	63	16
			Stage 1 (%)	11	21	10
			Stage 2 (%)	49	48	58
			Stage 3 and 4 (%)	40	31	32
			Survival (%)	47.5	63	57.4
Ibrahim *et al* (10)	2005-2009	HKL	No	501	218	149
			Prevalence (%)	58	25	17
			Stage3-4 (%)	46	36	34
			5 year survival (%)	39.7	48.2	47.2
			(95% CI)	(37.3-42.1)	(44.4-52.0)	(43.2-51.2)
N Bhoo Pathy *et al* (13)	1990-2007	UMMC and NUH Singapore combined	No	968	3767	529
			Prevalence (%)	18.4	71.6	10
			Median size (mm)	35	25	30
			Lymph node involved (%)	53.6	42.9	48.9
			Metatastic (%)	16	9	4
			5 year survival (%)	58.5	75.8	68
			(95% CI)	(55.2-61.7)	(74.4-77.3)	(63.8-72.2)

Note: This review contains articles published from 1996 and 2014, however the literature outside year 2000-2013 were not thoroughly searched.

ACKNOWLEDGEMENT

I would like to sincerely thank the Director General of Health, Malaysia for his permission to publish this paper. I wish to thank Clinical Research Centre team for their contribution and support.

REFERENCES

1. Lim GCC RS, Halimah Y. (Eds.) Cancer Incidence in Peninsular Malaysia 2003-2005. National Cancer Registry. Kuala Lumpur 2008.
2. Azizah Ab M DT, Bina Rai S, Norbayah Y, Nooraihan M, Noorshila S. Penang Cancer Regisstry 2004-2008.
3. http://globocan.iarc.fr Ga.
4. Pathy NB, Yip CH, Taib NA, Hartman M, Saxena N, Iau P, et al. Breast cancer in a multi-ethnic Asian setting: results from the Singapore-Malaysia hospital-based breast cancer registry. Breast. 2011 Apr; 20 Suppl 2: S75-80.
5. http://data.un.org/Data.aspx?d=PopDiv&f=variableID%3A41.
6. Yip CH, Taib NA, Mohamed I. Epidemiology of breast cancer in Malaysia. Asian Pac J Cancer Prev. 2006 Jul-Sep; 7(3): 369-74.
7. Yip CH, Ng EH. Breast cancer--a comparative study between Malaysian and Singaporean women. Singapore Med J. 1996 Jun; 37(3): 264-7.
8. Saxena N, Hartman M, Bhoo-Pathy N, Lim JN, Aw TC, Iau P, *et al.* Breast cancer in South East Asia: comparison of presentation and outcome between a middle income and a high income country. World J Surg. 2012 Dec; 36(12): 2838-46.
9. Ng CH, Pathy NB, Taib NA, Teh YC, Mun KS, Amiruddin A, *et al.* Comparison of breast cancer in Indonesia and Malaysia--a clinico-pathological study between Dharmais Cancer Centre Jakarta and University Malaya Medical Centre, Kuala Lumpur. Asian Pac J Cancer Prev. 2011; 12(11): 2943-6.
10. Hisham AN, Yip CH. Spectrum of breast cancer in Malaysian women: overview. World J Surg. 2003 Aug; 27(8): 921-3.
11. Taib NA, Akmal M, Mohamed I, Yip CH. Improvement in survival of breast cancer patients - trends over two time periods in a single institution in an Asia Pacific country, Malaysia. Asian Pac J Cancer Prev. 2011; 12(2): 345-9.
12. Ibrahim NI, Dahlui M, Aina EN, Al-Sadat N. Who are the breast cancer survivors in Malaysia? Asian Pac J Cancer Prev. 2012; 13(5): 2213-8.
13. Leong BD, Chuah JA, Kumar VM, Yip CH. Breast cancer in Sabah, Malaysia: a two year prospective study. Asian Pac J Cancer Prev. 2007 Oct-Dec; 8(4): 525-9.
14. Taib NA, Yip CH, Ibrahim M, Ng CJ, Farizah H. Breast cancer in malaysia: are our women getting the right message? 10 year-experience in a single institution in Malaysia. Asian Pac J Cancer Prev. 2007 Jan-Mar; 8(1): 141-5.
15. Agarwal G, Pradeep PV, Aggarwal V, Yip CH, Cheung PS. Spectrum of breast cancer in Asian women. World J Surg. 2007 May; 31(5): 1031-40.
16. Bhoo-Pathy N, Hartman M, Yip CH, Saxena N, Taib NA, Lim SE, *et al.* Ethnic differences in survival after breast cancer in South East Asia. PLoS One. 2012; 7(2): e30995.
17. Hisham AN, Yip CH. Overview of breast cancer in Malaysian women: a problem with late diagnosis. Asian J Surg. 2004 Apr; 27(2): 130-3.
18. Matalqah L, Radaideh K, Yusoff ZM, Awaisu A. Predictors of breast cancer among women in a northern state of Malaysia: a matched case-control study. Asian Pac J Cancer Prev. 2011; 12(6): 1549-53.
19. Razif SM, Sulaiman S, Hanie SS, Aina EN, Rohaizak M, Fuad I, *et al.* The contribution of reproductive factors and family history towards premenopausal breast cancer risk in Kuala Lumpur, Malaysia. Med J Malaysia. 2011 Aug; 66(3): 220-6.
20. Norsa'adah B, Rusli BN, Imran AK, Naing I, Winn T. Risk factors of breast cancer in women in Kelantan, Malaysia. Singapore Med J. 2005 Dec; 46(12): 698-705.
21. Hejar AR, Chong FB, Rosnan H, Zailina H. Breast cancer and lifestyle risks among Chinese women in the Klang Valley in 2001. Med J Malaysia. 2004 Jun; 59(2): 226-32.
22. Kamarudin R, Shah SA, Hidayah N. Lifestyle factors and breast cancer: a case-control study in Kuala Lumpur, Malaysia. Asian Pac J Cancer Prev. 2006 Jan-Mar; 7(1): 51-4.
23. Rejali L, Jaafar MH, Ismail NH. Serum selenium level and other risk factors for breast cancer among patients in a Malaysian hospital. Environ Health Prev Med. 2007 May; 12(3): 105-10.
24. Shahar S, Salleh RM, Ghazali AR, Koon PB, Mohamud WN. Roles of adiposity, lifetime physical activity and serum adiponectin in occurrence of breast cancer among Malaysian women in Klang Valley. Asian Pac J Cancer Prev. 2010; 11(1): 61-6.
25. Sulaiman S, Shahril MR, Shaharudin SH, Emran NA, Muhammad R, Ismail F, *et al.* Fat intake and its relationship with pre- and post-menopausal breast cancer risk: a case-control study in Malaysia. Asian Pac J Cancer Prev. 2011; 12(9): 2167-78.
26. Suzana S, Cham BG, Ahmad Rohi G, Mohd Rizal R, Fairulnizal MN, Normah H, *et al.* Relationship between selenium and breast cancer: a case-control study in the Klang Valley. Singapore Med J. 2009 Mar; 50(3): 265-9.
27. Sharhar S, Normah H, Fatimah A, Fadilah RN, Rohi GA, Amin I, *et al.* Antioxidant intake and status, and oxidative stress in relation to breast cancer risk: a case-control study. Asian Pac J Cancer Prev. 2008 Apr-Jun; 9(2): 343-49.
28. Shahril MR, Sulaiman S, Shaharudin SH, Akmal SN. Healthy eating index and breast cancer risk among Malaysian women. Eur J Cancer Prev. 2013 Jul; 22(4): 342-7.
29. Ho CC, Rohaizak M, Zulkifli SZ, Siti-Aishah MA, Nor-Aini U, Sharifah-Noor-Akmal SH. Serum sex hormone levels in pre- and postmenopausal breast cancer patients. Singapore Med J. 2009 May; 50(5): 513-8.
30. Balraj P, Khoo AS, Volpi L, Tan JA, Nair S, Abdullah H. Mutation analysis of the BRCA1 gene in Malaysian breast cancer patients. Singapore Med J. 2002 Apr; 43(4): 194-7.
31. Toh GT, Kang P, Lee SS, Lee DS, Lee SY, Selamat S, *et al.* BRCA1 and BRCA2 germline mutations in Malaysian women with early-onset breast cancer without a family history. PLoS One. 2008; 3(4): e2024.
32. Kang P, Mariapun S, Phuah SY, Lim LS, Liu J, Yoon SY, *et al.* Large BRCA1 and BRCA2 genomic rearrangements in Malaysian high risk breast-ovarian cancer families. Breast Cancer Res Treat. 2010 Nov; 124(2): 579-84.
33. Sharifah NA, Nurismah MI, Lee HC, Aisyah AN, Clarence-Ko CH, Naqiyah I, *et al.* Identification of novel large genomic rearrangements at the BRCA1 locus in Malaysian women with breast cancer. Cancer Epidemiol. 2010 Aug; 34(4): 442-7.
34. Thirthagiri E, Lee SY, Kang P, Lee DS, Toh GT, Selamat S, *et al.* Evaluation of BRCA1 and BRCA2 mutations and risk-prediction models in a typical Asian country (Malaysia) with a relatively low incidence of breast cancer. Breast Cancer Res. 2008; 10(4): R59.
35. Yip CH, Taib NA, Choo WY, Rampal S, Thong MK, Teo SH. Clinical and pathologic differences between BRCA1-, BRCA2-, and non-BRCA-associated breast cancers in a multiracial developing country. World J Surg. 2009 Oct; 33(10): 2077-81.
36. Phuah SY, Looi LM, Hassan N, Rhodes A, Dean S, Taib NA, *et al.* Triple-negative breast cancer and PTEN (phosphatase and tensin homologue)loss are predictors of BRCA1 germline mutations in women with early-onset and familial breast cancer, but not in women with isolated late-onset breast cancer. Breast Cancer Res. 2012 Nov 2; 14(6): R142.
37. Yoon SY, Thong MK, Taib NA, Yip CH, Teo SH. Genetic counseling for patients and families with hereditary breast and ovarian cancer in a developing Asian country: an observational descriptive study. Fam Cancer. 2011 Jun; 10(2): 199-205.
38. Taib N, Woo Y, Yoon S, Kartini R, Thong M, Yip C, *et al.* Early experience in a breast and ovarian cancer risk management clinic in Malaysia. Hered Cancer Clin Pract. 2012; 10(Suppl 2): A58.
39. Lee DS, Yoon SY, Looi LM, Kang P, Kang IN, Sivanandan K, *et al.* Comparable frequency of BRCA1, BRCA2 and TP53 germline mutations in a multi-ethnic Asian cohort suggests TP53 screening should be offered together with BRCA1/2 screening to early-onset breast cancer patients. Breast Cancer Res. 2012; 14(2): R66.
40. Phuah SY, Lee SY, Kang P, Kang IN, Yoon SY, Thong MK, *et al.* Prevalence of PALB2 mutations in breast cancer patients in multi-ethnic Asian population in Malaysia and Singapore. PLoS One. 2013; 8(8): e73638.
41. Thirthagiri E, Cheong LS, Yip CH, Teo SH. CHEK2*1100delC does not contribute to risk to breast cancer among Malay, Chinese and Indians in Malaysia. Fam Cancer. 2009; 8(4): 355-8.
42. Leong PP, Muhammad R, Ibrahim N, Cheong SK, Seow HF. HLA-A and breast cancer in West Peninsular Malaysia. Med Oncol. 2011 Mar; 28(1): 51-6.
43. Zheng W, Zhang B, Cai Q, Sung H, Michailidou K, Shi J, *et al.* Common genetic determinants of breast-cancer risk in East Asian women: a collaborative study of 23 637 breast cancer cases and 25 579 controls. Human molecular genetics. 2013 Jun 15; 22(12): 2539-50.

44. Al-Dubai SA, Qureshi AM, Saif-Ali R, Ganasegeran K, Alwan MR, Hadi JI. Awareness and knowledge of breast cancer and mammography among a group of Malaysian women in Shah Alam. Asian Pac J Cancer Prev. 2011; 12(10): 2531-8.
45. Kanaga KC, Nithiya J, Shatirah MF. Awareness of breast cancer and screening procedures among Malaysian women. Asian Pac J Cancer Prev. 2011; 12(8): 1965-7.
46. Abdul Hadi M, Hassali MA, Shafie AA, Awaisu A. Knowledge and perception of breast cancer among women of various ethnic groups in the state of Penang: a cross-sectional survey. Med Princ Pract. 2010; 19(1): 61-7.
47. Dunn RA, Tan AK. Utilization of breast cancer screening methods in a developing nation: results from a nationally representative sample of Malaysian households. Breast J. 2011 Jul-Aug; 17(4): 399-402.
48. Al-Dubai SA, Ganasegeran K, Alabsi AM, Abdul Manaf MR, Ijaz S, Kassim S. Exploration of barriers to breast-self examination among urban women in Shah Alam, Malaysia: a cross sectional study. Asian Pac J Cancer Prev. 2012; 13(4): 1627-32.
49. Akhtari-Zavare M, Juni MH, Said SM, Ismail IZ. Beliefs and behavior of Malaysia undergraduate female students in a public university toward breast self-examination practice. Asian Pac J Cancer Prev. 2013; 14(1): 57-61.
50. Al-Naggar RA, Bobryshev YV, Al-Jashamy K. Practice of breast self-examination among women in Malaysia. Asian Pac J Cancer Prev. 2012; 13(8): 3829-33.
51. Al-Naggar RA, Al-Naggar DH, Bobryshev YV, Chen R, Assabri A. Practice and barriers toward breast self-examination among young Malaysian women. Asian Pac J Cancer Prev. 2011; 12(5): 1173-8.
52. Rosmawati NH. Knowledge, attitudes and practice of breast self-examination among women in a suburban area in Terengganu, Malaysia. Asian Pac J Cancer Prev. 2010; 11(6): 1503-8.
53. Dahlui M, Gan DE, Taib NA, Lim JN. Breast screening and health issues among rural females in Malaysia: how much do they know and practice? Prev Med. 2013; 57 Suppl: S18-20.
54. Dahlui M, Ng C, Al-Sadat N, Ismail S, Bulgiba A. Is breast self examination (BSE) still relevant? A study on BSE performance among female staff of University of Malaya. Asian Pac J Cancer Prev. 2011; 12(2): 369-72.
55. Dunn RA, Tan A, Samad I. Does performance of breast self-exams increase the probability of using mammography: evidence from Malaysia. Asian Pac J Cancer Prev. 2010; 11(2): 417-21.
56. Dahlui M, Gan DE, Taib NA, Pritam R, Lim J. Predictors of breast cancer screening uptake: a pre intervention community survey in Malaysia. Asian Pac J Cancer Prev. 2012; 13(7): 3443-9.
57. Al-Naggar RA, Bobryshev YV. Practice and barriers of mammography among Malaysian women in the general population. Asian Pac J Cancer Prev. 2012; 13(8): 3595-600.
58. Rosmawati NH. The usage and knowledge of mammography among women in sub-urban area in Terengganu, Malaysia. Asian Pac J Cancer Prev. 2010; 11(3): 767-71.
59. Parsa P, Kandiah M. Predictors of adherence to clinical breast examination and mammography screening among Malaysian women. Asian Pac J Cancer Prev. 2010; 11(3): 681-8.
60. Chan PY, Latip LS. A case control study in factors that affect mammogram compliance. Med J Malaysia. 2011 Dec; 66(5): 456-61.
61. Abdullah NN, Aziz NA, Rampal S, Al-Sadat N. Mammography screening uptake among hospital personnel in Kuala Lumpur tertiary hospital. Asian Pac J Cancer Prev. 2011; 12(10): 2643-7.
62. Subramanian P, Oranye NO, Masri AM, Taib NA, Ahmad N. Breast cancer knowledge and screening behaviour among women with a positive family history: a cross sectional study. Asian Pac J Cancer Prev. 2013; 14(11): 6783-90.
63. Yip CH, bt Mohd Taib NA, Lau PC. Does a positive family history influence the presentation of breast cancer? Asian Pac J Cancer Prev. 2008 Jan-Mar; 9(1): 63-5.
64. Taib NA, Yip CH, Low WY. Recognising symptoms of breast cancer as a reason for delayed presentation in Asian women--the psycho-socio-cultural model for breast symptom appraisal: opportunities for intervention. Asian Pac J Cancer Prev. 2011; 12(6): 1601-8.
65. Devi BC, Tang TS, Corbex M. Reducing by half the percentage of late-stage presentation for breast and cervix cancer over 4 years: a pilot study of clinical downstaging in Sarawak, Malaysia. Ann Oncol. 2007 Jul; 18(7): 1172-6.
66. Ho EL, Ng KH, Wong JH, Wang HB. Quality assurance in mammography: College of Radiology Survey in Malaysia. Med J Malaysia. 2006 Jun; 61(2): 204-8.
67. Ranganathan S, Faridah Y, Ng KH. Moving into the digital era: a novel experience with the first full-field digital mammography system in Malaysia. Singapore Med J. 2007 Sep; 48(9): 804-7.
68. Thevi Rajendran P, Krishnapillai V, Tamanang S, Kumari Chelliah K. Comparison of Image Quality Criteria between Digital Storage Phosphor Plate in Mammography and Full-Field Digital Mammography in the Detection of Breast Cancer. Malays J Med Sci. 2012 Jan; 19(1): 52-9.
69. Zulfiqar M, Rohazly I, Rahmah M. Do the majority of Malaysian women have dense breasts on mammogram? Biomed Imaging Interv J. 2011 Apr; 7(2): e14.
70. Voon NS, Chelliah KK. Is there an influence of dietary habits on breast density as seen on digital mammograms? Asian Pac J Cancer Prev. 2011; 12(8): 1969-72.
71. Jamal N, Ng KH, Looi LM, McLean D, Zulfiqar A, Tan SP, *et al.* Quantitative assessment of breast density from digitized mammograms into Tabar's patterns. Phys Med Biol. 2006 Nov 21; 51(22): 5843-57.
72. Alhabshi SM, Rahmat K, Abdul Halim N, Aziz S, Radhika S, Gan GC, *et al.* Semi-quantitative and qualitative assessment of breast ultrasound elastography in differentiating between malignant and benign lesions. Ultrasound Med Biol. 2013 Apr; 39(4): 568-78.
73. Hasni H, Meah FA, Norlia A, Sharifah NA, Zulfiqar A. Ultrasound in the assessment of the palpable breast mass. Med J Malaysia. 2004 Oct; 59(4): 486-94.
74. Suppiah S, Rahmat K, Mohd-Shah MN, Azlan CA, Tan LK, Aziz YF, *et al.* Improved diagnostic accuracy in differentiating malignant and benign lesions using single-voxel proton MRS of the breast at 3 T MRI. Clin Radiol. 2013 Sep; 68(9): e502-10.
75. Tan SL, Rahmat K, Rozalli FI, Mohd-Shah MN, Aziz YF, Yip CH, *et al.* Differentiation between benign and malignant breast lesions using quantitative diffusion-weighted sequence on 3 T MRI. Clin Radiol. 2014 Jan; 69(1): 63-71.
76. Yip CH, Paramsothy M. Value of routine 99mTc-MDP bone scintigraphy in the detection of occult skeletal metastases in women with primary breast cancer. Breast. 1999 Oct; 8(5): 267-9.
77. Tham TM, Iyengar KR, Taib NA, Yip CH. Fine needle aspiration biopsy, core needle biopsy or excision biopsy to diagnose breast cancer - which is the ideal method? Asian Pac J Cancer Prev. 2009 Jan-Mar; 10(1): 155-8.
78. Hisham AN, Harjit K, Fatimah O, Yun SI. Prebiopsy localisation of impalpable breast lesions. Med J Malaysia. 2004 Aug; 59(3): 402-5.
79. Ng CH, Lee KT, Taib NA, Yip CH. Experience with hookwire localisation excision biopsy at a medical centre in Malaysia. Singapore Med J. 2010 Apr; 51(4): 306-10.
80. Yip CH, Jayaram G, Alhady SF. The experience with fine needle aspiration cytology in the management of palpable breast lumps in the University Hospital Kuala Lumpur. Med J Malaysia. 2000 Sep; 55(3): 363-7.
81. Jayaram G, Alhady SF, Yip CH. Cytological analysis of breast lesions: a review of 780 cases. Malays J Pathol. 1996 Dec; 18(2): 81-7.
82. Jayaram G, Elsayed EM. Cytologic evaluation of prognostic markers in breast carcinoma. Acta Cytol. 2005 Nov-Dec; 49(6): 605-10.
83. Jayaram G, Swain M, Chew MT, Yip CH. Cytologic appearances in invasive lobular carcinoma of the breast. A study of 21 cases. Acta Cytol. 2000 Mar-Apr; 44(2): 169-74.
84. Jayaram G, Swain M, Chew MT, Yip CH, Moosa F. Cytology of mucinous carcinoma of breast: a report of 28 cases with histological correlation. Malays J Pathol. 2000 Dec; 22(2): 65-71.
85. Yeap BH, Muniandy S, Lee SK, Sabaratnam S, Singh M. Specimen shrinkage and its influence on margin assessment in breast cancer. Asian J Surg. 2007 Jul; 30(3): 183-7.
86. Sheikh MK, Khan FA, Imran Abdul Khalid IK, Kumar G. Age specific histologic types of carcinoma breast in Malaysians. J Coll Physicians Surg Pak. 2009 Mar; 19(3): 201-2.
87. Yip CH, Pathy NB, Uiterwaal CS, Taib NA, Tan GH, Mun KS, *et al.* Factors affecting estrogen receptor status in a multiracial Asian country: an analysis of 3557 cases. Breast. 2011 Apr; 20 Suppl 2: S60-4.
88. Tan GH, Choo WY, Taib NA, Yip CH. Factors associated with HER2 overexpression in breast cancer: Experience in an Asian developing country. Asian Pac J Cancer Prev. 2009; 10(5): 837-40.
89. Tan GH, Taib NA, Choo WY, Teo SH, Yip CH. Clinical characteristics of triple-negative breast cancer: experience in an Asian developing country. Asian Pac J Cancer Prev. 2009 Jul-Sep; 10(3): 395-8.
90. Teoh KH, Looi LM, Sabaratnam S, Cheah PL, Nazarina AR, Mun KS. An analysis of predictive biomarkers in routine histopathological reporting of infiltrating ductal breast carcinoma in a tertiary hospital in Malaysia

with a focus on limitations and directions for future development. Malays J Pathol. 2011 Jun; 33(1): 35-42.

91. Ch'ng ES, Tuan Sharif SE, Jaafar H. Characteristics of invasive breast ductal carcinoma, NOS, diagnosed in a tertiary institution in the East Coast of Malaysia with a focus on tumor angiogenesis. Asian Pac J Cancer Prev. 2012; 13(9): 4445-52.
92. Kanapathy Pillai SK, Tay A, Nair S, Leong CO. Triple-negative breast cancer is associated with EGFR, CK5/6 and c-KIT expression in Malaysian women. BMC Clin Pathol. 2012; 12: 18.
93. Devi CR, Tang TS, Corbex M. Incidence and risk factors for breast cancer subtypes in three distinct South-East Asian ethnic groups: Chinese, Malay and natives of Sarawak, Malaysia. Int J Cancer. 2012 Dec 15; 131(12): 2869-77.
94. Ng CH, Pathy NB, Taib NA, Mun KS, Rhodes A, Yip CH. The estrogen receptor negative-progesterone receptor positive breast carcinoma is a biological entity and not a technical artifact. Asian Pac J Cancer Prev. 2012; 13(4): 1111-3.
95. Aziz SA, Pervez S, Khan S, Kayani N, Rahbar MH. Relationship of p53 expression with clinicopathological variables and disease outcome: a prospective study on 315 consecutive breast carcinoma patients. Malays J Pathol. 2001 Dec; 23(2): 65-71.
96. Dean SJ, Perks CM, Holly JM, Bhoo-Pathy N, Looi LM, Mohammed NA, et al. Loss of PTEN Expression Is Associated With IGFBP2 Expression, Younger Age, and Late Stage in Triple-Negative Breast Cancer. Am J Clin Pathol. 2014 Mar; 141(3): 323-33.
97. Velaiutham S, Taib NA, Ng KL, Yoong BK, Yip CH. Does the pre-operative value of serum CA15-3 correlate with survival in breast cancer? Asian Pac J Cancer Prev. 2008 Jul-Sep; 9(3): 445-8.
98. Rohaizak M, Khan FJ, Jasmin JS, Mohd Latar NH, Abdullah SS. Ultracision versus electrocautery in performing modified radical mastectomy and axillary lymph node dissection for breast cancer: a prospective randomized control trial. Med J Malaysia. 2013 Jun; 68(3): 204-7.
99. Rica MA, Norlia A, Rohaizak M, Naqiyah I. Preemptive ropivacaine local anaesthetic infiltration versus postoperative ropivacaine wound infiltration in mastectomy: postoperative pain and drain outputs. Asian J Surg. 2007 Jan; 30(1): 34-9.
100. Haron NH, Taib NA, Yip CH. Is clinical assessment of the axilla a reliable indicator for lymph node metastases in breast cancer? ANZ J Surg. 2008 Nov; 78(11): 943-4.
101. Yip CH, Taib NA, Tan GH, Ng KL, Yoong BK, Choo WY. Predictors of axillary lymph node metastases in breast cancer: is there a role for minimal axillary surgery? World J Surg. 2009 Jan; 33(1): 54-7.
102. Pathy NB, Verkooijen HM, Taib NA, Hartman M, Yip CH. Impact of breast surgery on survival in women presenting with metastatic breast cancer. Br J Surg. 2011 Nov; 98(11): 1566-72.
103. Shameem H, Yip CH, Fong E. Immediate breast reconstruction after mastectomy--why do women choose this option? Asian Pac J Cancer Prev. 2008 Jul-Sep; 9(3): 409-12.
104. Wijayahadi N, Haron MR, Stanslas J, Yusuf Z. Changes in cellular immunity during chemotherapy for primary breast cancer with anthracycline regimens. J Chemother. 2007 Dec; 19(6): 716-23.
105. Hassan BA, Yusoff ZB, Hassali MA, Othman SB, Weiderpass E. Impact of chemotherapy on hypercalcemia in breast and lung cancer patients. Asian Pac J Cancer Prev. 2012; 13(9): 4373-8.
106. Phua CE, Bustam AZ, Yusof MM, Saad M, Yip CH, Taib NA, *et al.* Risk of treatment related death and febrile neutropaenia with taxane-based adjuvant chemotherapy for breast cancer in a middle income country outside a clinical trial setting. Asian Pac J Cancer Prev. 2012; 13(9): 4623-6.
107. Tiong V, Rozita AM, Taib NA, Yip CH, Ng CH. Incidence of Chemotherapy-Induced Ovarian Failure in Premenopausal Women Undergoing Chemotherapy for Breast Cancer. World J Surg. 2014 Apr 4.
108. Azrif M, Ibrahim J, Aslan NM, Fong KV, Ismail F. Neoadjuvant chemotherapy for locally advanced breast cancer in a malaysian tertiary hospital. Asian Pac J Cancer Prev. 2011; 12(1): 157-62.
109. Chong HY, Taib NA, Rampal S, Saad M, Bustam AZ, Yip CH. Treatment options for locally advanced breast cancer--experience in an Asian tertiary hospital. Asian Pac J Cancer Prev. 2010; 11(4): 913-7.
110. Hassan BA, Yusoff ZB. Genetic polymorphisms in the three malaysian races effect granisetron clinical antiemetic actions in breast cancer patients receiving chemotherapy. Asian Pac J Cancer Prev. 2011; 12(1): 185-91.
111. Teh LK, Mohamed NI, Salleh MZ, Rohaizak M, Shahrun NS, Saladina JJ, et al. The risk of recurrence in breast cancer patients treated with tamoxifen: polymorphisms of CYP2D6 and ABCB1. AAPS J. 2012 Mar; 14(1): 52-9.
112. Shaharudin SH, Sulaiman S, Emran NA, Shahril MR, Hussain SN. The use of complementary and alternative medicine among Malay breast cancer survivors. Altern Ther Health Med. 2011 Jan-Feb; 17(1): 50-6.
113. Leong BD, Chuah JA, Kumar VM, Rohamini S, Siti ZS, Yip CH. Trends of breast cancer treatment in Sabah, Malaysia: a problem with lack of awareness. Singapore Med J. 2009 Aug; 50(8): 772-6.
114. Biswal BM, Sulaiman SA, Ismail HC, Zakaria H, Musa KI. Effect of Withania somnifera (Ashwagandha) on the development of chemotherapy-induced fatigue and quality of life in breast cancer patients. Integr Cancer Ther. 2013 Jul; 12(4): 312-22.
115. Nesaretnam K, Selvaduray KR, Abdul Razak G, Veerasenan SD, Gomez PA. Effectiveness of tocotrienol-rich fraction combined with tamoxifen in the management of women with early breast cancer: a pilot clinical trial. Breast Cancer Res. 2010; 12(5): R81.
116. Abdullah NA, Wan Mahiyuddin WR, Muhammad NA, Ali ZM, Ibrahim L, Ibrahim Tamim NS, et al. Survival rate of breast cancer patients in Malaysia: a population-based study. Asian Pac J Cancer Prev. 2013; 14(8): 4591-4.
117. Mohd Taib NA, Yip CH, Mohamed I. Survival analysis of Malaysian women with breast cancer: results from the University of Malaya Medical Centre. Asian Pac J Cancer Prev. 2008 Apr-Jun; 9(2): 197-202.
118. Ong TA, Yip CH. Short-term survival in breast cancer: the experience of the University of Malaya Medical Centre. Asian J Surg. 2003 Jul; 26(3): 169-75.
119. Saxena N, Hartman M, Yip CH, Bhoo-Pathy N, Khin LW, Taib NA, *et al.* Does the axillary lymph node ratio have any added prognostic value over pN staging for South East Asian breast cancer patients? PLoS One. 2012; 7(9): e45809.
120. Choong LP, Taib NA, Rampal S, Saad M, Bustam AZ, Yip CH. High tumour stage and margin clearance are still important prognostic factors for post-mastectomy locoregional recurrence in Malaysia. Asian Pac J Cancer Prev. 2010; 11(5): 1409-16.
121. Bhoo Pathy N, Uiterwaal CS, Taib NA, Verkooijen HM, Yip CH. Gradually implemented new biomarkers for prognostication of breast cancer: complete case analysis may introduce bias. J Clin Epidemiol. 2012 May; 65(5): 568-71.
122. Al-Naggar RA, Isa ZM, Shah SA, Nor MI, Chen R, Ismail F, *et al.* Eight year survival among breast cancer Malaysian women from University Kebangsaan Malaysia Medical Centre. Asian Pac J Cancer Prev. 2009; 10(6): 1075-8.
123. Mujar M, Dahlui M, Yip CH, Taib NA. Delays in time to primary treatment after a diagnosis of breast cancer: does it impact survival? Prev Med. 2013 Mar; 56(3-4): 222-4.
124. Lim GC, Aina EN, Cheah SK, Ismail F, Ho GF, Tho LM, *et al.* Closing the global cancer divide- performance of breast cancer care services in a middle income developing country. BMC Cancer. 2014; 14: 212.
125. Nor Aina E. National Cancer Patient Registry--Breast Cancer (NCPR-Breast Cancer). Med J Malaysia. 2008 Sep; 63 Suppl C: 72-3.
126. Bhoo-Pathy N, Yip CH, Hartman M, Saxena N, Taib NA, Ho GF, *et al.* Adjuvant! Online is overoptimistic in predicting survival of Asian breast cancer patients. Eur J Cancer. 2012 May; 48(7): 982-9.
127. Phua CE, Bustam AZ, Yip CH, Taib NA. Prognostic factors for elderly breast cancer patients in University Malaya Medical Centre, Malaysia. Asian Pac J Cancer Prev. 2010; 11(5): 1205-11.
128. Yip CH, Taib NA, Abdullah MM, Wahid I. Breast cancer in pregnancy--our experience with six patients in the University Hospital, Kuala Lumpur. Med J Malaysia. 2000 Sep; 55(3): 308-10.
129. Sharifah NA, Lee BR, Clarence-Ko CH, Tan GC, Shiran MS, Naqiyah I, et al. C-erbB-2 onco-protein expression in breast cancer: relationship to tumour characteristics and short-term survival in Universiti Kebansaan Malaysia Medical Centre. Asian Pac J Cancer Prev. 2008 Oct-Dec; 9(4): 663-70.
130. Nik Jaafar NR, Selamat Din SH, Mohamed Saini S, Ahmad SN, Midin M, Sidi H, et al. Clinical depression while caring for loved ones with breast cancer. Compr Psychiatry. 2014 Jan; 55 Suppl 1: S52-9.
131. Loh SY, Packer T, Chinna K, Quek KF. Effectiveness of a patient self-management programme for breast cancer as a chronic illness: a non-randomised controlled clinical trial. J Cancer Surviv. 2013 Sep; 7(3): 331-42.
132. Loh SY, Ong L, Ng LL, Chew SL, Lee SY, Boniface G. Qualitative experiences of breast cancer survivors on a self-management intervention: 2-year post-intervention. Asian Pac J Cancer Prev. 2011; 12(6): 1489-95.
133. Ram S, Narayanasamy R, Barua A. Effectiveness of Group Psycho-education on Well-being and Depression Among Breast Cancer Survivors of Melaka, Malaysia. Indian J Palliat Care. 2013 Jan; 19(1): 34-9.

134. Muhamad M, Afshari M, Kazilan F. Family support in cancer survivorship. Asian Pac J Cancer Prev. 2011; 12(6): 1389-97.

135. Abu Kassim NL, Mohd Hanafiah K, Samad-Cheung H, Rahman MT. Influence of Support Group Intervention on Quality of Life of Malaysian Breast Cancer Survivors. Asia Pac J Public Health. 2013 Feb 4.

136. Yusuf A, Ahmad Z, Keng SL. Quality of life in Malay and Chinese women newly diagnosed with breast cancer in Kelantan, Malaysia. Asian Pac J Cancer Prev. 2013; 14(1): 435-40.

137. Yusuf A, Ab Hadi IS, Mahamood Z, Ahmad Z, Keng SL. Understanding the breast cancer experience: a qualitative study of Malaysian women. Asian Pac J Cancer Prev. 2013; 14(6): 3689-98.

138. Yusoff N, Low WY, Yip CH. Reliability and validity of the Brief COPE Scale (English version) among women with breast cancer undergoing treatment of adjuvant chemotherapy: a Malaysian study. Med J Malaysia. 2010 Mar; 65(1): 41-4.

139. Yusoff N, Low WY, Yip CH. Psychometric properties of the Malay version of the Breast Module (BR23). Singapore Med J. 2012 Jan; 53(1): 36-9.

140. Zainal NZ, Shuib N, Bustam AZ, Sabki ZA, Guan NC. Reliability and validity of the Malay Version of the Breast- Impact of Treatment Scale (MVBITS) in breast cancer women undergoing chemotherapy. Asian Pac J Cancer Prev. 2013; 14(1): 463-8.

141. Yusoff N, Low WY, Yip CH. Psychometric properties of the Malay Version of the hospital anxiety and depression scale: a study of husbands of breast cancer patients in Kuala Lumpur, Malaysia. Asian Pac J Cancer Prev. 2011; 12(4): 915-7.

142. Hassan BA, Yusoff ZB. Negative impact of chemotherapy on breast cancer patients QOL - utility of antiemetic treatment guidelines and the role of race. Asian Pac J Cancer Prev. 2010; 11(6): 1523-7.

143. Shaharudin SH, Sulaiman S, Shahril MR, Emran NA, Akmal SN. Dietary changes among breast cancer patients in Malaysia. Cancer Nurs. 2013 Mar-Apr; 36(2): 131-8.

144. Yaw YH, Kandiah M, Shariff ZM, Mun CY, Hashim Z, Yusof RM, *et al.* Pattern of weight changes in women with breast cancer. Asian Pac J Cancer Prev. 2010; 11(6): 1535-40.

145. Yaw YH, Shariff ZM, Kandiah M, Mun CY, Yusof RM, Othman Z, *et al.* Weight changes and lifestyle behaviors in women after breast cancer diagnosis: a cross-sectional study. BMC Public Health. 2011; 11: 309.

146. Loh SY, Chew SL, Lee SY. Barriers to exercise: perspectives from multiethnic cancer survivors in Malaysia. Asian Pac J Cancer Prev. 2011; 12(6): 1483-8.

147. Saibul N, Shariff ZM, Rahmat A, Sulaiman S, Yaw YH. Use of complementary and alternative medicine among breast cancer survivors. Asian Pac J Cancer Prev. 2012; 13(8): 4081-6.

148. Muhamad M, Merriam S, Suhami N. Why breast cancer patients seek traditional healers. Int J Breast Cancer. 2012; 2012: 689168.

149. Norsa'adah B, Rahmah MA, Rampal KG, Knight A. Understanding barriers to Malaysian women with breast cancer seeking help. Asian Pac J Cancer Prev. 2012; 13(8): 3723-30.

150. Norsa'adah B, Rampal KG, Rahmah MA, Naing NN, Biswal BM. Diagnosis delay of breast cancer and its associated factors in Malaysian women. BMC Cancer. 2011; 11: 141.

151. Ghazali SM, Othman Z, Cheong KC, Hock LK, Wan Mahiyuddin WR, Kamaluddin MA, et al. Non-practice of breast self examination and marital status are associated with delayed presentation with breast cancer. Asian Pac J Cancer Prev. 2013; 14(2): 1141-5.

152. Yusoff N, Taib NA, Ahmad A. The health seeking trajectories of Malaysian women and their husbands in delay cases of breast cancer: a qualitative study. Asian Pac J Cancer Prev. 2011; 12(10): 2563-70.

153. Taib NA, Yip CH, Low WY. A Grounded Explanation of Why Women Present with Advanced Breast Cancer. World J Surg. 2013 Nov 27.

154. Abdullah A, Abdullah KL, Yip CH, Teo SH, Taib NA, Ng CJ. The decision-making journey of malaysian women with early breast cancer: a qualitative study. Asian Pac J Cancer Prev. 2013; 14(12): 7143-7.

155. Gopal RL, Beaver K, Barnett T, Ismail NS. A comparison of the information needs of women newly diagnosed with breast cancer in Malaysia and the United kingdom. Cancer Nurs. 2005 Mar-Apr; 28(2): 132-40.

156. Lei CP, Har YC, Abdullah KL. Informational needs of breast cancer patients on chemotherapy: differences between patients' and nurses' perceptions. Asian Pac J Cancer Prev. 2011; 12(3): 797-802.

157. Tan FL, Loh SY, Su TT, Veloo VW, Ng LL. Return to work in multi-ethnic breast cancer survivors--a qualitative inquiry. Asian Pac J Cancer Prev. 2012; 13(11): 5791-7.

158. Bhoo-Pathy N, Yip CH, Hartman M, Uiterwaal CS, Devi BC, Peeters PH, et al. Breast cancer research in Asia: adopt or adapt Western knowledge? Eur J Cancer. 2013 Feb; 49(3): 703-9.

A Review of Colorectal Cancer Research in Malaysia

Lim Kean Ghee, FRCS

Dept of Surgery, International Medical University, Clinical School, Jln Rasah, Seremban.

SUMMARY

105 articles related to colorectal cancer(CRC) were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. 56 articles were selected and reviewed on the basis of clinical relevance and future research implications. Research into the genetic basis for colorectal cancer included studies in germline mutations of known syndromes as well as polymorphisms that conferred individuals a higher odds ratio for developing CRC. Several studies also documented the variety of somatic mutations seen in cases of sporadic CRC in Malaysia. Studies into the knowledge and attitudes of Malaysians regarding CRC revealed poor appreciation of the common symptoms, risk factors and available measures for its early detection. This may explain the observed facts that more Malaysians present with late stage CRC than seen in developed countries. The small amount of data recorded concerning the outcome of treatment also suggests overall survival of Malaysian CRC patients for comparable stage of CRC is lower than achieved in developed countries.

KEY WORDS: *Colorectal cancer, Malaysia, Review, genetics, screening, diagnosis, staging, treatment, outcome*

INTRODUCTION

A literature search of articles as detailed in the paper *Bibliography of clinical research in Malaysia: methods and brief results*[1] was undertaken and 105 articles found. Of these, 56 abstracts were considered relevant to basic science and clinical practice by the author [a general surgeon] and full text articles were reviewed. The aim of this review article is to summarise what has already been published on colorectal cancer in Malaysia, to discuss the impact of the research findings to clinical practice, and to identify gaps in colorectal cancer research in Malaysia.

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY

Colorectal cancer (CRC) is the most common cancer in Peninsular Malaysia among men and the third most common among women, according to the National Cancer Registry Report 2003-2005[2]. There were slightly more affected men than women [1.1:1]. The cumulative lifetime risk of developing CRC was 1:38 in men and 1:50 in women. The Age-Standardised Rate (ASR) was highest among Chinese men (31.5 per 100,000), in whom it is more than twice of that in Indian (15.7 per 100,000) and Malay men (12.3 per 100,000). Chinese women also had an ASR (26.2 per 100,000), which was more than twice that of Indian (12.9 per 100,000) and Malay (9.7 per 100,000) women.

RISK FACTORS

A number of lifestyle (e.g. dietary intake of fibre and red meat) and genetic factors (e.g. hereditary nonpolyposis colorectal cancer) cause an increased risk for colorectal cancer and these are true for Malaysians. However, knowledge of risk factors of colorectal cancer remain low in Malaysia. A survey of 991 subjects from an urban middle class area of Kuala Lumpur between 2006-2008[3], using a standard questionnaire for the Asia Pacific Colorectal Cancer Working Group, found that the majority of Malaysians (57%) could not identify risk factors for the disease. The most commonly recognised risk factor was family history (24%), followed by low fibre diet (16%), age (11%), high fat diet (9%), smoking (9%) and obesity (4.5%).

Diet

A case control study of 59 cases and 59 controls at Hospital Kuala Lumpur (HKL) using quantitative food frequency questionnaires showed that soy bean and soy products (OR=0.38), higher servings of fruits (OR=0.47) and vegetables (OR=0.49) were associated with a reduced risk for colorectal adenomas, while tubers, such as potatoes (OR=4.14) and red meat (OR=2.51) were associated with an increased risk (OR = 4.14)[4].

Metabolic risk factors

Obesity, high fasting blood glucose, hypertension and abnormal blood lipids, which are collectively recognised as features associated with metabolic syndromes, are associated with increased risk to colorectal cancer. A cross-sectional study of 140 colorectal cancer patients diagnosed in 2010 in hospitals in Kuala Lumpur, Putrajaya, Selayang, Alor Star and Penang found that 71% (99/140) had features of metabolic syndromes, and this was more common in men than in women[5]. Consistent with data in other countries, individuals with two or more metabolic syndrome features were at a three-fold increased risk for CRC. Furthermore, a study in Kelantan, shows that patients with type 2 diabetes and hypertension were more likely to present with late stage CRC and with cancers located distal to the transverse colon (89% and 85% in diabetic and hypertensive patients respectively)[6].

Streptococcus gallolyticus

Colonisation by *Streptococcus gallolyticus* (the new name of *S. bovis* biotype I) has been suggested for its association with colorectal cancer, but it remains unclear whether this is causal, or whether colorectal cancer tissue is more easily colonised by the microbe. Ahmed SA *et.al.* reported a higher prevalence of *S. Gallolyticus* in Malaysian colorectal cancer patients compared to healthy volunteers (68% vs 17%), as detected by serology[7]. Other studies reported a higher prevalence of *S. gallolyticus* and its subspecies in faeces of CRC patients compared with matched controls (46% compared to 7%)[8,9], and in tumour tissue of CRC patients compared to normal controls (13%-20% compared to 2%)[9].

Corresponding Author: keanghee_lim@imu.edu.my

Colonic polyps

Two-thirds of CRC are known to arise from adenomatous polyps and the presence of these polyps are a significant risk factor for the development of CRC. Using a standard colonoscope and methylene blue dye to look for flat adenomas, Rajendra et.al studied 426 consecutive patients who underwent colonoscopy between 1997 and 2000, and reported finding 29 adenomas in 12 patients, 15 of which were polypoid, 14 were flat, and none were depressed lesions[10]. Notably, the flat adenomas were all less than 5 mm which could easily be missed without the methylene blue dye spraying technique at colonoscopy.

In view of the ethnic difference in incidence of CRC in Malaysia, Rajendran *et.al.* also sought to determine whether ethnic differences in the prevalence of adenomas correlated with ethnic differences of CRC. In their series of 311 consecutive patients undergoing colonoscopy, ethnicity was not associated with prevalence of adenomas. However, only 63 adenomas in 36 patients were observed in this cohort and larger studies are required to validate this observation[11].

Inherited CRC syndromes

There are two most prevalent cancer susceptibility syndromes that result from germline mutation of key genes involved in CRC, namely Hereditary Non Polyposis Colon Cancer (HNPCC) and Familial Adenomatosis Polyposis Coli (FAP). Other rare syndromes are also associated with higher risk for CRC but less clearly defined features, such as Cowden's disease and Peutz-Jegher's syndrome.

Familial Adenomatous Polyposis (FAP)

Familial Adenomatous Polyposis is caused by germline mutations in the APC gene on chromosome 5q and is classically inherited in an autosomal dominant fashion by affected individuals. It is responsible for approximately 1% of all colon cancer. It is characterised by the development of at least a 100 or more adenomatous polyps in the colorectum. A subset of these polyps ultimately acquire additional somatic changes required for the transition to cancer. The mean age for cancer development is 42 years. More than 600 mutations have been reported in the APC gene[12].

Zulqarnain *et al.* reported FAP inheritance in nine individuals in three generations of a Chinese family[13]. Sequence analysis revealed that the affected individuals are heterozygous for a C847T transition that produced a stop codon at amino acid position 283 in place of the usual arginine (Arg283Ter) located in exon 8 of the APC gene.

Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer, HNPCC)

The Lynch Syndrome is an old terminology for HNPCC which is responsible for 2-3% of all colon cancer. It is an autosomal dominant inheritance with a penetrance of about 90%. It is caused by mutation in one of five genes that function in DNA mismatch repair (MMR genes -ie. MLH1, MSH2, MSH6, PMS1 and PMS2) which results in development of colonic carcinoma at early age but in the absence of multiple colonic adenoma such as seen with FAP.

Mohd Nizam *et al.* utilised the revised Bethesda Guidelines to identify 34 CRC patients with features of Lynch Syndrome from Kelantan, Kedah and Sabah[14]. The initial immunohistochemistry testing of the tumour samples from these patients found loss of MLH1 and MSH2 protein expressions in three and four patients respectively. Genomic DNA was then extracted from the blood cells of these patients and subjected to polymerase chain reaction (PCR) amplification analysis. Germline mutations were identified in four out of seven patients.

Low penetrance single nucleotide polymorphisms

Besides the known germline mutations that predispose to CRC, it is possible that other inherited mutations or polymorphisms increase an individual's risk for CRC. For example, the genetic variant that predisposes an individual to inflammatory bowel may also constitute a risk factor for CRC. Published studies on a few such polymorphisms have been conducted in Malaysia, but these require validation in large cohorts. Moreover, there have been no studies conducted to determine the significance of variants identified through genome-wide association studies in Caucasian populations in the Malaysian population.

1. MLH1 promoter polymorphism

Besides defective MMR genes, it is thought that the influence of hereditary low penetrance alleles such as the MLH1 promoter polymorphism -93G>A gene may predispose an individual to CRC. The influence of this gene was studied in a case-control study comprising of 104 histopathologically confirmed CRC patients as cases (52 sporadic CRC and 52 suspected Lynch Syndrome patients) and 104 normal healthy individuals from across Malaysia[15]. DNA was extracted from peripheral blood and the polymorphism was genotyped. The genotypes were categorised into homozygous wild type (G/G), heterozygous (G/A) and homozygous variants (A/A). When risk association was investigated for all CRC patients as a single group, the heterozygous (G/A) genotype showed a significantly higher risk for CRC susceptibility with an Odds Ratio (OR) of 2.3. When analysed specifically for the two types of CRC, the heterozygous (G/A) genotype showed significantly higher risk for sporadic CRC susceptibility (OR of 3.7) than for suspected Lynch Syndrome patients (OR: 1.6). The risk was not statistically significant (p=0.253) for suspected Lynch Syndrome patients. Even though homozygous variant (A/A) also showed higher OR value of 2.357 for sporadic CRC risk, the difference was not statistically significant. MLH1 promoter polymorphism -93G>A does appear to modulate susceptibility risk in Malaysian CRC patients, especially those with sporadic disease.

2. p53 polymorphism

In a risk factor prevalence study of blood samples of 202 sporadic CRC patients matched with controls, Abdul Aziz et al reported that the frequency of the P53Arg72Pro Single Nucleotide Polymorphism (SNP) homozygous variant (Pro/Pro) genotype of the p53 genes was significantly higher in cases compared to controls (21% vs 13%), (p=0.013)[16].

3. Interleukin-8-251T>A polymorphism

Chronic inflammation has been linked to increased risk of cancer in patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis. It is suspected that interleukin (IL)-8, a chemokine mediator of inflammation, may play a role in the pathogenesis of CRC. The mutation IL-8-251T>A may predispose a person to inflammatory bowel disease leading on to CRC. M Aminudin et al. compared DNA from blood samples of 255 CRC patients from Alor Star and Kelantan with age and sex matched controls[17]. They found that individuals with the homozygous variant AA genotype had a 3.6 times higher risk of having CRC compared to those carrying the homozygous wild TT genotype. The variant A allele was calculated to carry a significantly higher risk (OR=1.3) for CRC.

4. Tumour Necrosis Factor-alpha (TNF-α) polymorphism

Tumour Necrosis Factor-alpha is another pro-inflamatory cytokine that was studied in 161 CRC patients and matched

controls by the same investigators in the same hospitals[18]. They found that individuals who were homozygous for the TNF-αG>A allele was 2.6 times more likely to have CRC compared to controls.

MANAGEMENT

Screening

There is currently no population-based screening for colorectal cancer in Malaysia.

Methodology

Faecal occult blood test is one method that could be used in screening for CRC, but the guaiac-based faecal occult blood tests (gFOBT) is hampered by the need to impose dietary restrictions prior to testing, whereas the faecal immunochemical tests (FIT) does not require it. The sensitivity for detecting any neoplasia in a study of 103 subjects screened at an endoscopy unit, comparing the two tests where dietary restriction was not imposed, was 53% for FIT and 40% for gFOBT. The specificity for excluding any neoplasia was 91.7% and 74% respectively. Of the 69 with normal colonoscopic findings, 4.3% were positive for FIT and 23% for gFOBT[19].

A seven-gene biomarker panel analysing gene expression of biomarkers (ANXA3, CLEC4D, TNFAIP6, LMNB1, PRRG4, VNN1 and IL2RB) that are differentially expressed in CRC patients as compared with controls was tested in blood samples from 210 individuals undergoing colonoscopy at Lam Wah Ee Hospital in Penang between 2007 and 2009[20]. The test had been previously validated in a North American population. Ninety nine were patients with CRC, 111 were controls. Logistic regression analysis of seven-gene panel found it had a 77% specificity, 61% sensitivity and 70% accuracy rate, comparable to the data obtained in the North American study making it not a proposed stand-alone test or screening tool.

Awareness of symptoms and risk factors

Despite the increasing incidence of colorectal cancer, awareness of the symptoms of CRC, its risk factors and availability of screening for early diagnosis remains low in the general Malaysian population. Indeed, all of the >1,000 patients diagnosed with CRC in Universiti Malaya Medical Centre (UMMC) and Kuching between 2000-2006 were symptomatic at presentation and none were diagnosed from a screening test[21].

Knowledge of symptoms and risk factors of colorectal cancer has been reported to be disturbingly low (Table I). The survey of 991 subjects in urban Kuala Lumpur found that 42% were unable to identify symptoms of CRC without being prompted or given a list of options and 57% could not identify any risk factor for CRC.3 On the positive side, 24% could identify family history as a risk factor. Other risk factors identified were low fibre diet (16%), age (11%), high fat diet (9%) smoking (9%) and obesity (4.5%). Surprisingly, ignorance was highest among the Chinese (53%). A survey of 2,379 participants from households across small towns in Perak found that the most frequently recalled symptoms were abdominal pain (15%, 346/2,379), followed by "bleeding from the back passage" (6.6%, 158/2,379). All other symptoms were identified by less than 5% of the subjects. When prompted with a list of symptoms, only 30% of the population were able to accurately identify CRC symptoms. Chinese had poorer recognition of CRC symptoms compared to Malays, despite having the highest incidence of CRC[22]. Symptom recognition appears to be higher in a cross-sectional study of 1,905 average risk individuals identified from 44 primary care clinics in West Malaysia from August 2009 to April 2010, with 35% to 74% accurately identifying each CRC symptom, albeit from a given list[23].

Awareness and uptake of screening

Given the low awareness of risk factors and signs and symptoms of colorectal cancer, it is perhaps not surprising that the majority of Malaysians were not aware of screening methods for CRC and uptake of screening was low. In the study of 991 participants in Kuala Lumpur3 the majority (65%) were not aware of any available screening tests for CRC, 33% were aware of colonoscopy and 14% were aware of the faecal occult blood test (FOBT). Two other cross-sectional studies also report low awareness of colorectal cancer screening methods. The first study of 300 students from the Management and Science University found the majority of the participants had no knowledge of colonoscopy (61%) or FOBT screening (62%)[24].

A second cross-sectional study involving 1,905 average risk individuals (those aged 50 years and older who were not known to have personal history of CRC or diseases with increased risk for CRC) from 44 primary care clinics throughout West Malaysia from August 2009 to April 2010 found that only 7% of respondents were aware of screening. Only 13 (0.7%) of respondents had undergone any form of CRC screening in the preceeding five years. The main reason for undergoing screening was advice from health care providers (84.6%)[25]. The main factors for not participating were embarrassment (35.2%) and feeling uncomfortable (30.0%). There were 11.2% of respondents who had never received advice to do screening. In the KL study of 991 subjects, only 15 (1.5%) had previously undergone a screening procedure (13 colonoscopy, two FOBT) and even after being provided with information on risk for CRC, only 39% were agreeable to undergo screening[3]. Malays and Indians were twice more likely compared to the Chinese to be agreeable for screening. Taken together, despite being at the highest risk, ignorance was highest among Chinese (53%) and Chinese were twice less likely to be agreeable to undergo screening.

Regional Comparison

In terms of regional comparison, Malaysia fairs poorly. In a large study (7,915 subjects) across 14 countries in the Asia-Pacific region* in 2007, Malaysia ranked second highest in terms of ignorance after India. Half of the 501 Malaysians surveyed were unaware of any symptoms of CRC, 58% were unaware of any risk factors for CRC, and 80% did not know of any test for colorectal cancer[26]. Malaysians gave the lowest score for the perceived severity of CRC and correspondingly, Malaysians saw the least need for screening. Despite many of the other countries having a lower per capita income than Malaysia, Malaysians were the least likely to have participated in CRC screening, with only 1.2% (3% among those >50 years old) of Malaysians reported previous screening compared to 49% in the Philippines, 38% in Australia and an average participation of 18% across the 14 countries surveyed. Only 38% of Malaysians expressed an intention to undergo screening, compared to 62% in Singapore and 95% in Thailand, both of which are our immediate neighbours. Overall, 20% of the subjects had received physician's recommendations to undergo CRC screening, but this rate was only 1% among Malaysians.

* Australia, Brunei, China, Philippines, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Pakistan, Singapore, Taiwan and Thailand

Diagnosis

In view of the anticipated need for colonoscopies to screen for CRC, adequate facilities and appropriate guidelines need to be in place. Chan and Goh have examined the usage of colonoscopies at the UMMC[27]. Of 380 patients referred for colonoscopy, 58% were classified as appropriate according to the American Society of Gastrointestinal Endoscopy guidelines. The most common appropriate indications were unexplained rectal bleeding (21%) followed by CRC surveillance (12%). The most common inappropriate indication was inappropriately timed colonic cancer surveillance (8.4%). Chronic constipation in 36 cases (9.5%) was the most common 'unlisted' indication. A positive colonoscopic finding was detected in 35% of examinations and CRC was found in 36 patients (9.5%). Appropriateness of indication was not a predictive factor for positive findings of CRC and there was no difference in the proportion of cases with positive findings or CRC in the three 'appropriateness categories'.

Tan *et al.* reported a prospective study of 485 consecutive patients who underwent colonoscopy during a 22-month period to determine the predictive factors for detecting CRC[28]. Analysis revealed that independent predictors were the presence of rectal bleeding (OR 4.3) and iron deficiency anaemia (OR 4.0). In those aged 50 and older, male gender (4.5) and abdominal pain (3.1) were also significant positive predictors for cancer.

The rate of detection of CRC was reported to be 6% (22/375) in one series[29] and 7% (228/3404) in another30. The first series from Universiti Kebangsaan Malaysia (UKM) found that 73% (16/22) of cancers were located within the recto-sigmoid area. The diagnostic yield for CRC was highest when the indication was rectal bleeding (13%, 11/88) and altered bowel habit (9%, 5/56)[29]. There was a total of 53 (14%) cases of adenomas detected with 79% (42/53) located within the recto-sigmoid area in the UKM series[40], while polyps were noted in 14% (470) of the patients in the UMMC series. Polyps detected concomitantly with cancer were noted in 55 patients (2%) Tumours were mainly left sided (80%, 198/248)] with the majority located in the recto-sigmoid region[30]. Adenomas were found most frequently at colonoscopies for cancer surveillance (24%, 14/59) and rectal bleeding (19%, 17/88)[29]. Four patients were diagnosed to have FAP and 8% (19) had synchronous lesions[30].

Delays in diagnosis

A five year retrospective audit from 1999-2004 involving 137 CRC patients was undertaken in UMMC[31]. The median time to diagnosis was nine days after the first UMMC Surgical Unit consultation with a mean of 19 days. Eleven percent had to wait more than four weeks for diagnosis. The median time from confirmation of diagnosis to surgery was 11 days with a mean of 19 days. Sixty two percent of patients underwent surgery within two weeks of diagnosis and more than 88% by four weeks. However, 10% of them had delayed surgery which was done beyond four weeks from diagnosis. Long colonoscopy waiting time was the main cause for delay in diagnosis while delay in staging CT scans were the main reason for treatment delays.

Patient delay in seeking consultation was examined in a cross-sectional study of patients presenting at the UKM endoscopy unit, between 2008 and 2009[32]. Among the 80 patients, aged 40 and older who presented with rectal bleeding, 60% had delayed consulting medical practitioners by more than two weeks. Fifty three percent (42/80) were not worried or little worried about the symptom, and those who delayed consultation were ten times more likely to not worry or worry less. Sixty four percent correctly identified rectal bleeding as a symptom of CRC but were not aware of the best screening method to detect colorectal cancer.

PRESENTATION AND TREATMENT

Patient characteristics

There have been four hospital-based series of CRC patients that recorded the sites of CRC published the last ten years, from Kuala Lumpur[30], Kota Bharu[33], Kuantan[34] and Penang[35]. Table II summarises the distribution of CRC seen throughout the colon and rectum. Left sided cancers predominate. About two-thirds of all CRC occur from the sigmoid colon to the anus. Malays, not surprisingly, accounted for 77% (88/115) of the patients in Kota Bharu and 59% (70/119) in Kuantan, where they account for a larger proportion of the population. The mean age of diagnosis was 64.4 years and the male to female ratio was 1.15 in the Kuala Lumpur series[30]. The mean age of CRC patients in Kota Bharu was 55.7 years. Eighty two percent of patients were older than 50 years old in Kuantan. In addition to the four, the National Cancer Patient Registry-Colorectal Cancer (NCPR-CC) which was set up in 2007 with pilot centres in Alor Star, Kuala Lumpur, Selayang, Serdang, Kota Bharu, Hospital Universiti Sains Malaysia (HUSM) Kubang Kerian, Johor Bahru, Kuching and Kota Kinabalu hospitals gives a similar picture of the location of CRC in Malaysian patients covering a more widespread sample[36]. Out of the 622 patients enrolled, 60% were males and 40% were females. Forty two percent were Malay, 38% Chinese, 6% Indians and other races accounted for the rest. The mean age was 61 years. The age profile and ethnic distribution in all the above series are reflective of the age standardised rates of CRC noted in Malaysia more accurately documented in the results of the National Cancer Registry[2].

A family history of CRC was noted in 11%[30] and 7%[36] of patients in two different studies. The NCPR study noted that 94% presented with symptoms, only 1% (4/622) was detected through screening[36].

Mohd Radzniwan et al. found that on average, 107 of their CRC patients had symptoms for 13 weeks before consultation[37].

Staging

Information on staging of CRC in Malaysia could be gleaned from a few sources, but exclusion of patients or incomplete data confound the findings. Eighty three percent (409/622) of patients in the NCCR report were not appropriately staged or had missing data for staging[36]. Azmi et al. noted that 41% of their patients were found to have Stage B2 disease and 45% had Stage C2 disease. Malays presented with later stage of cancer compared to Chinese. Fifty four percent of Malays had Stage C2 while 58% of Chinese had Stage B2. Fifty percent of the patients younger than 50 years old were diagnosed with stage C2[34].

Treatment

At UMMC, 84% (147/176) of the patients underwent surgery, 28% (50/176) received either adjuvant or palliative chemotherapy[30]. Ghazali *et al.* at HUSM excluded patients who had more than 30% incomplete information in their medical records and noted 27% (31/115) had surgery alone while 69% (79/115) had surgery with chemotherapy and/or radiotherapy. Another 4% (5/115) had only chemotherapy and/or radiotherapy[33]. The NCCR records noted that 492 of the 622 patients with CRC underwent surgery, 16 of whom had two

surgeries. Eighty two (16%) received only palliative surgery. Two hundred forty one patients (39%) underwent chemotherapy; 175/241(73%) had adjuvant chemotherapy, i.e. postoperatively; and 36/241 (15%) had neoadjuvant chemotherapy. Seventy eight patients received radiotherapy, most with chemotherapy. Only 12 had radiotherapy as palliative monotherapy.

Neoadjuvant Chemoradiation

Lee *et al.* have retrospectively analysed all newly diagnosed patients with rectal adenocarcinoma who underwent long course preoperative RT at the Department of Radiotherapy and Oncology, HKL between 2004 and 2010[39]. Sixty seven out of 507 CRC patients who underwent long course preoperative RT were eligible for this study. The median tumour location was 6 cm from the anal verge. Most patients (95%) had suspicion of mesorectum involvement while 28.4% of patients had enlarged pelvic nodes on staging CT scan. The median age of this group at diagnosis was 60 years old with a range of 26-78 years. All patients underwent preoperative chemo-irradiation except for five who had preoperative RT alone. The radiation dose prescribed was 45Gy in 25 fractions given daily over five weeks. The chemotherapy regime given concurrently with RT for all patients consists of intravenous bolus 5-Flourouracil (5FU)300-325mg/m^2 and folinic acid 20mg/m^2 administered daily for five days on weeks 1 and 5 of pelvic RT. Only 38(57%) patients underwent definitive surgery. Post-operatively, patients received another four cycles of adjuvant chemotherapy. Five patients were deemed to be inoperable radiologically and three patients were found to have unresectable disease intraoperatively. The remaining 21 (31%) patients defaulted surgery.

Complications

The NCPR[36] records show 30 (6%) patients had to return to the operation theatre because of surgical complications, the commonest cause being an anastomotic leak (n=15). Medical complications occurred in 19% (94/508) of surgical operations. Sixty one of these complications were not specified. Chest infection and cardiac events occurred only in 16 and ten cases respectively. Medical complications were more likely in patients who had emergency surgery (26%) compared to those who had elective surgery (16%). In contrast, surgical complications were not related to whether the surgery was elective or emergency. Inpatient mortality was 6% (36/431).

Teoh *et al.* evaluated various risk factors associated with anastomotic leakage after anterior resection surgery for rectal cancer in 64 patients whom were operated from 2001 until 2003 in HUKM[40]. Ten (16%) patients who had demonstrated anastomotic leakage were further analysed. There was significantly more anastomotic leakage in patients with very distal tumour less than 4 cm from anal verge (42% - 3/17) when compared to very proximal tumour of more than 15 cm from anal verge (4.3% -1/23). There was a higher percentage of anastomosis leakage in patients with diabetes, low albumin level, higher staging, poorly differentiated tumours and who had neoadjuvant radiotherapy but the difference was not statistically significant because of the small sample size.

Pathology

Histological information was available from 466 patients in the NCPR report. Ninety six percent (446/466) had adenocarcinomas and of these 81% (301/446) were moderately differentiated. Fifty three percent (118/224) of specimens with lymph nodes showed tumour involvement of the nodes. From 296 resected specimens, 12(4%) had proximal or distal margins involved[36].

Biomarkers

The mutational events that occur in sporadic CRC can serve as biomarkers to differentiate and prognosticate the disease of patient groups. In addition they may indicate what future therapy may benefit subsets of patients. However, many of these biomarkers have yet to possess any clinical relevance today, but are windows to the future. The presence of KRAS gene mutation for example, has recently been found to indicate a poor response to anti-EGFR monoclonal antibody therapy[41].

Gene mutations that occur early in CRC tumourigenesis include the APC gene and KRAS proto-oncogene. The DCC gene and P53 gene mutations occur later, although the exact order may vary. Different types of mutation can occur in each of these genes. The array of somatic genetic mutations that promote CRC include point mutations, small insertion/deletion events, translocations, copy number changes, and loss of heterozygosity (LOH), which eventually attenuate gene expression.

Variety

Sporadic gene mutations are generally known to occur in a particular locus, but these defective gene mutations can occur at many different loci. The different types of mutations that occur in the genes associated with colorectal cancer has been described for the APC, KRAS, MSH2 and MLH1 genes in tissue samples of 76 Malaysian colorectal cancer patients[42]. Seventeen types of missense mutations were found in 38 of these 76 patients. Nine different mutations were identified in the APC gene, five different mutations were detected in the KRAS gene, and two types of mutations were identified in the MSH2 gene. Only one mutation was identified in MLH1. Out of these 17 mutations, eight types of mutations (47%) were predicted to be pathogenic. Seven patients were identified with multiple mutations (3: MSH2 and KRAS, 1: KRAS and APC, 1: MLH1 and APC, 2: APC and APC). Another study examined mutations in the APC and beta-catenin (CTNNB1) genes (genes in the Wnt signalling pathway) as well as MMR genes[43]. They found 15/73 (21%) cases with mutations in the APC gene. Fourteen were exonic mutations, of which 12 were found within the mutation cluster region concurring with studies by Miyoshi *et al.*[44] and Polaski[45]. They found only one CTNNB1 mutation and 23% (16/70) of the cases also had some form of MMR defect. They looked for racial differences in the prevalence of these mutations but found none.

Yam *et al.* used a commercially available single-nucleotide polymorphism genotyping array to detect both copy number abnormalities and copy-neutral loss of heterozygosity (LOH) in sporadic colorectal carcinomas[46]. Matched tumour and normal tissues of 13 colorectal carcinomas were analysed using a 250K single nucleotide polymorphism array. Copy number gain (92.3%) was most common, followed by copy number loss (53.8%) and copy-neutral LOH (46.2%). Frequent copy number gains and losses were observed on chromosomes 7p, 8, 13q, 17p, 18q, and 20q, and copy-neutral LOH was observed on chromosomes 2, 6, 12, 13q, 14q, 17, 20p, 19q, and 22q. Even though genomic alterations are associated with colorectal cancer development and progression, the results showed that DNA copy number abnormalities and copy-neutral LOH did not reflect disease progression in at least 50% tumours. Copy-neutral LOH was observed in both early and advanced tumours, which favours the involvement of these genomic alterations in the early stages of tumour development.

Prevalence

As the genetic basis of cancers continue to be unravelled in the 21st century, it remains to be seen if the various mutations

responsible for colorectal carcinoma are similar throughout the world, or if different mutations play different roles in different localities. There have been several studies describing the prevalence of the genes responsible for CRC in Malaysia.

Zulhabri found a 20% (14/70) prevalence of KRAS mutations in his series from Universiti Kebangsaan Malaysia, Kuala Lumpur. This gene mutation was significantly more common in larger tumours (>35cm) but were not significantly different when compared according to different races, sex, stage, and microscopic differentiation. There was a tendency for left sided colon tumours to be KRAS mutated[47].

Another study of 49 CRC samples by Yip WK et al., reported a frequency of 25% (11/44) for KRAS mutation (codons 12, 13, and 61), 2.3% (1/43) for BRAF mutation (V600E), and 77% (33/43) for phosphoinositol-3-kinase, catalytic, alpha (PIK3CA) amplification mutations[48]. No mutations for the Phosphatase and tensin homolog (PTEN) mutation was detected, a finding which was confirmed in another study (0/27)[49].

Loss of the normal P53 tumour suppressor gene, is also associated with CRC. However, the loss of a gene product rather than an emergence of a rogue molecule is unlikely to be a potential target for chemotherapy. Nonetheless, its occurrence in CRC is quite common in Malaysia. One study at UMMC reported a 68% (79/116) rate of P53 overexpression[50]. No significant association of P53 overexpression with stage (Dukes' stage) and grade of tumours was found, nor was there any significant relationship between P53 positivity with overall recurrence-free disease interval and survival. A notable finding was a significantly lower rate in P53 overexpression in the tumours among Indian patients (39%, 5/13) when compared to non-Indian patients.

Gene expression

Genetic mutations can either result in the loss or overexpression for some protein products. However gene expression is also mediated by alterations other than changes in the primary base pair sequence of DNA, i.e. epigenetics.

Using immunohistochemical staining, Yip WK *et al.* demonstrated a 55% (24/44) loss of the PTEN protein in their study even though no mutations of the gene were found[48].

Balraj *et al.* found that mutations that produce amplification of PIK3CA produced no significant difference in PI3K p110 alpha expression between CRCs and the adjacent normal colonic mucosa.49 However, a male:female difference was found. It was noted that 100% of male cases vs 56% of female cases harboured amplified PIK3CA($p = 0.002$). PI3K p110 alpha expression was significantly higher in poorly/moderately differentiated carcinoma compared with well-differentiated carcinoma. K-ras mutation, PIK3CA amplification, PTEN loss, and PI3K p110 alpha expression did not correlate with Akt phosphorylation or Ki-67 expression. K-ras mutation, PIK3CA amplification, and PTEN loss were not mutually exclusive. This report on CRC in Malaysia shows comparable frequency of K-ras mutation and PTEN loss, lower BRAF mutation rate, higher PIK3CA amplification frequency, and rare PTEN mutation, in Malaysia compared with other published reports.48 These results have implication for designing targeted therapy drugs. Khor et al. had shown that PI3K/Akt overexpression, found in 21/47 (45%) of their patients by immunohistochemistry, was associated with increased expression of two downstream proteins. They were, glycogen synthase kinase-3β (GSK-3β) in the pathway that promotes cell proliferation, and BCL-2 antagonist of cell death (BAD) in the pathway that blocks cell death[51]. Except for age, there was no correlation between the immunohistochemical scores of the various biomolecules with sex, race and stage and grade of tumour.

Loss of any of the MMR genes (MLH1, MSH2, PMS1, PMS2, GTBP/MSH6) leads to incapacity to recognise and repair errors that occur during DNA replication, resulting in microsatellite instability[52]. The loss of DNA MMR activity accelerates the rate of accumulation of mutations in other genes involved in apoptosis and growth control that predispose to a more rapid adenoma-to-carcinoma transition. Proteins associated with the MMR genes can be detected by immunohistochemistry. A total of 150 colorectal carcinomas from 148 patients from Penang, not distinguishing sporadic and hereditary types, were subjected to immunohistochemistry study[52]. Three patients had synchronous tumours. Twenty eight cancers (18.6%) from 26 subjects (17.6%) had no immunohistochemical expression of any MMR gene proteins, indicating protein inactivation from an MMR gene defect. This comprised three cases with absent MLH1 only, three with absent MSH2 only, two with absent MSH6 only, three with absent PMS2 only, 14 with absent MLH1 and PMS2, two with absent MSH2 and MSH6 and one with absent MLH1, MSH6 and PMS2. There was significant association between abnormal MMR gene protein expression and proximal colon cancers, mucinous, signet ring and poorly differentiated morphology. However, this study did not examine the germline mutations of these genes.

Three synchronous adenocarcinomas has been reported in one patient with histopathological loss of expression of MLH1 and MSH, believed to be a sporadic case[53].

CD133 is a cell surface marker for the AC133 antigen which is the human homologue of murine Prominin-1 found in hematopoietic and neural stem cells and considered a marker of cancer. Studying 56 formalin-fixed, paraffin-embedded tissue blocks of CRC at the UMMC, Chew et al. demonstrated that CD133 expression was present in significantly higher frequency in 49 (88%) colorectal adenocarcinoma tissue compared with 15 (26.8%) adjacent benign colorectal epithelium[54].

The Wnt proteins are regulators of signalling pathways that attenuate p53-mediated apoptosis and progression of the phases of the cell cycle. Wnt-1 (26/47) and its downstream effectors WISP-1 (15/47), cyclin D1 (5/47) and survivin (28/47) were found to be overexpressed in 47 samples of CRC tissue from Kuala Lumpur between 1999-2000[55]. They were overexpressed in relation to 40 samples of adjacent normal tissue, 26vs7 for Wnt-1, 15vs5 for WISP-1, 5vs13 for surviving and 28vs0 for cyclin D1. WISP-1 in CRC tissue was positively correlated with patients older than 60 years and with well-differentiated tumours. Cyclin-D1 expression was associated with poorly differentiated tumour.

Notes on experimental chemotherapy

Gene therapy targeting cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) could prospectively modulate treatment of colorectal cancer, if tumour tissue expressed the right profile. A study on 101 archival, formalin-fixed, paraffin-embedded tissue samples of colorectal cancers that were surgically resected found COX-2 production was detected more in tumour tissue compared to adjacent normal tissue (60vs34). More tumours expressed iNOS (82/101, 81.2%) than COX-2. No iNOS expression was detected in adjacent normal tissue[56]. Poorly differentiated tumours had significantly lower total beta-catenin ($p = 0.009$) and COX-2 scores ($p = 0.031$). No significant relationships were established between pathological stage and beta-catenin, COX-2 and iNOS scores.

These findings suggest COX-2 and iNOS inhibitors may be potentially useful as chemotherapeutic agents in the management of colorectal cancer.

Malaysian investigators have reported that alpha-Mangostin enhances betulinic acid cytotoxicity and inhibits cisplatin cytotoxicity on HCT 116 colorectal carcinoma cells[57]. Experimental studies have also shown one fraction of Kenaf seed oil (Hibiscus cannabinus) appears to have cytotoxic effects on an HT29 colorectal cancer cell line[58].

It has also been reported that ciglitazone treatment suppressed colon cancer cell growth via induction of apoptosis[59].

OUTCOME

In the HUSM series over 10 years from 1996–2005, which excluded patients with more than 30% incomplete information in their medical records, the five-year survival rate noted was 68% for Duke's B patients and 12% for Duke's C patients[33]. Comorbidities were not important prognostic factors. Tumour site was not a predictor of survival. The pre-operative CEA level was only significantly related to survival prognosis in univariate analysis but not an independent factor in multivariate analysis (i.e. taking staging into account).

In a five-year follow-up study, Mohd Radzniwan *et al.* were able to review their experience with 107 CRC patients. All patients were traced by telephone interview and their outcome determined. More than half had defaulted follow-up and this happened most frequently (62%) during the first two years following treatment. Adjuvant chemotherapy and/or radiotherapy was offered to Stage C patients and those with insufficient margin clearance for rectal carcinomas. Local recurrence occurred at a rate of 9.7% for early and 19.6% for late cancers respectively. Metastases were seen in 26% of patients who had adjuvant therapy compared to 6% of those who did not. The overall survival at five-year follow-up was 40%[37].

Kong CK *et al.* compared patients presenting with CRC in UMMC, Kuala Lumpur and Sarawak General Hospital (SGH), Kuching over seven years from 2000-2006[21]. They were interested in the differences that may be seen at presentation and in survival, noting that per capita Gross Domestic Product (GDP) and monthly household income in Kuala Lumpur are double of that in Sarawak. They found no significant difference in terms of age, gender, ethnic group, socio-economic class, duration of symptoms or stage at presentation between the two centres, although patients in Kuching tended to have a longer duration of symptoms and more advanced disease at presentation. There were 565 new cases of CRC at UMMC and 642 patients in SGH. Within centres, however, lower socio-economic class was a significant factor for late and more advanced stage at diagnosis at both centres. As a result they also had poorer three-and five-year survival rates. Five-year survival rates by stage were: Stage I (79%) Stage II (65%) Stage III (44%) and Stage IV (9.3%) at UMMC and Stage I (75%) Stage II (53%), Stage III (36%) and Stage IV (5.2%) in SGH. Survival was lower for patients in Kuching compared to Kuala Lumpur, even after matching for socio-economic class. Reasons cited for this were no colorectal-trained surgeons at SGH and relatively more junior surgeons at SGH compared to UMMC. Besides, CRC patients in Sarawak had limited options for adjuvant treatment and as Sarawak is a larger state, its patients may have had more difficulty accessing health services.

Neoadjuvant Chemoradiation

Lee *et al.* studying neoadjuvant chemoradiation observed a three-year overall survival rate of 57.3% for 67 patients. All patients with pathological positive Circumferential Resection Margin status died within four years. With a median follow-up of 38.8 months, there were 25 patients who were alive without recurrence. Three patients were alive with recurrence, six alive with unknown status and 33 patients had died. The main result of this study was the three-year local recurrence rate of 33% which was much higher compared to the current accepted rate of below 10%. The high rate of local recurrence is worrying and is mainly due to patient defaulting post-preoperative chemoirradiation or delayed definitive surgery.

QUALITY OF LIFE

Sharifa Ezat *et al.* surveyed the quality of life in a sample of 160 CRC patients from three public hospitals using the EORTC QLO C-30 questionaire[60]. Ninety one percent of respondents had stage III and IV CRC (mean age of 58 years. The median global health status (GHS) score was 83. Scoring in this system ranges from 0-100, with a higher score representing a higher quality of life. Male respondents had better cognitive and social function compared to females. Functional status deteriorated measurably with stage of disease. The more advanced stage of disease, the higher the symptom scores (fatigue, pain, nausea/vomiting, constipation, diarrhoea, insomnia, dyspnoea, loss of appetite). Women had worse scores for pain, fatigue and dyspnoea. Diarrhoea was significantly worse in younger patients. Overall, the findings of this study were comparable with studies done in developed countries.

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

The range of publications from Malaysia looking into the genetic causes and biomarkers of CRC shows investigators are keeping their finger on the pulse of scientific research into the biology of CRC, which may one day give rise to a breakthrough in the treatment of this disease. It is difficult to judge how productive such research will be and whether greater investment will yield more benefit. It is not easy to translate any of this research into clinical practice but as often in basic science research, unexpected finding may surprise us.

More predictable however, is research and audit into clinical practice. These may be less exciting but has revealed perhaps the findings of greatest clinical relevance to CRC management. Audit of patient delay and hospital delay in scheduling diagnostic tests for detecting and assessing CRC patients need to be on-going processes. The capacity for colorectal surgery and delays from time of diagnosis to treatment should also be investigated.

In addition, the revelation that Malaysians are placed in jeopardy by their poor knowledge and attitude towards CRC calls out for action to translate the findings into clinical practice[26]. Health education measures to raise the awareness of our population regarding the severity of the disease as well as its symptoms and risk factors should be mapped out and implemented. Awareness of screening has to be developed alongside provision for colonoscopy. Incentives for the populace to undergo screening colonoscopy, such as tax relieve or through SOCSO benefits or EPF funds, might be considered.

In view of the poor awareness of symptoms and risk factors of CRC among Malaysians, and in addition, the low perception of its severity, it is of great interest to know if Malaysians present with a later stage of the disease compared with other countries. Table IV shows results of CRC disease stage in a few other countries to compare with the data in Table III. If the un-

Table I: Knowledge and Attitude Regarding Colorectal Cancer Screening among Malaysians

	Unaware of Symptoms	Unaware of Risk Factors	Unaware of Screening	Undergone Screening	Agreeable for Screening
Hilmi 2006-8[3] (n=991)	42%	57%	65%	1.5%	39%
Koo 2007[26] (n=501)	50%	58%	80%	1.2%	38%
Harmy 2009-10[32] (n=1905)				0.7%	
Al-Naggar 2013[24] (n=300)			61%		

Table II: Location of Colorectal Cancer in Malaysia Patients

	N	Rectum	Rectosigmoid	Sigmoid	Descending	Transverse	Ascending	Caecum
Goh KL[30] (1999-2003)	248	36%		32%	11%	6%	7%	6%
Ghazali AK[25] (1996-2005)	115	36%	23%	42%				
Azmi[34] (2001-2005)	119	55%		26%			19%	
Kaur G[35] (2001-2005)	148	46%		20%	8%	6%	9%	10%
NCPR[36] (2007-2008)	622	33%	16%	18%	4% +splenic 4%	3% +hepatic 6%	5%	6%

Table III: Location of Colorectal Cancer in Malaysia Patients

	N	Stage A (%)	Stage B (%)	Stage C (%)	Stage D (%)	Unstaged
M Radzniwan[37] (1997-2000)	107	3	36	40	21	Includes only patients with compete five-year follow up
Goh KL[30] (1999-2003)	154	5	42	15	39	Includes only those who had surgery
Ghazali AK[33] (1996-2005)	115	0	44	33	24	Patients with 30% of records incomplete excluded
Penang CR[38] (2004-2008)	1642	12	31	28	29	721 (excluded)

Table IV: Stage of Colorectal Cancer at Presentation in Other Countries

	n	Carcinoma in situ	Stage A (%)	Stage B (%)	Stage C (%)	Stage D (%)	Unknown
Singapore[61] (2003-2007)	7303	1%	10%	25%	32%	19%	14%
United States[62] (1996-1998)	12,099		17% (14-23)	28% (24-36)	38% (29-46)	10% (7-18)	7% (3-10)
Europe[63] (1996-1998)	3,337		17% (11-28)	30% (25-37)	21% (24-30)	21% (11-33)	10% (4-24)
Xin Jiang, China[64] (2000-2007)	1,210		11%	30%	45%	14%	

Table V: Knowledge and Attitude Regarding Colorectal Cancer Screening among Malaysians

	Stage I	Stage II	Stage III	Stage IV
Ghazali AK[33] (1996-2005)		68%	12%	
UMMC (Kong[21]) 2000-2006	79%	65%	44%	9.3%
SGH (Kong[21]) 2000-2006	75%	53%	36%	5.2%
United Kingdom[65] (1996-2002)	93%	77%	48%	6.6%
United States[62] (1991-2000)	93%	79%	64%	8%

staged group in the Malaysian series was included in the total, the percentage in all the other stages falls so low, comparisons cannot made. However, it should be suspected that un-staged patients are more likely to have late stage disease. Even so, when comparing data with the Singapore Cancer Registry over a similar period and a collection of United States and European studies a decade earlier, Malaysian records show a much lower percentage with Stage A disease and a high proportion with late (Stage C and D) disease. The true percentage of Malaysian patients presenting with late disease still needs to be determined. The overall picture, however, indicates that more Malaysian patients are presenting with later stage disease than in developed countries, even if we cannot quantify by exactly how much.

The poor survival rate for all stages of CRC reported in Malaysia in Table V compared with other international studies is also of great concern. There is a difference or up to more than 10% in survival in patients presenting in early colorectal cancer compared to the best centres. Issues such as delay in treatment, optimum use of neo-adjuvant and adjuvant therapy, as well as safe and effective surgery in Malaysia need to be studied and audited.

SECTION 3: FUTURE RESEARCH DIRECTION

As disease prevention is always more effective than curing cancer, studies into the prevalence of known risk factors for CRC and how they might be reduced in the Malaysian population is an area to be explored. Reducing obesity and promoting a healthier diet of less carcinogenic food and greater intake of fibre in the diet to reduce constipation need not only to be studied but also implemented. To document the way Malaysians present and audit outcomes of treatment, the National Cancer Patient Registry-Colorectal Cancer needs to be supported and expanded.

ACKNOWLEDGEMENTS

I wish to thank Mastura Md Yusof and Teo Soo Hwang for reviewing this manuscript.

I would like to sincerely thank the Director General of Health, Malaysia for his permission to publish this paper.

REFERENCES

1. Teng CL, Bibliography of clinical research in Malaysia: methods and brief results. Med J Malaysia 2014; 69 (Supplement A): 4-7.
2. Lim GCC, Rampal S, Halimah Y. (Eds.) Cancer Incidence in Peninsular Malaysia 2003-2005. National Cancer Registry. Kuala Lumpur 2008.
3. Hilmi I, Hartono JL, Goh K. Negative perception in those at highest risk--potential challenges in colorectal cancer screening in an urban asian population. Asian Pac J Cancer Prev 2010; 11(3): 815-822.
4. Amutha R, Mirnalini K. Food intake and colorectal adenomas: a case-control study in Malaysia. Asian Pac J Cancer Prev 2009; 10(5): 925-932.
5. Ulaganathan V, Kandiah M, Zalilah MS, *et al.* Colorectal cancer and its association with the metabolic syndrome: a Malaysian multi-centric case-control study. Asian Pac J Cancer Prev 2012; 13(8): 3873-3877.
6. Nor Hayati O, Anani Aila MZ. Association of colorectal carcinoma with metabolic diseases; experience with 138 cases from Kelantan, Malaysia. Asian Pac J Cancer Prev 2008; 9(4): 747-751.
7. Ahmed SA, Rand RH, Layla KM, *et al.* Investigation into the controversial association of Streptococcus gallolyticus with colorectal cancer and adenoma. BMC Cancer 2009; 9: 403-2407-9-403.
8. Al-Jashamy K, Murad A, Zeehaida M, *et al.* Prevalence of colorectal cancer associated with Streptococcus bovis among inflammatory bowel and chronic gastrointestinal tract disease patients. Asian Pac J Cancer Prev 2010; 11(6): 1765-1768.
9. Ahmed SA, Rand RH, Fatimah AB. Molecular detection, quantification, and isolation of Streptococcus gallolyticus bacteria colonizing colorectal tumours: inflammation-driven potential of carcinogenesis via IL-1, COX-2, and IL-8. Mol Cancer 2010; 9: 249-4598-9-249.
10. Rajendra S, Kutty K, Karim N. Flat colonic adenomas in Malaysia: fact or fancy? J GastroenterolHepatol 2003; 18(6): 701-704.
11. Rajendra S, Ho JJ, Arokiasamy J. Risk of colorectal adenomas in a multiethnic Asian patient population: race does not matter. J GastroenterolHepatol 2005; 20(1): 51-55.
12. http:/www.hgmd.cf.ac.uk/gene.php?gene=APC)
13. Zulqarnain M, Rahimah A, Ng SY, Zubaidah Z, Harun A and Tong HY. A nonsense mutation in exon 8 of the APC gene (Arg283Ter) causes clinically variable FAP in a Malaysian Chinese family. Cancer Science. 2003; 94(8): 725-728.
14. Zahary MN, Kaur G, Abu Hassan MR, et al. Germline mutation analysis of MLH1 and MSH2 in Malaysian Lynch syndrome patients. World J Gastroenterol2012; 18(8): 814-820.
15. Zahary MN, Ahmad Aizat AA, Gurjeet Kaur, *et al.* Contribution of the MLH1 -93G>a promoter polymorphism in modulating susceptibility risk in Malaysian colorectal cancer patients. Asian Pac J Cancer Prev 2013; 14(2): 619-624.
16. Abdul Aziz AA, Siti Nurfatimah MS, Mohd Aminudin M, *et al.* Association of Arg72Pro of P53 polymorphism with colorectal cancer susceptibility risk in Malaysian population. Asian Pac J Cancer Prev2011; 12(11): 2909-2913.
17. Mustapha MA, Shahpudin SN, Aziz AA, *et al.* Risk modification of colorectal cancer susceptibility by interleukin-8 -251T>A polymorphism in Malaysians. World J Gastroenterol2012; 18(21): 2668-2673.
18. Mustapha MA, Shahpudin SN, Aziz AA *et.al.* Polymorphism in the Tumour Necrosis Factors alpha promoter region and its influence on colorectal cancer promotion risk in Malaysian population. International Medical Journal 2011; 4: 275-278.
19. Roslani AC, Abdullah T, Arumugam K. Screening for colorectal neoplasias with fecal occult blood tests: false-positive impact of non-dietary restriction. Asian Pac J Cancer Prev 2012; 13(1): 237-241.
20. Yip KT, Das PK, Suria D, *et al.* A case-controlled validation study of a blood-based seven-gene biomarker panel for colorectal cancer in Malaysia. J ExpClin Cancer Res 2010; 29: 128-9966-29-128.
21. Kong C, April Camilla R, Law C, *et al.* Impact of socio-economic class on colorectal cancer patient outcomes in Kuala Lumpur and Kuching, Malaysia. Asian Pac J Cancer Prev 2010; 11(4): 969-974.
22. Loh KW, Hazreen AM, Maznah D, *et al.* Sociodemographic predictors of recall and recognition of colorectal cancer symptoms and anticipated delay in help- seeking in a multiethnic asian population. Asian Pac J Cancer Prev 2013; 14(6): 3799-3804.
23. Harmy MY, Norwati D, Noor NM, *et al.* Knowledge and attitude of colorectal cancer screening among moderate risk patients in West Malaysia. Asian Pac J Cancer Prev 2011; 12(8): 1957-1960
24. Al-Naggar RA, Bobryshev YV. Knowledge of colorectal cancer screening among young Malaysians. Asian Pac J Cancer Prev 2013; 14(3): 1969-1974.
25. Harmy MY, Norwati D, Norhayati MN, *et al.* Participation and barriers to colorectal cancer screening in Malaysia. Asian Pac J Cancer Prev 2012; 13(8): 3983-3987.
26. Koo JH, Leong RW, Ching J, *et al.* Knowledge of, attitudes toward, and barriers to participation of colorectal cancer screening tests in the Asia-Pacific region: a multicenter study. GastrointestEndosc 2012; 76(1): 126-135.
27. Chan TH, Goh KL. Appropriateness of colonoscopy using the ASGE guidelines: experience in a large Asian hospital. Chin J Dig Dis 2006; 7(1): 24-32.
28. Tan YM, Rosmawati M, Ranjeev P, *et al.* Predictive factors by multivariate analysis for colorectal cancer in Malaysian patients undergoing colonoscopy. J GastroenterolHepatol 2002; 17(3): 281-284.
29. Cheong KL, Roohi S, Jarmin R, *et al.* The yield for colorectal cancer and adenoma by indication at colonoscopy. Med J Malaysia 2000; 55(4): 464-466.
30. Goh KL, Quek KF, Yeo GT, *et al.* Colorectal cancer in Asians: a demographic and anatomic survey in Malaysian patients undergoing colonoscopy. Aliment PharmacolTher 2005; 22(9): 859-864.
31. Law CW, Roslani AC, Ng LL. Treatment delay in rectal cancer. Med J Malaysia 2009; 64(2): 163-165.
32. Syahnaz MH, Tong SF, Khairani O, *et al.* Knowledge of colorectal cancer among patients presenting with rectal bleeding and its association with delay in seeking medical advice. Asian Pac J Cancer Prev 2011; 12(8): 2007-2011.

33. Ghazali AK, Musa KI, Naing NN, *et al.* Prognostic factors in patients with colorectal cancer at Hospital UniversitiSains Malaysia. Asian J Surg 2010; 33(3): 127-133.
34. Azmi MN, Zailani MA, Norashikin MN, *et al.* Five-year review of histopathological findings of colorectal cancer patients operated in Hospital TengkuAmpuanAfzan, Kuantan, Pahang, Malaysia. International Medical Journal (IIUM) 2007; 6 (1).
35. Kaur G, Masoud A, Raihan N, *et al.* Mismatch repair genes expression defects & association with clinicopathological characteristics in colorectal carcinoma.Indian J Med Res 2011; 134: 186-192.
36. Hassan MR and Lim W. The first Annual Report of the National Cancer Patient Registry-Colorectal Cancer 2007-2008. Kuala Lumpur, Malaysia 2010.
37. Mohd Radzniwan AR, AznidaFirzah AA, Saharuddin A, *et al.* Colorectal cancer patients in a tertiary referral centre in Malaysia: a five year follow-up review. Asian Pac J Cancer Prev2009; 10(6): 1163-1166
38. Azizah AM, Devaraj T, Saraswathi BR. Penang Cancer Registry Report 2004-2008. Penang Cancer registry 2010.
39. Lee WC, Mastura MY, Lau FN, *et al.* Preoperative long course chemoirradiation in a developing country for rectal carcinoma: Kuala Lumpur Hospital experience. Asian Pac J Cancer Prev2013; 14(6): 3941-3944.
40. Teoh CM, Gunasegaram T, Chan KY, *et al.* Review of risk factors associated with the anastomosis leakage in anterior resection in Hospital UniversitiKebangsaan Malaysia. Med J Malaysia2005; 60(3): 275-280.
41. Allegra CJ, Jessup JM, Somerfield MR, *et.al.* American Society of Clinical Oncology Provisional Clinical Opinion: Testing for KRAS Gene Mutations in Patients with Metastatic Colorectal Carcinoma to Predict Response to Anti–Epidermal Growth Factor Receptor Monoclonal Antibody Therapy. 2014 http://www.therosesheet.com/~/media/Images/Publications/Archive/ /The%20Gray%20Sheet/35/003/01350030013/011909_asco_kras.pdf
42. Abdul Murad NA, Othman Z, Khalid M, *et al.* Missense mutations in MLH1, MSH2, KRAS, and APC genes in colorectal cancer patients in Malaysia. Dig Dis Sci2012; 57(11): 2863-2872.
43. Tan LP, Ng BK, Balraj P, *et al.* No difference in the occurrence of mismatch repair defects and APC and CTNNB1 genes mutation in a multi-racial colorectal carcinoma patient cohort. Pathology 2007; 39(2): 228-234.
44. Miyoshi Y, IwaoK, NagasawaT *et.al.* Activation of the -catenin gene in primary hepatocellular carcinomas by somatic alterations involving exon 3. Cancer Res 1998; 58: 2524-7.
45. Polaski P. Mutations in the APC gene and their implications for protein structure and function. Curr Opin Genet Dev 1995; 5:66-71.
46. Yam YY, Hoh BP, Othman NH, *et al.* Somatic copy-neutral loss of heterozygosity and copy number abnormalities in Malaysian sporadic colorectal carcinoma patients. Genet Mol Res 2013; 12(1): 319-327.
47. Zulhabri O, Rahman J, Ismail S, *et al.* Predominance of G to A codon 12 mutation K-ras gene in Dukes' B colorectal cancer. Singapore Med J 2012; 53(1): 26-31.
48. Yip WK, Choo CW, Leong VC, *et al.* Molecular alterations of Ras-Raf-mitogen-activated protein kinase and phosphatidylinositol 3-kinase-Akt signalling pathways in colorectal cancers from a tertiary hospital at Kuala Lumpur, Malaysia. APMIS 2013; 121(10): 954-966.
49. Balraj P, Ruhana S. PTEN mutation studies in Malaysian colorectal cancer patients. Asia Pacific Journal of Molecular Biology and Biotechnology 2007; 15(1): 23-25.
50. Goh KS, Ong TA, Peh SC, *et al.* P53 expression in colorectal carcinoma: the University of Malaya Medical Centre's experience. Med J Malaysia2004; 59(4): 515-521.
51. Khor TO, Gul YA, Ithnin H, *et al.* Positive correlation between overexpression of phospho-BAD with phosphorylated Akt at serine 473 but not threonine 308 in colorectal carcinoma. Cancer Lett2004; 210(2): 139-150.
52. Kaur G, Masoud A, Raihan N, *et al.* Mismatch repair genes expression defects & association with clinicopathological characteristics in colorectal carcinoma.Indian J Med Res 2011; 134: 186-192.
53. Leong BD, Ramu P, Kumar VM, *et al.* Synchronous adenocarcinoma of caecum, transverse colon and jejunum. Med J Malaysia 2008; 63(2): 148-149
54. Chew MF, Teoh KH, Cheah PL. CD133 marks for colorectal adenocarcinoma. Malays J Pathol 2012; 34(1): 25-28.
55. Khor TO, Gul YA, Ithnin H, et al. A comparative study of the expression of Wnt-1, WISP-1, survivin and cyclin-D1 in colorectal carcinoma. Int J Colorectal Dis 2006; 21(4): 291-300.
56. Hong SK, Gul YA, Ithnin H, *et al.* Expression of beta-catenin, COX-2 and iNOS in colorectal cancer: relevance of COX-2 adniNOS inhibitors for treatment in Malaysia. Asian J Surg 2004; 27(1): 10-17.
57. Aisha AF, Abu-Salah KM, Ismail Z, *et al.* alpha-Mangostin enhances betulinic acid cytotoxicity and inhibits cisplatin cytotoxicity on HCT 116 colorectal carcinoma cells. Molecules 2012; 17(3): 2939-2954.
58. Siti Aisyah AG, Maznah I, Latifah SY, *et al.* Cytotoxic Activity of Kenaf Seed Oils from Supercritical Carbon Dioxide Fluid Extraction towards Human Colorectal Cancer (HT29) Cell Lines. Evid Based Complement Alternat Med 2013; 2013: 549705.
59. Yaacob NS, Darus HM, Norazmi MN. Modulation of cell growth and PPAR gamma expression in human colorectal cancer cell lines by ciglitazone. ExpToxicolPathol 2008; 60(6): 505-512.
60. SharifaEzat WP, Natrah MS, Syed Mohd A, *et al.* Quality of life in Malaysian colorectal cancer patients. Asia Pac Psychiatry 2013; 5Suppl 1: 110-117.
61. Singapore Cancer Registry Report 2003-2007.
62. Allemani C, RachetB, Weir HK, Richardson LC *et.al.* Colorectal cancer survival in the USA and Europe: a CONCORD high-resolution study. BMJ open, 2013; 3e003055.
63. UK Cancer Research. Colorectal Cancer Survival by Stage, 1996-2002. http://www.cancerresearchuk.org/cancer-info/cancerstats/types/bowel/survival/bowel-cancer-survival-statistics
64. US National Cancer Institute. SEER stat fact sheets.
65. Yusup A, Wang HJ, Rahmutula A, Sayim P, Zhao ZL, Zhang GQ. Clinical features and prognosis in colorectal cancer patients with different ethnicities in Northwest China. World J Gastroenterol2013 19(41): 7183-7188.

A Review of Cervical Cancer Research in Malaysia

Zaridah S, MOG UKM

Gynecology oncologist, Obstetric & Gynaecology Department, Hospital Tuanku Fauziah, Kangar, Jalan Kolam, 01000 Kangar, Perlis.

SUMMARY

Despite cervical cancer being potentially preventable, it is the second most common cancer among women in Malaysia. One hundred and five articles related to Cervical Cancer were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. Fifty seven articles were selected and reviewed for the articles' clinical relevance and future research implications. This article reviews the various aspects of cervical cancer in Malaysia, mainly persistent infection of high risk human papillomavirus (HPV), primary prevention (HPV vaccination), screening method (Pap smear issues), and the attitude and knowledge of various groups of Malaysian women that contributed to the failure to reduce the incidence and mortality of cervical cancer. Most of the studies focused on prevention, Pap smear issues, HPV DNA testing, HPV vaccination and various recommendations for prevention of cervical cancer. Secondary prevention by screening is still an important aspect because even with HPV vaccination, screening still plays an important role as vaccination does not cover all high risk HPVs. There is a need to seriously consider a properly organised screening programme, taking into consideration what we already know about the attitude and knowledge of Malaysian women, economic factors and psychosocial issues of the screening method. There is also a large gap in clinical studies on the outcome, management and survival of cervical cancer patients in Malaysia.

KEY WORDS: *cervical cancer Malaysia, prevention, screening, HPV vaccination*

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY/INCIDENCE

The Malaysian National Cancer Registry Report (2003) found that the most frequently occurring cancers in Malaysian women (in descending order) cancers of the breast, cervix, colon, ovary, leukaemia, and lungs. Cervical Cancer caused about 12.9% of all female cancers (an age standardised incidence rate of 19.7 per 100,000) in Malaysia. This was higher than other Asian and Western countries, and even globally (National Cancer Registry, 2003). Deaths from cervical cancer are rare amongst young women but its incidence increased from the age of 30 years and peaked at 60-69 years. Half (54.7%) of the cases involved women ages 40-59 years. Incidence rates were, in general, highest among Chinese women (28.8/100,000), followed by Indians (22.4/100,000) and the lowest amongst the Malays (10.5/100,000)[1].

The Ministry of Health Malaysia reported an average of 2000 to 3000 hospital admissions of cervical cancer cases per year in the country; most of them presenting late into the disease[2]. The annual cervical cancer death rate is 5.6 per 100,000 (Cervical Cancer Incidence and Mortality Rates 2011). The mortality rate due to cervical cancer in Malaysia is more than two times higher than the Netherlands, United Kingdom and Finland. Even with the introduction of screening programmes and immunisation against cervical cancer, the mortality rate has not decreased to a desirable level. The economic burden due to cervical cancer is enormous. It costs about RM312 million (USD76 million) to manage cervical cancer (from prevention to managing invasive diseases) annually in Malaysia. A big proportion (67%) of this is spent to manage invasive cancer cases[3].

Syed M AlJunid discussed the burden of cervical cancer in Malaysia and the potential cost and consequences of human papillomavirus (HPV) vaccination[4]. Since cervical cancer is treated primarily within regional hospitals, while precancerous lesions are treated within an ambulatory care set up, the burden was estimated as the direct, indirect and total annual costs associated with cervical cancer and precancerous lesions in Malaysia. This retrospective study to estimate the burden associated with cervical cancer was conducted at four hospitals[4]. A total of 444 hospital admissions attributable to cervical cancer were identified. Treatment for preinvasive disease is much cheaper. The average cost of atypical squamous cell of undetermined significant (ASCUS), cervical intraepithelial neoplasia 1 (CIN1), and CIN 2/3 in Malaysia were RM898, RM1453, RM1948 respectively compared to RM10,540 for cervical cancer. A prevalence-based model that used 1-year cross-sectional data was developed to estimate the number of events (cases of precancerous lesions, cervical cancer and genital warts) and costs (direct+indirect) that could be avoided by vaccination, Data from World Health Organization (WHO) and Global cancer incidence, mortality and prevalence (GLOBOCAN) estimated 4696 prevalent cases of cervical cancer annually in Malaysia. Based on this, Syed M AlJunid found the estimated treatment cost to be RM37,652,528 for inpatients and outpatients. There were 1372 cases estimated for precancerous lesions (ASCUS, CIN 1 and CIN 2/3), with the cost of outpatient treatment calculated as RM1,501,171, making the direct total management of HPV related disease to be RM39,153,699, with an additional RM12.4 million in indirect costs due to lost productivity[4].

Shanti et al, in her supplementary paper, recommended that the bulk of effort in managing cervical cancer should be allocated for preventive strategies – mainly screening, followed by combined screening-vaccination. The Malaysian government spends RM150 million annually to operate the nation's HPV immunisation programme but it takes only RM 32 million to operate the Pap smear screening program[5].

Corresponding Author: dr_zaridah@yahoo.com.sg

RISK FACTOR

Human papillomavirus and cervical cancer

The World Health Organization (WHO) had linked persistent high risk HPV infection, particularly HPV 16 and 18, to cervical cancer. Human papillomavirus infection is cleared within two years in most women. It is the persistent high risk HPV infection that puts the infected individual at high risk to develop CIN 3 and cervical cancer later on 6. Many studies in Malaysia also showed this association (Table I).

An independent, prospective, multi-centred, hospital-based cross-sectional studies involving Malaysia, Vietnam, Singapore, South Korea and the Philippines evaluate the prevalence of human papillomavirus (HPV) in women older than 21 years old with invasive cervical cancer (ICC) and high-grade precancerous lesions[9]. Out of 500 women confirmed with ICC, the HPV types detected were HPV 16 (36.8%-61.3%), HPV 18 (12.9%-35.4%), HPV 52 (5.4%-10.3%), and HPV 45 (1.5%-17.2%), whereas among the CIN 2/3/AIS cases, HPV 16 (29.7%-46.6%) was the most commonly observed type followed by HPV 52 (17.0%-66.7%) and HPV 58 (8.6%-16.0%)[9].

The prevalence of HPV infection were demonstrated in these two studies by Chong PP and Tay *et al* (Table II). Tay et al studied the prevalence of high-risk HPV DNA among 2364 women[10]. The overall prevalence of high risk HPV DNA was 25.6%. The prevalence of high risk HPV showed the peak age to be in women between 20-24 years old (49.1%) and a second peak prevalence in women 50-54 years old (30%). This pattern of peak prevalence is similar to the general trend published from other parts of the world. High risk HPV DNA detection was associated with 2.44-3.18 fold higher risk of developing cervical cytology abnormality or 9.8 fold higher risk for HSIL compared to HPV-negative women. In this study, the natural history of high-risk HPV infection showed that 90% of HPV infection regressed within the first 12 months of follow-up. Therefore, recommended implementation of a comprehensive cervical cancer screening and anti-HPV-16/18 vaccination program is an important and urgent measure for reducing the burden of cervical cancer in Malaysia and Singapore[10].

CERVICAL CANCER PREVENTION

Cervical cancer is a potentially preventable disease. There is a need to look into why this easily prevented and detected disease still has high prevalence and mortality. Many studies done in Malaysia revolved around cervical cancer prevention. There are three modalities of cervical cancer prevention: primary prevention by preventing HPV infection, sexual abstinence and healthy lifestyle, and HPV vaccination. Secondary cervical cancer prevention is through the detection and treatment of precancerous or preinvasive lesion; and tertiary prevention is the detection and treatment of the early stage of cancer.

Primary prevention

The prophylactic HPV vaccine was licensed in our country in November 2006, and recommended for routine use in girls aged 11 to 12 years and permissive use for females aged 9 to 26 years. According to the Annual Report of Malaysia Ministry of Health (2012), the immunisation coverage of a complete three dosage of HPV vaccine was achieved (87.12%) among 13 year old girls in year 2011.

HPV vaccination: knowledge and attitude

The studies on knowledge, attitude and practices on HPV infection and vaccination were conducted in various groups including secondary school, children, teachers, university students, and other groups of women from various level of education. All the studies below concluded that overall knowledge on HPV infection, vaccination and cervical cancer is poor and that knowledge and attitude translated to vaccine acceptance. There is a need to improve women's awareness and knowledge, and improve their attitude towards HPV vaccination.

Teenagers

Two cross-sectional studies on teenagers' knowledge of cervical cancer and its prevention were conducted; one in Sarawak involving 76 students[12] and the other involving eight schools in Kuala Lumpur*13*. In Sarawak, 61.8 % had poor knowledge of cervical cancer and its prevention, and 60.5 % of students were aware of cervical cancer (the highest rate of awareness involving the Chinese students). The main source of cervical cancer information were their parents (25.9 %). Race, socioeconomic status, father's education level, mother's education level and cervical cancer awareness were associated with the knowledge of cervical cancer prevention ($p< 0.05$). Not many students (22.3%) accepted HPV vaccination.

In the Kuala Lumpur study, although 80.4% have heard about cervical cancer, 74.4% had low knowledge of cervical cancer, 70.4% had low knowledge of the preventive measures of cervical cancer. Most students (69.3%) agreed to take the vaccination if the service was available in schools, 82.2% agreed that the vaccination of teenagers should be made compulsory. Both studies concluded that most students had low knowledge of cervical cancer and its prevention but they had a positive attitude toward vaccination. The Kuala Lumpur students agreed that vaccination should be made compulsory. Therefore, suitable educational programmes should be developed to improve the knowledge of secondary school students on the prevention of cervical cancer.

A study among secondary schools in Melaka looked into the HPV vaccination practice. The study involved a total of 612 secondary school girls aged from 13 to 17 years old from six secondary schools in Melaka, majority were from rural areas and with a family income of RM3000 or less. In this study, the prevalence of HPV vaccination was 77.9%. About 69% knew about cervical cancer and 77.6% knew about HPV vaccine. This study concluded that vaccination in schools significantly influenced vaccine uptake. Vaccine uptake were also improved with encouragement from healthcare workers and teachers (49.3%), parents (28.6%); and friends (0.2%)[14].

Hersham et al concluded that medical students had the highest level of knowledge of cervical cancer, HPV infection and HPV vaccination compared to dentistry and pharmacy students[15]. The studies recommended enhancing their knowledge level by organising educational and awareness programs in University campuses.

Women

In a survey among 233 young women (majority had tertiary education), 82.4% reported having knowledge of HPV, and 71.7% knew that having multiple sex partners increase the risk of HPV. Majority of the participants knew that sex before the age of 16 years increase the risk of HPV (58.4%). More than half of them have been vaccinated (51.5%). The paper concluded that promoting HPV and HPV vaccine campaigns all over Malaysia, especially in schools and through public campaigns, are crucial to raise the awareness and knowledge[16].

A questionaire which assessed the knowledge and attitudes of 449 young rural women in Malaysia towards HPV, HPV vaccination, and cervical cancer revealed extremely poor

knowledge emphasising the importance of educating rural residents on HPV. Acceptance of HPV vacination was significantly associated with knowledge of cervical screening and cervical cancer risk factors. Reasons for vaccine refusal include doubts about its safety and efficacy (27.4%); and the perceived embarrassment of receiving an STI vaccine (20.7%). Twenty percent perceived that they were not at risk for HPV infection. Most (90%) of the study participants reported that they required more information on the need for vaccination and who would need to be vaccinated (85.3%), as well as the potential risks or side effects of HPV vaccination (85.7%)[17]. Wong LP et al also revealed that 21.7% have heard about HPV and 10.3% have heard about the new HPV vaccine[18].

A cross-sectional study conducted among 300 Malaysian women in the obstetrics and gynaecology outpatient clinic in a selected hospital in Bangi, Selangor also found that educating the public on vaccination was highly recommended and the barriers to being vaccinated should be dealt with seriously. Only 12% to 25% correctly answered the questions but half of the respondents (53%) had a positive attitude toward HPV vaccination. Age, marital status, and level of education were significantly associated with this attitude[19].

A questionnaire was distributed among mothers in May 2007 in the University of Malaya Medical Centre, in Kuala Lumpur, Malaysia. A total of 362 mothers were included in the study. The study showed low knowledge of HPV and HPV vaccine. Although 57.3% were worried of the side effect, 65.7% accepted HPV vaccination for their daughters. Many of the mothers (83.9%) were unwilling to vaccinate their children if they had to pay, but if it was routine and freely available, acceptability rate increased to 97.8%[20].

Choice of HPV vaccine

The Malaysian government approved HPV vaccination program with three doses of HPV vaccine freely given to all 13-year-old girls from public or private schools on 21st February 2008; and the cabinet approved the budget on 19th August 2009[21]. World Health Organization (WHO) recommended that routine HPV vaccination be included in National Immunisation programmes.

Sharifah ezat compare and look at cost effectiveness of HPV vaccination in prevention of cervical cancer in Malaysia.This cross sectional economic burden study with 502 respondents were interviewed from six public Gynecology-Oncology hospitals in 2006-2009. In this study, cost effectiveness options were compared for three programs i.e. screening via Pap smear; modeling of HPV vaccination (Quadrivalent vaccine (QV) and Bivalent vaccine (BV) and combined strategy (screening plus vaccination). A scenario based sensitivity analysis was conducted using screening population coverages (40-80%) and costs of vaccines (RM 100-200/dose) were calculated. This study concluded vaccination increase life expectancy with better Quality of life (QOL) of women when cancer can be avoided. Cost effective strategies will include increasing the Pap smear coverage to 70% or higher. Since Malaysian women attitude regarding screening is doubtful , vaccination of young women is a more cost effective strategy against cervical cancers. The QV combined strategy was more cost effective (CE) than any method including Pap smear screening at high population coverage[3,22].

Secondary prevention of cervical cancer: Screening

Cervical cancer fulfills the criteria for an effective screening program because it is a major health problem, has a preinvasive stage, and is treatable at an early stage. Cervical cancer screening had shown to be a cost-effective mean of controlling the cancer and Pap smear screening is recognised for secondary prevention. The procedure is easy, and inexpensive with acceptable sensitivity and specificity.

Pap smear screening in Malaysia

In Malaysia, Pap smear screening started in the 1960s, and available for free in government health facilities since 1995. Many healthy life style campaign and publicity were made to promote this procedure, yet it did not achieve above 70-80% coverage of the population to reduce cervical cancer morbidity and mortality[23]. World Health Organization recommends that routine HPV vaccination should be included in national immunisation programmes if prevention of cervical cancer constitutes a public health priority, taking into account that vaccine introduction is programmatically feasible and financing can be secured[24]. It would be a great challenge for Malaysia to provide HPV vaccination for the entire adolescent populations. A cross-sectional study among 116 participants from Penang shows that only 42.2% have heard of the HPV vaccine and they were only willing to pay an average of RM96.7 for the full course of vaccine (actual price RM1200). This mean that screening will still remain an important strategy to combat cervical cancer and every effort is needed to ensure that the investments made in screening are effective and efficient[25].

Pap smear challenges

1. Coverage

Pap smear failed to achieve a broad coverage because it is only done opportunistically and poor awareness[23]. There were many studies addressing various issues of Pap smear. Although it is simple, cheap, safe and readily acceptable by Malaysian women, Pap smear is never popular.

Pap smear coverage was less than 2% in 1992, 3.5% in 1995, 6.2% in 1996 to 47.3% in 2006; this low coverage was caused by lackluster nationwide Pap smear campaign. The public is largely unaware of the benefits of screening[19,26]. Many papers highlighted that poor coverage was caused by human factors (i.e. the negative attitude of women and health care providers, including unfriendly service). Malaysian women still had poor knowledge and awareness of cervical cancer and screening [27,28].

An article on the challenges of cervical cancer screening in Malaysia revealed that the lack of manpower and facilities of health care system contributed to poor Pap smear coverage[23]. The average doctor to (total) population ratio in Malaysia is 1:1400. The public sector hospitals, which provide care for the majority (80-90%) of the population, have shortages of specialists, doctors, nurses, and technologists. Although the service in public hospitals is free, the long waiting time affected working womenPrivacy issue, screening test procedure, unsystematic approach of follow up and result notification, call-recall system and limited resources are other reasons for the poor coverage. The focus should be on policies, improving awareness and the screening infrastructure, and making the service better accessible to women[23].

A quality Pap smear should be taken from the transformation zone (an area between the old squamocolumnar junction and the new squamocolumnar junction), and sampling should include the ecto- and endocervix. This paper quoted several papers that showed 42.8% to 70.4% of the Pap smears done in Hospital Universiti Sains Malaysia and Kota Bharu hospital was not taken from the transformation zone of the cervix, where 95% of preinvasive lesions and cervical cancers occur[26].

Eleven policy makers and health care providers from the Ministry of Health in Malaysia from October 2009 to May 2010 were interviewed. Interviewees' perceptions were explored on current and organised cervical screening program based on their expertise and experience. In their opinion, the opportunistic cervical screening program failed to address the needs assessment of the program mainly in four aspects: 1) the receiver i.e. the women's needs, accessibility and affordability, 2) providing the providers need, 3) allocating resources, coverage and providers correct attitude. Poor quality health management in terms of leadership, motivation, communication, time management and resources planning, make the service seems unfriendly, leading to failure and missed opportunities for health care providers to screen women[29].

Pap smear subsequent visits or follow up

One of the approaches that fulfilled all these criteria is an organised cervical screening program with a systematic call, recall, follow-up and surveillance system .A prospective randomised controlled study of 250 women in Klang who attended cervical screening and had a normal Pap smear in the previous year, and were due for a repeat smear were recruited and randomly assigned to four different methods of recall for repeat smear. The rates of recall messages reaching the women were 79% when using letter, 87% with registered letter, 66% with SMS and 68% with phone calls. However, direct communication via phone call was better for recalls as the positive responses to recall by telephone call was 50.9% compared to 23.9% by letter, 23.0% by registered letter, and 32.9% by phone messages ($p<0.05$)[30].

2. Knowledge and attitude

Generally, women's attitudes and beliefs towards cervical cancer and the importance of screening test will affect their uptake and compliance of Pap smear. Studies in various group of women of different ages, involving rural, urban and even university students to assess knowledge on cervical cancer, Pap smear screening, HPV infection and HPV vaccination, in the hope that the results can be used to plan strategies to prevent a potentially preventable cervical cancer. Most studies showed that the lack of knowledge seriously impacted preventive measures and attitude (Table III).

Another questionnaire survey was done on 221 cervical cancer patients at eight hospitals with gynaeoncologist, in women aged 25-85 years. Majority (56.3%) had none or only primary education and 61.1% had a household income of RM1000 or less. Forty eight percent reported never having had a Pap smear, whereas 95% did not have a smear within the past three years. The main responses for not having had a Pap smear were "Never heard about it" (36.2%), "Shy" (10.4%), "Afraid to do it" (13.1%), "Think the test is not important"(8.1%) and "No encouragement from family" (4.5%). A large majority (95.9%) of the patients did not know the optimal interval. The survey concluded, a large number of cervical cancer patients had inadequate knowledge and had not had a Pap smear within three years preceding cancer development.27The result strongly showed the need for an effective cervical screening program which is proactive, consistent, and has a systematic follow up.

Publicity / Source of Information

In one study, more than half of the participants (57.7%) mentioned that doctors/hospitals/clinics were their sources of information on Pap smear test, and 43.7% got their information from printed media such as newspapers, magazine, books and flyers, and 31.7% from electronic media such as radio and television. The workplace was the least common source (12.7%)[30]. Despite the government posting open invitations and flyers advising free Pap smear in all government clinics and hospitals and other public places, radio and television and awareness programmes organised by MOH, 96% of patients reported not knowing the recommended Pap smear screening intervals[27].

In a study among rural Southeast Asian women, half (45.7%) have heard about the vaccine from friends. The second most common source of information was the public media (31.4% television, 20% newspapers, 17.1% radio, and 10.0% magazines)[34]. In a cross-sectional study conducted from July 2008 to September 2008 in Universiti Kebangsaan Malaysia, female students of two different faculties (pharmacy and allied health science), who participated reported receiving their information from the mass media (59.1%), through health education (48.6%), and from posters in University campus (39.4%)[37].

Barriers to cervical cancer prevention (HPV vaccination and pap smear barriers)

Psychosocial aspects

Both HPV vaccination and Pap smear had challenges and barriers as shown in various studies.

Malaysian men and women receive equal educational opportunities. In 2001, 95% of girls attended primary school, and 74% continued to secondary level. In 2005, 60% of women were part of the Malaysian labour force, primarily as sales workers and clerks, 27% were housewives, and 11% were in school. The unemployment rate among women has been below 4%, and fewer than 3% were hardcore poor. Among those married, 80-85% of their husbands were working, with an average monthly income of RM1500[23].

A bilingual questionnaire was sent to 1500 secondary school teachers from 20 urban schools in Malaysia; 1166 completed questionnaires were returned. From this group, 46.1% had never heard of HPV while 50.9% had never had a Pap smear. However, 73.8% have heard of the HPV vaccine with 75% of them agreeing to have it. Almost all (96%) considered themselves religious with 79.8% of them agreeing to have the vaccine. The highest factors that influence the teachers' decision to accept the vaccine was the safety of the vaccine (84%). Other factors that affected the acceptance were its risk (55.4%), effectiveness (55%) and doctor's advice (54.4%). Less than half (35.8%) considered the 'halal-ness' of the vaccine as a factor. Only 145 (12.7%) teachers felt they have enough knowledge to counsel parents, and 670 (58.7%) felt they did not have enough knowledge to do so. Majority of the teachers (n=1104; 96.8%) felt they needed to be given more information about the vaccine. Almost all (n=1077; 94.6%) of the teachers felt the government should provide more information to educate the public about cervical cancer and the vaccine. Many (n=822; 72.3%) teachers would encourage their students to take this vaccine and 781 (68.5%) teachers would be comfortable discussing the vaccine with their students/parents. Some (n=291; 25.5%) were unsure. This review concluded that a national school-based HPV immunisation program can be implemented effectively in a multiethnic, cultural and religious country despite limited knowledge of HPV-related pathology among teachers[38]. The focus group discussion of 47 participants also showed the same concern regarding safety and side effects, cost and Muslims concerned on the 'halalness' of the vaccine[39].

Al-Dubai et al in his paper looked into the barriers of HPV vaccine in 300 participants; 131 participants (43.7%) reported non awareness of the vaccine, 120 (40%) were concerned about the side effects of the HPV vaccine, 81 (27%) of the participants were afraid of needles and 71 (23.7%) of the participants were afraid of the social stigma related to HPV vaccination. Other barriers reported by the participants were 'no time to take the vaccine' (20.3%), 'vaccine was expensive' (15.7%), 'vaccine is not reachable' (11.7%), and'vaccination was not needed because they were not sexually active' (10.7%)[19].

Physicians' experiences in providing HPV immunisation were assessed by a mailed questionnaire and 41.4% responded. Malay Muslim physicians considered cultural sensitivity an issue when recommending HPV vaccines more than paediatricians and family physicians who were more likely to agree that acceptance is better if vaccines were recommended as prevention against cervical cancer rather than a sexually transmitted disease. Almost 70% had poor success in recommending HPV vaccines in their practice, with the majority of patients preferring to postpone immunisation. Physicians reported cultural disparities in vaccine uptake. Majority (95.5%) agreed that the HPV vaccines show great promise in cervical cancer prevention in the country. Many physician think (77.3%) cost is the commonest barrier for the vaccine acceptance followed by vaccine safety and effectiveness (13.8%). Many agreed (87.0%) that the Malaysian government should introduce a school based HPV vaccination program, and 74.5% agreed that HPV vaccination of all adolescent (girls) should be made mandatory[40].

The National Health Morbidity survey (NHMS) 2006 showed that the uptake of screening was particularly low among uneducated and low-income women. In 2007, 23% of cervical cancer patients who were surveyed had no education and 38% had only primary school education. Among these patients, 36% were not familiar with the screening test, 13% were afraid of taking it, 10% felt shy, and 3% did not have their screening because they could not find a female doctor. Improving screening coverage will remain an important strategy for combating cervical cancer in Malaysia.The focus should be on the policy-making context, improving awareness and the screening infrastructure, and making the service better accessible to women. Approaches to screening must look into these factors: women or population, provider, and program or service[23,28,41].

Twenty three medical students in Shah Alam, Malaysia discussed the procedure of the Pap smear test. They found the main barriers for not performing a Pap smear test is the lack of awareness 16 (70%), shyness 12 (52%) and the cost of the test 12 (52%). Another study cited the place of screening (15.5%) and the lack of time (11.3%), lack of a female doctor, the unavailability of a hospital or clinic close by, and the loss of virginity (2.1%) as barriers[31].

A study focused on the reasons for not screening given by different population subgroups . Indian women were the least likely to have had a Pap smear test (PST) and also the least likely to know the reasons why one should be screened. Malay women were less likely than Chinese women to have received a PST and were more likely to report embarrassment as the reason for not being tested. Urban women were less likely than rural women to have been tested and more likely to state the lack of time as the reason. These results suggest targeted interventions may be necessary to increase screening rates in Malaysia[42]. A possible solution may be to implement worksite cervical screening programs in which eligible women can be easily tracked and invited to have a Pap test[43].

Cervical cancer prevention cost

In Malaysia, only 10.3% (RM32 million) of the annual expenditure was allocated for Pap smear screening while 68% (RM167 million) were used for managing invasive cervical cancer. As the average monthly income for women is RM 500 ($125), this should be affordable since Pap smears were provided free in the public health care setting, and was between RM15 and RM 25 ($4.4 to $7.4) in private healthcare. Most Malaysians can easily access any healthcare provider by land, as 96% of the population live near paved land roads[23].

The introduction of widespread vaccination of females against HPV can potentially prevent 89% of cervical cancer cases at steady rate and this could potentially lead to an annual savings of over RM45 million in terms of HPV related treatment costs[3].

However, the ultimate success of HPV vaccines in reducing the incidence of cervical cancer will be dictated by its uptake and affordability since there are no health insurance coverage for HPV vaccines. Initially, two years after the first vaccine was released in Malaysia, the administration cost (actual cost of the HPV vaccine plus vaccine administration cost) was approximately RM400 per dose. Vaccination uptake of about 80% was required for "herd immunity." The median household monthly income in the present study population was RM1700. Their perceived savings per month was only RM205.69. The estimated cost of treatment was RM 1200 for the full course of vaccine and RM400 per injection, which is equal to almost 25% of their monthly income[28]. How many women can afford this?

DIAGNOSIS AND PATHOLOGY

HPV DNA testing

HPV DNA testing can be used as triage. This study compared the performance of nested MY/*GP* Polymerase Chain Reaction (PCR) and FDA approved-Hybrid Capture II (HClI) using clinical cervical scrapings from 40 patients. It was found that PCR was more sensitive (81.8%) compared to HCII (36.4%) in detecting HPV, but the specificity of HClI was much higher (96.6%) than PCR (58.6%). The Negative Predictive Value (NPV) of both the techniques were quite similar but Positive Predictive Value (PPV) of HClI was much higher (80.0%) compared to PCR (42.9%). While the HCII method showed good specificity for HPV detection, it is less sensitive than PCR[44]. Another study of 200 cervical swab samples by Chong also concluded that PCR was a reliable method to detect HPV[11]. Both studies concluded that PCR was an ideal and reliable method for detecting HPV from clinical samples.

A study that compared conventional Pap smear to split sampling using ThinPrep® smears, found split sampling from discarded sampling devices after conventional Pap smear retain adequate sample cells for diagnostic purposes[45].

Biomarkers in cervical cancer

Proteomics in cancer research may uncover potential biomarkers of cervical cancer. This study identified 18 proteins to be differentially expressed in the plasma of CIN 3 and SCC stage IV samples. The expression of cytokeratin 19 and tetranectin could be explored for further role in cervical cancer treatment and monitoring[46].

A clinicopathological immunohistochemistry study from 40 hysterectomy specimens to predict the aggressiveness of adenocarcinoma of cervix found that certain subset p21WAF1 expression is significantly associated with infiltration of the corpus and lymph node metastasis. p27Kip1 expression is significantly associated with lymph node invasion. The presence of lymph node metastasis is strongly associated when p16INK4a and p27Kip1 expressions are analysed in combination[47].

In a study of 109 cases of 29 low squamous intraepithelial lesion (LSIL), 27 high squamous intraepithelial lesion (HSIL) and 53 squamous cell carcinoma (SCC), diffuse continuous staining with p16INK4a involving >75% of LSIL or HSIL and SCC was noted in 1 (3.4%) LSIL, 24 (88.9%) HSIL, 46 (86.8%) SCC. The increased p16INK4a immunopositivity in HSIL and SCC appears in line with the integrated existence of the hrHPV and may provide more insightful information on risk of malignant transformation of cervical squamous intraepithelial lesions than mere hrHPV detection[48].

Immunohistochemical stain was used to study the involvement of Bcl-2 and Bax proteins in cervical carcinogenesis. Sixteen low grade (LSIL), 22 high grade (HSIL) squamous intraepithelial lesions, 28 invasive (13 stage I and 15 stage II-IV) squamous cell carcinoma (SCC) and 15 benign cervices were immunohistochemically studied. 4-µm sections of the cases were immunostained for Bcl-2 (Clone 124: Dako) and Bax (Dako) and staining intensity was rated as 1 (light), 2 (moderate) and 3 (strong) and percentage cellular staining as 0 (negative), 1 (1-25%), 2 (26-50%), 3 (51-75%) and 4 (>75%). Bcl-2 and Bax appeared to be upregulated at different stages of cervical carcinogenesis, Bcl-2 in HSIL and Bax after invasion. Intensification of staining of Bcl-2 at the basement membrane in some HSIL and SCC may augur for increased aggressiveness[49].

In a retrospective study on 61 cases of cervical neoplasms comprising 25 cases of CIN 3 and 36 SCC, all cases were evaluated by immunohistochemistry using Ki-67 and p53 monoclonal antibodies. Results showed that the differences of Ki-67 and p53 expression between CIN 3 and SCC were statistically significant. In conclusion, Ki-67 and p53 may serve as helpful adjuncts to routinely-stained histological sections in differentiating between CIN 3 and SCC[50].

An automated cervical pre-cancerous diagnostic system was proposed to be developed to reduce detection error due to poor diagnostic skill of the cytotechnologists and cytopathologists. The automatic diagnostic system used a new algorithm that is referred as region-growing- based features extraction (RGBFE) to extract the features of cervical cell (i.e. size of nucleus, size of cytoplasm, grey level of nucleus and grey level of cytoplasm). These features will then be fed into the H2MLP network, which classify the cervical cells into normal, LSIL or HSIL cell. The effectiveness of the proposed diagnostic system has been demonstrated empirically using 550 reported Pap smear tests[51].

In a study evaluating Fourier transform infrared (FTIR) spectroscopy as a new tool for screening of cervical cancer compared with cervical cytology (gold standard), a total of 800 cervical scrapings were taken by cytobrush and placed in ThinPrep medium. The samples were dried over infrared transparent matrix. Beams of infrared light were directed at the dried samples at frequency of 4000 to 400 cm-1. The absorption data were produced using a Spectrum BX II FTIR spectrometer. Data were compared with the reference absorption data of known samples using FTIR spectroscopy software. The results showed the sensitivity was 85%, specificity 91%, positive predictive value 19.5% and negative predictive value of 99.5%. This study suggests that FTIR spectroscopy could be used as an alternative method for screening for cervical cancer[52].

Role of imaging

This retrospective study that was aimed at evaluating the role of CT scan in predicting parametrium involvement in the early stage of cervical carcinoma was conducted in a Gynaecologic Oncology Centre, Hospital Alor Star from January 2004 till December 2008. All 104 patients with operable stage I and II cervical cancer had pelvic CT scan for evaluation of parametrium involvement. Parametrial streakiness or presence of infiltration suggested local invasion. Following radical hysterectomy, the specimens were sent for histological confirmation, and the correlation between CT scan finding and the histopathology result was studied. The result revealed the sensitivity and the specificity of CT scan in assessing parametrial involvement was 33.3% and 84.8%, respectively; indicating that CT scan had high specificity but low sensitivity in determining parametrial involvement in early stage of cervical cancer[53].

PRESENTATION AND TREATMENT

A questionnaire survey showed that 181/221 stages known cases, 76% of all cases were diagnosed in FIGO stage 2 or higher[23,27]. A USM study showed only 21% was diagnosed at stage 1 with majority of the cases were diagnosed at stage II onwards[54]. A retrospective study of 444 cervical cancer patients by Al Junid et al showed that 64.4% of cases were at either stage I or stage II disease and the occurrence of disease is strongly related to age[3]. This study showed that 34.5% of cases occurred in women aged 50-59 years old compared to NCR peak age 60-65 years old. Al Jashamy reported a retrospective study of 77 cervical cases from the histopathology laboratory of Ipoh hospital from 1st January, 2005 to 31st December, 2006This study showed cervical intraepithelial neoplasia (CIN) was found in 33/77 (42%) cases, cervical carcinoma in 12/77 (15.6 %)cases and metastatic squamous cell carcinoma in 10 /77 (13.0%) cases and adenocarcinoma in 13/77(17%)cases, CIN III accounting for 27%, and 5% each for CIN I, CIN II and CIN II-III. The highest rate for CIN was in the 41-50 year age group (43%) and the lowest rate was in the group aged 61-70 years (6%)55. Another study among 8 major hospitals showed squamous cell carcinoma was commonest (76.1%) and adenocarcinoma was 17.6%[27].

OUTCOME

A retrospective study by Hospital Universiti Sains Malaysia to determine the five-year survival rate among patients with cervical cancer who were treated, found that the overall five-year survival was 39.7% (median survival time of 40.8 months). The log-rank test showed that there were significant survival differences between the groups, stage at diagnosis (p=0.005); and primary treatment (p=0.0242). Late stage (III-IV) had the lowest survival (18.4%) compared to stage I (54.7%) and II (40.8%).The five-year survival was statistically significantly higher in patients who received surgery (52.6%) compared to non-surgical treatment[54].

In one study review of 55 patients with FIGO IB1 lymph nodes negative cervical cancer managed from 1997-1999 post radical hysterectomy, adjuvant RT was tailored according to the Gynecology Oncology (GOG) risk score. Radiotherapy (RT) was omitted for patients with risk score < 40 (RS); RS >40 to <120 were given modified field RT; and RS > 120 were given standard field RT. This study showed the adjuvant RT to patients with RS 120 significantly improved their five-year recurrence rate and disease free survival[56].

Table I: Human papillomavirus and cervical cancer in Malaysia

	Summary	HPV detection	HPV 16	HPV 18
Cheah PL[7]	a. 29 invasive squamous cell carcinoma (SCC) (between 1 January 1991 and 31 December 1992)	17/29 (58.6%)	16 (55.1%)	1 (3.44%)
	b. 43 cases invasive SCC (between 1 January 1995 and 31 December 2000)	38/43 (88.4%)	21/43 (48.8%)	5/43 (11.6%)
Al Junid[4]	Data on HPV type and distribution were derived from Castellsague et al. 2007 and the WHO/ICO Information Centre on HPV and Cervical Cancer		74.9% detected HPV 16/18	
Sharifah Noor Akmal *et al*[8]	UKMMC-38 abnormal smear	95% HR HPV detected	9 (23.7%)	2 (5.2%)

Table II: Prevalence of HPV infection from cervical swab samples

		HPV detection	HPV 16	HPV 18
Chong *et al*[11]	200 cervical swabs (180 qualified for PCR analysis) from March 2007 until September 2007 from women who underwent Pap smear screening from the Gynaecology and Obstetrics Clinics in several hospitals in Southern Selangor and Health clinics.	84/180(46.6%)	72 (85.7%)	6 (7.1%)
Tay[10]	2364 cervical swab samples from women attending obstetric and gynaecological clinics in Southern Malaysia and Singapore.	280 (24.3%) HPV detected	606 (25.6%) positive for high-risk HPV DNA	
	1153 liquid base and HPV DNA simultaneously –(HPV DNA genotypes not performed)	25 (8.9%) has intraepithelial abnormalities 3HSIL (1.08%)		

Sivanesaratnam, in his review of pregnant mothers with malignant conditions, recommended colposcopy and a directed biopsy if an abnormality was detected at colposcopy. If this reveals normal histology, re-evaluation can be done 8 weeks after delivery. If the biopsy reveals CIN, repeat cytology and colposcopy every 6±8 weeks, repeat biopsy if disease progressed. Performing a cold knife cervical cone procedure during pregnancy can cause significant morbidity, excessive cervical bleeding in 5±15% and up to 25% spontaneous abortion rate. For stage 1B and early 11A lesions, radical hysterectomy and pelvic lymphadenectomy are the preferred method of treatment. Before 20 weeks of pregnancy, radical surgery is carried out without delay with the foetus in utero. Between 20 and 32 weeks' gestation, treatment may be delayed until the foetus has better survival, delivered via a high classical caesarean section before radical hysterectomy, avoiding surgery on the lower uterine segment and cervix during delivery. Vaginal delivery carries the risk of the dissemination of malignant cells into lymphatics or vascular channels. Radiotherapy is an effective therapy for cervical cancer in pregnancy; the complications were similar to those in non-pregnant patients[57].

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Cervical cancer is preventable. A combination of HPV vaccination and Pap smear screening programmmes was shown to be cost effective to prevent cervical cancer. There is a large gap in knowledge, attitude and practices among Malaysian women on cervical cancer screening. Even with adequate knowledge, this was not translated to practice. There is a need to individualise/ personalise the approach as well as continue with public awareness to ensure the women come for the screening and also has support to do so.

The psychosocial aspect and economic burden formed a difficult barrier that affect cervical cancer screening and prevention programme. There is a need to find alternative approach to increase Pap smear coverage to 70-80%, improve follow-up or explore possibilities of screening for HPV infection as an alternative or additional to Pap smear. There is a need to look into incorporating healthcare activities, i.e. promoting and performing Pap smear or HPV DNA cervical sampling during home visits or work place visits, having a dedicated team, and following the school health team system.

The study's recommendations that should be considered include promoting awareness among medical practitioners, and including men in promotional campaigns. Employees (including men) from both government and private sectors should be reminded about screening. Another recommendation is linking with data of the National Registration Department, so that women could be invited for screening at regular intervals after they reach the eligible age[12].

SECTION 3: FUTURE RESEARCH DIRECTION

There is a large gap in clinical research on cervical cancer. Areas such as cervical cancer presentation, investigations and managements could be studied. In terms of cervical cancer treatment, patients should have more options, for example radical surgery and adjuvant chemotherapy, for women who refused radiotherapy. The taboos of modern treatment and belief in traditional complementary medicine can be explored to curb the misconception of cervical cancer treatment, as there were patients who, although were diagnosed early, delayed treatment for traditional options and only presented to hospital at an advanced stage; thus leading to poorer prognosis. There is also a need to explore other screening methods such as cervical smear self sampling for HPV DNA screening that could possibly increase screening coverage.

Table III: Summary of some of the studies on knowledge and attitude of Pap smear screening

Studies	Summary	Results	Reasons
Cross sectional descriptive study[31]	A convenience sample of 142 women aged 18 to 70 years at Tengku Ampuan Rahimah Hospital, Klang, in Selangor, Malaysia. Data collection in September 2011 till January 2012.	72.5% had heard about Pap smear test 57.7% got their information from doctors, 43% from printed material, and 31% from the media.	The barriers to Pap smear test include place of screening (15.5%) which was mentioned as the main barrier, followed by the lack of time (11.3%).
Focus group discussion-perception of medical students[32]	23 medical students from International Medical School, Management and Science University, Shah Alam.		Main barriers for women are the lack of awareness (n=16; 70%), followed by shyness (n=12;52%) and the cost of the test (n=12;52%).
Cross-sectional design[33]	A total of 287 female university students (response rate of 95.9%) from the Management and Science University (MSU), Shah Alam.	61-77% provided the correct answer.	The most common barriers were the worrying about the test (95.8%), followed by lack of encouragement or information from healthcare workers (61.2%).
A cross-sectional household survey[34]	231 women in Petaling Jaya city in 2007. The association between risk perceptions of cervical cancer and screening practice.	14% have had Pap test Women had limited knowledge on the established risks for cervical cancer.	Majority perceived certain types of food (instant noodles or chemical substances embedded in foods); smoking; taking drugs; family history; side effects of hormone replacement therapy; adultery; cleanliness of both husband and wife; environmental or air pollution; use of public toilets; poor feminine hygiene; contraceptive use, unclean abortion; frequent sex' and sexual activities against the norm of religion as risks for cervical cancer.
A questionnaire Survey[35]	403 female teachers from 40 public secondary schools in Malaysia selected by cluster random sampling Jan-March 2010.	62% never had Pap smear. This means that regardless of a participant's educational level and employment status, school teachers also perceived Pap smear screening test negatively, consistent with most of the studies which cited factors such as embarrassment, shyness, reluctance, and time-consuming service.	Reasons: shy, afraid, don't know, no information, no awareness 59-74%.
Cross sectional study[36]	280 women from Mukim Jaya Setia Kota Bharu, Kelantan.	51.4 % had Pap smear screening, Impact of Health care worker campaigns.	3 main reasons for not screening were unawareness (36.7%), unnecessary (23.7%), and lack of time (13.7%).

ACKNOWLEDGEMENT

I would like to sincerely thank the Director-General of Health, Malaysia for his permission to publish this paper. I wish to thank the Clinical Research Centre team for its contribution and support.

REFERENCES

1. Malaysian National Cancer Registry Report (2003). Ministry of Health, Malaysia.
2. Devi Beena CR, Tang TS, Gerard LC. Preliminary results from the pilot study on the National Cancer Patient Registry--Cervical Cancer. Med J Malaysia 2008; 63 Suppl C: 63-65.
3. Sharifa Ezat WP, Syed Aljunid. Cost-effectiveness of HPV vaccination in the prevention of cervical cancer in Malaysia. Asian Pac J Cancer Prev 2010; 11(1): 79-90.
4 Syed M Aljunid, Zafar A, Saperi S, *et al.* Burden of disease associated with cervical cancer in Malaysia and potential costs and consequences of HPV vaccination. Asian Pac J Cancer Prev 2010; 11(6): 1551-1559.
5. Shanthi V, Majdah M, Syed Aljunid, *et al.* Cervical cancer in Malaysia: can we improve our screening and preventive practice? BMC Public Health 2012; 12(Suppl 2): A17.
6. Gravitt PE. The known unknowns of HPV natural history. J Clin Invest 2011; 121(12): 4593-4599.
7. Cheah PL, Looi LM, Sivanesaratnam V. Human papillomavirus in cervical cancers of Malaysians. J Obstet Gynaecol Res 2011; 37(6): 489-495.
8. Sharifah Noor Akmal, Seeni A, Nurismah M, *et al.* Prevalence of human papillomavirus in abnormal cervical smears in Malaysian patients. Asian Pac J Cancer Prev 2009; 10(2): 303-306.
9. Quek SC, Lim BK, Domingo E, *et al.* Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical intraepithelial neoplasia across 5 countries in Asia. Int J Gynecol Cancer 2013; 23(1): 148-156.
10. Tay SK, Tay YK. The prevalence and significance of high-risk human papillomavirus DNA test in southern Malaysia and Singapore. Aust N Z J Obstet Gynaecol 2009; 49(3): 323-327.
11. Chong PP, Asyikin N, Rusinahayati M, *et al.* High prevalence of human papillomavirus DNA detected in cervical swabs from women in southern Selangor, Malaysia. Asian Pac J Cancer Prev 2010; 11(6): 1645-1651.

12. Hesham R, Syarif Husin L, Kiat AN. Knowledge of cervical cancer and acceptance of HPV vaccination among secondary school students in Sarawak, Malaysia. Asian Pac J Cancer Prev 2011; 12(7): 1837-1841.
13. Rashwan H, Ishak I, Sawalludin N. Knowledge and views of secondary school students in Kuala Lumpur on cervical cancer and its prevention. Asian Pac J Cancer Prev 2013; 14(4): 2545-2549.
14. Al-Naggar RA, Bobryshev YV, Al-Jashamy K, *et al.* Practice of HPV vaccine and associated factors among school girls in Melaka, Malaysia. Asian Pac J Cancer Prev 2012; 13(8): 3835-3840.
15. Hesham HR, Nur Zakiah, N Mohd Saat, Dahlia Nadira AM. Knowledge, attitude and practice of malaysian medical and pharmacy students towards human papillomavirus vaccination. Asian Pac J Cancer Prev 2012; 13(5) :2279-2283.
16. Al-Naggar RA, Bobryshev YV. Practice towards human papillomavirus vaccines among Malaysian women: a survey of a general youth population. Asian Pac J Cancer Prev 2011; 12(8): 2045-2049.
17. Wong LP. Knowledge and attitudes about HPV infection, HPV vaccination, and cervical cancer among rural southeast Asian women. Int J Behav Med 2011; 18(2): 105-111.
18. Wong LP, Sam IC. Ethnically diverse female university students' knowledge and attitudes toward human papillomavirus (HPV), HPV vaccination and cervical cancer. Eur J Obstet Gynecol Reprod Biol 2010; 148(1): 90-95.
19. Al-Dubai SAR, Alshagga MA, Al-Naggar RA, *et al.* Knowledge, attitudes and barriers for human papilloma virus (HPV) vaccines among Malaysian women. Asian Pac J Cancer Prev 2010; 11(4): 887-892.
20. Sam IC, Wong LP, Rampal S, *et al.* Maternal acceptance of human papillomavirus vaccine in Malaysia. J Adolesc Health 2009; 44(6): 610-612.
21. Saidatul Norbaya Buang, Introduction of National HPV immunization program: sharing Malaysia Experience presented at Global Meeting on cervical cancer prevention programme 29 Nov-2 Disember 2010.
22. Sharifa Ezat WP, Syed Aljunid. Comparative cost-effectiveness of HPV vaccines in the prevention of cervical cancer in Malaysia. Asian Pac J Cancer Prev 2010; 11(4): 943-951.
23. Nor Hayati O, Rebolj M. Challenges to cervical screening in a developing country: the case of Malaysia. Asian Pac J Cancer Prev 2009; 10(5): 747-752.
24. Woo YL, Omar SZ. Human papillomavirus vaccination in the resourced and resource-constrained world. Best Pract Res Clin Obstet Gynaecol 2011; 25(5): 597-603.
25. Khoo CL, Teoh S, Abdul Rashid Khan, *et al.* Awareness of cervical cancer and HPV vaccination and its affordability among rural folks in Penang Malaysia. Asian Pac J Cancer Prev 2011; 12(6): 1429-1433.
26. Nor Hayati O. Cancer of the cervix - from bleak past to bright future; a review, with an emphasis on cancer of the cervix in malaysia. Malays J Med Sci 2003; 10(1): 13-26.
27. Nor Hayati O, Beena CD, Halimah Y. Cervical cancer screening: patients understanding in major hospitals in Malaysia. Asian Pac J Cancer Prev 2009; 10(4): 569-574.
28. Wong LP, Wong YL, Low WY, *et al.* Cervical cancer screening attitudes and beliefs of Malaysian women who have never had a pap smear: a qualitative study. Int J Behav Med 2008; 15(4): 289-292.
29. Fauziah A, Su TT. Enhancement of the cervical cancer screening program in Malaysia: a qualitative study. Asian Pac J Cancer Prev 2010; 11(5): 1359-1366.
30. Rima Marhayu AR, Majdah M, Zaleha AH, *et al.* Is the phone call the most effective method for recall in cervical cancer screening? - results from a randomised control trial. Asian Pac J Cancer Prev 2013; 14(10): 5901-5904.
31. Al-Naggar, Practice and Barriers towards Pap Smear test from a public Hospital in Malaysia. J Community Med Health Edu 2012, 2:3.
32. Al-Naggar RA, Zaleha MI. Perception and opinion of medical students about Pap smear test: a qualitative study. Asian Pac J Cancer Prev 2010; 11(2): 435-440.
33. Al-Naggar RA, Low WY, Zaleha MI. Knowledge and barriers towards cervical cancer screening among young women in Malaysia. Asian Pac J Cancer Prev 2010; 11(4): 867-873.
34. Wong YL, Chinna K, Mariapun J, *et al.* Correlates between risk perceptions of cervical cancer and screening practice. Prev Med 2013; 57 Suppl: S24-6.
35. Fauziah A, Norlaili AA, Su TT. Factors related to poor practice of Pap smear screening among secondary school teachers in Malaysia. Asian Pac J Cancer Prev 2011; 12(5): 1347-1352.
36. Asmani AR , Aziah D Pap smear practice among women in Mukim Jaya Setia, Kelantan. Malaysia Journal of Public Health Medicine 2007,vol 7 (1): 20-24.
37. Tan YY, Hesham R, Qodriyah HM. Knowledge and attitude of university students in health sciences on the prevention of cervical cancer. Med J Malaysia 2010; 65(1): 53-57.
38. Woo YL, Sharina MR, Chong KR, *et al.* Does the success of a school-based HPV vaccine programme depend on teachers' knowledge and religion? -- A survey in a multicultural society. Asian Pac J Cancer Prev 2012; 13(9): 4651-4654.
39. Wong LP. Preventing cervical cancer through human papillomavirus vaccination: perspective from focus groups. J Low Genit Tract Dis 2009; 13(2): 85-93.
40. Wong LP. Physicians' experiences with HPV vaccine delivery: evidence from developing country with multiethnic populations. Vaccine 2009; 27(10): 1622-1627.
41. Mohd Rushdan MN. Current status and future direction of cervical cancer prevention program in Malaysia. 2008.
42. Richard A. Dunn , Andrew K.G. Tan Cervical cancer screening in Malaysia: Are targeted interventions necessary?Social Science & Medicine 71 (2010) 1089-1093.
43. Fauziah Abdullah, Michael O'Rorke, Liam Murray, and Tin Tin Su. Evaluation of a Worksite Cervical Screening Initiative to Increase Pap Smear Uptake in Malaysia: A Cluster Randomized Controlled Trial : BioMed Research InternationalVolume 2013 (2013), Article ID 572126, 7 pages http://dx.doi.org/10.1155/2013/572126
44. Saini R, Shen TH, Othman NH, *et al.* Evaluation of polymerase chain reaction (PCR) method and hybrid capture II (HCII) assay for the detection of human papillomavirus in cervical scrapings. Med J Malaysia 2007; 62(3): 206-209.
45. Norodiyah O, Othman NH. Adequacy of cellular material in split-sampling of cervical scrapings for routine cancer screening: an analysis of 702 smears. Malays J Pathol 2012; 34(2): 115-121.
46. Looi ML, Karsani SA, Rahman MA, *et al.* Plasma proteome analysis of cervical intraepithelial neoplasia and cervical squamous cell carcinoma. J Biosci 2009; 34(6): 917-925.
47. Farveen Marican AB, Nik Raihan NM, Nor Hayati O. Clinicopathological comparison of adenocarcinoma of cervix and endometrium using cell cycle markers: P16ink4a, P21waf1, and p27Kip1 on 132 cancers. Infect Dis Obstet Gynecol 2011; 2011: 857851.
48. Cheah PL, Looi LM, KH Teoh, KS Mun, Abdul Rahman Nazarina p16INK4a is a Useful Marker of Human Papillomavirus Integration and Risk Stratification Asian Pacific J Cancer Prev, 13, 469-472)
49. Cheah PL, Looi LM. Significance of Bcl-2 and Bax proteins in cervical carcinogenesis: an immunohistochemical study in squamous cell carcinoma and squamous intraepithelial lesions. Malays J Pathol 2006; 28(1): 1-5.
50. Tan GC, Sharifah Noor Akmal, Shiran MS, *et al.* Utility of Ki-67 and p53 in distinguishing cervical intraepithelial neoplasia 3 from squamous cell carcinoma of the cervix. Asian Pac J Cancer Prev 2008; 9(4): 781-784.
51. Mat-Isa NA, Mashor MY, Othman NH. An automated cervical pre-cancerous diagnostic system. Artif Intell Med 2008; 42(1): 1-11.
52. Shady G El –Tawil, Rohana A, Zaki N.Muhamed , Norhayati O. Comparative study between Pap smear cytology and FTIR spectroscopy:a new tool for screening for cervical cancer, Pathology (October 2008) 40(6), pp. 600–603.
53. Mohamad Nasir S, Nazimah I, Rushdan MN. The Role of Computed Tomography (CT) Scan in Assessment of the Parametrial Involvement in Early Stage Cervical Carcinoma. Journal of Surgical Academia 2012; 2(1): 14.
54. Nuradhiathy AR, Khattak M, Yong Zulina Z, *et al.* Estimating the five-year survival of cervical cancer patients treated in hospital universiti sains malaysia. Asian Pac J Cancer Prev 2013; 14(2): 825-828.
55. Al-Jashamy K, Al-Naggar RA, San P, *et al.* Histopathological findings for cervical lesions in Malaysian women. Asian Pac J Cancer Prev 2009; 10(6): 1159-1162.
56. Rushdan MN, Tay EH, Khoo-Tan HS, *et al.* Tailoring the field and indication of adjuvant pelvic radiation for patients with FIGO stage Ib lymph nodes-negative cervical carcinoma following radical surgery based on the GOG score--a pilot study. Ann Acad Med Singapore 2004; 33(4): 467-472.
57. Sivanesaratnam V. Management of the pregnant mother with malignant conditions. Curr Opin Obstet Gynecol 2001; 13(2): 121-125.

A Review of Depression Research in Malaysia

Ng Chong Guan, MPM

Department of Psychological Medicine, Faculty of Medicine, University Malaya, 50603 Kuala Lumpur.

SUMMARY

Depression is a debilitating illness and has become a leading cause of morbidity globally. We aim to summarise the evidence available in regard to the prevalence, type of assessment tools used and treatment options for depression in Malaysia. Two hundred and forty seven articles related to depression were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. Fifty seven articles were selected and reviewed on the basis of clinical relevance and future research implications. Findings were summarised, categorised and presented according to prevalence of depression, depression in women, depression in clinical condition, assessment tools, and treatment of depression. The prevalence of depression in Malaysia was estimated to be between 8 and 12%. The figures were higher among women of low socio-economic background or those with comorbid medical condition. The common assessment tools used in Malaysia include Beck Depression Inventory (BDI), Depression, Anxiety and Stress Scale (DASS), Patient Health Questionnaire 9 (PHQ-9) and Hospital Anxiety and Depression Scale (HADS). They were translated into the Malay language and their psychometric properties were established. Both pharmacological treatment and psychotherapy were commonly used in Malaysia, and were highly recommended in local clinical practice guidelines. There are discrepancies in the reported rates of depression in Malaysia and this needs to be addressed. There were lack of studies looking into the depression among subgroups in Malaysia especially in the male population. There were several instruments available for assessment of depression in Malaysia but their suitability for the local setting need further research. Both pharmacotherapy and psychotherapy were recommended in the local treatment guideline in Malaysia. With the emergence of generic medication, we need to compare their clinical efficacy and tolerability with original products.

KEY WORDS: *Depression, prevalence, instrument, treatment, Malaysia*

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY

Depression is one of the most common mental disorders worldwide[1]. It is characterised as deterioration from previous function with the presence of psychological complaints such as depressed mood, loss of interest or pleasure, feelings of worthlessness or guilt and recurrent thoughts of death or suicide, together with somatic symptoms which include significant weight change, sleep disturbance, physical agitation or retardation, fatigue and inability to concentrate[2]. Depression has become a leading cause of morbidity over the past decades. It is projected that depression, will be among the major causes of worldwide disability by the year 2020 and the highest disorder in high income countries[3].

In Malaysia, national surveys were conducted in community households by trained medical professionals every decade; and these surveys found that mental health problems had increased from 10.7% in 1996 to 11.2% in 2006[4,5]. In the National Health Morbidity Survey IV (NHMS IV) 2011 report, the prevalence of lifetime depression was 2.4% and current depression was only 1.8%6. The figures were surprisingly low and could be related to under-reporting by the informants and the poor validity of assessment tools. This survey also found that depression was high in urban areas, and among females, Indians, widowed, singles, divorced and those with lower education[6].

In view of its high prevalence and morbidity, depression has become a popular topic of research in Malaysia. Various studies have been conducted to look into the prevalence, risk factors, treatment options and outcome of depression in different populations in Malaysia.

According to the review article by Firdaus and Tian, the prevalence of depression in Malaysia varied from 3.9 to 46%. The authors advised caution about the interpretation of the result as some studies used depressive symptoms, while others used current depression or lifetime depression[7]. In addition, the studies used different scales and involved different populations. In the context of geographical variation, there were differences in the ethnic composition, economic growth and cultural background among different states in Malaysia. A study conducted by Siti et al in Selangor, one of the most developed states in Malaysia, showed that the prevalence of depression was 10.3%. In the study, Patient Health Questionnaire 9 (PHQ-9) with the cut-off score of 10 or more was used to determine the presence of depression[8]. This finding showed a slightly higher rate than a prior study by Sherina et al (8.3%), which also used a similar scale and was conducted among adult women in Selangor[9]. However, another study by Sidik et al, conducted in the government clinic in Selangor, reported the prevalence of depression as 12.1%[10]. This was in line with the finding of a study done in a poor urban district area in Selangor, in which the reported prevalence of depression was 12.3%[11].

As comparison, a study by Wong et al, was conducted in the rural area in the East Coast of Malaysia. The aim of the study was to determine the rate of anxiety and depression among the rural folk in Malaysia using the Hospital Anxiety and Depression Scale (HADS)[12]. Results from the study showed that the rate of depression in the rural community was 11.3% and surprisingly corresponded with the studies involving urban or

Corresponding Author: chong_guan1975@yahoo.co.uk

metropolitan communities in Malaysia. Overall, the prevalence of depression in the general population in Malaysia is about 8 to 12 % regardless of the geographical differences of the study settings.

RISK FACTORS

Depression in Women and during Pregnancy

Most studies found that mental illness was more prevalent in women. This could be associated with the hormonal changes in women during the fertility, pregnancy, and menopausal period[13]. In addition, there was generally higher level of stress in women due to their multitasking responsibilities. Most women, especially for those staying in the urban area have to juggle their job and household duties. In the long run, this creates an unbearable amount of mental burden for the women.

Based on the Malaysian National Health and Morbidity Survey (NHMS), the prevalence of poor mental health among Malaysian women was increased from 11.2 % to 12.1% within a decade[4,5]. Study by Sherina et al, showed that the prevalence of depression among Malaysian women was 8.3% and significantly associated with history of miscarriage within the past 6 months or absence of formal education[9]. In a subsequent study in a different setting, the authors found that the prevalence was as high as 12.3% and associated with social factors such as financial problem, parent-child relationship, family relationship, work stress and history of serious illness[10]. The figure was much higher in women a from low socio-economic background. A study by Omar Din and Mohd Noor, which involved Malay women from rural and urban areas of low socio-economic status showed that the prevalence of current depression was as high as 34.5% and lifetime prevalence of depression was 27.5%[14].

The occurrence of mood changes after delivery which is generally known as postpartum blues is common[15]. If the condition becomes severe and lasts longer than expected, it is considered postpartum depression. It has deleterious effects on the mother. There were two review reports of the prevalence of postpartum depression in Malaysia. The first review paper by Klainin P, Arthur[16] compared the prevalence of postpartum depression across Asian countries. A total of 64 studies from 17 countries were included in the review. One of the Malaysian studies displayed the lowest rate of postpartum depression (6.5%) but another study reported a prevalence as high as 22.8%16. These findings corresponds with the results of the second review paper by Firdaus and Tian[7]. There are various biological and psychological models postulated to explain postpartum depression. The physiological changes in the women during and after pregnancy were believed to contribute to the emotional changes[13]. The lack of self-control, learned helplessness and distorted thought processes in post-delivery women are some of the psychological models for postpartum depression[17,18,19].

Depression in Patient Groups

Existing medical conditions or chronic illnesses cause a lot of stress to the patients. As a result, depression is a common comorbidity in patients with chronic diseases. The co-existence of both conditions worsen the illness outcome and quality of life, reduce compliance to medication, and delay the recovery process of the patients. A study by Hairi et al, found that a higher proportion of older people with combined chronic diseases and depressive symptoms reported having functional limitation (44.7%) compared with older people with chronic diseases alone (12.5%) and depressive symptoms alone (18.1%)[20].

Diabetes mellitus is a common medical condition in Malaysia. A study by Kaur et al, was conducted in 12 government clinics in Klang Valley, Malaysia to determine the prevalence of depression, anxiety and stress in diabetic patients. The results showed that the prevalence of depression was 11.5% which was not higher than the findings in community studies[21]. In contrast, another study by Ng showed that the prevalence of depression in diabetic patients was high as 22%[22]. The prevalence of depression was even higher in post stroke patients where the figure reported was 36% by Sulaiman et al and 66% by Glamcevski II *et al*[23,24]. This finding is similar with the study on vascular dementia patients by Khoo et al, in which the reported prevalence of depression was 31.6%[25].

Overall, the prevalence of depression was significantly higher in patients with comorbid clinical condition as compared to the general community. However, there were lack of comparison studies between the two groups in Malaysia. Zuraida *et al* conducted a case control study to compare the prevalence of depression in patients with headache. The findings showed that the lifetime prevalence of major depression among the subjects with headache was 17% (n=18) vs 0.9% (n=1) among the controls. The current prevalence of major depression was 8.4% (n=9) among the subjects vs 0% among the controls[26].

Assessment Tools

Various assessment tools have been developed for the measurement of depression. Beck Depression Inventory was one of the most common tools used in Western studies. A review of the assessment tools used for depression in Malaysia were done by Firdaus and Tian. The common tools used were Beck Depression Inventory (BDI), Depression, Anxiety and Stress Scale (DASS), Patient Health Questionnaire (PHQ), and Hospital Anxiety Depression Scale (HADS)[27].

All of the tools developed from the Western setting were in English. The applicability of the instruments in Malaysia was restricted by the language and cultural influence. Thus, it is important to translate the instruments into local languages if possible and establish their validity and reliability in the local setting in Malaysia.

Beck Depression Inventory II was translated into the Malay Language and its psychometric properties were studied by Wan Mahmud et al among a group of postpartum women in Malaysia. The findings showed that the internal reliability of the tool was high (Cronbach alpha =0.89). The tool also showed a good discriminant and concurrent validity[28].

The validation study of Malay version of DASS 21 was done by Ramli *et al.* The results showed that Malay version of DASS-21 had very good Cronbach's alpha values of 0.75, 0.74 and 0.79, respectively for depression, anxiety and stress subscales. For construct validity, it also had good factor loading values for 17 out of 21 items[29].

Criterion validity study of PHQ was conducted by Sherina et al in a primary care setting in Malaysia. The PHQ-9 was validated in the Malay language against the Composite International Diagnostic Interview (CIDI) depression module. The results showed that the PHQ-9 had a sensitivity of 87% (95% confidence interval 71% to 95%), a specificity of 82% (74% to 88%), positive Likelihood Ratio (LR) of 4.8 (3.2 to 7.2) and negative LR of 0.16 (0.06 to 0.40). The authors concluded that the Malay version of the PHQ-9 was a valid and reliable case-finding instrument for depression.

The psychometric properties of the Malay version of HADS were done by Nasir et al among husbands of cancer patients in Kuala Lumpur, Malaysia. The findings demonstrated the scale's excellent internal consistency, with Cronbach's alpha of 0.88 for the Anxiety subscale and 0.79 for the Depression subscale. The Malay version of HADS was recommended as an appropriate tool to measure depression and anxiety in Malaysia[31].

MANAGEMENT AND OUTCOME

There were not many investigator-initiated studies on the treatment of depression in Malaysia. The review article by Firdaus and Tian, found that, until 2007, there were only 12 studies on the treatment outcomes of depression in Malaysia[27]. Out of these, 8 were randomised controlled trials. There was a recent study examining the efficacy of methylphenidate as add on therapy to mirtazapine for the treatment of depression in cancer patients and a positive rapid response was found in the intervention group[32].

In Malaysia, the Ministry of Health with the collaboration of the Academy of Medicine and Malaysian Psychiatric Association had introduced a Clinical Practice Guideline (CPG) for the Management of Depression[33]. The guideline was developed to provide evidence-based guidance to manage major depressive disorder (mild/moderate/severe) in adults and the elderly. The guideline recommends both psychotherapy (Cognitive Behavioural Therapy, CBT) and pharmacotherapy. In severe cases of depression with psychosis, pharmacotherapy or electro-convulsive therapy was the main choice of treatment. With regard to the algorithm of pharmacotherapy, the first line treatment recommended in the guideline was monotherapy with selective serotonin reuptake inhibitor (SSRI). The treatment period recommended was 4 weeks or longer for the acute phase till remission, 6 to 9 months for the continuation phase, and at least two years for the maintenance phase.

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Despite the high prevalence of depression reported in the literature, we believe that there are still a significant number of undiagnosed depressed cases in Malaysia. This may be related to the lack of awareness and fear of stigmatisation among the Malaysian population, the clinicians' over focus on the physical complaints, and the culture of seeking alternative treatment. With the latest advancement in the treatment of depression, it is crucial to identify depressive cases at an early stage. This will enable patients to receive the necessary intervention to minimise the level of their suffering and ensure a better quality of life.

Primary care physicians are the gatekeepers of Malaysia's healthcare systems. Most of them have long-term follow-ups with the family members and established good rapport with the patients. They are the principal care provider who screen, identify and manage depression in the Malaysian population. In view of the high number of patients seen in the primary care setting, a quick and easy-to-use tool is needed for the physicians. The awareness of the risk of depression should be spread to encompass all subgroups of the population including those who are medically ill, cancer patients, children and adolescents, and their caretakers.

SECTION 3: FUTURE RESEARCH DIRECTION

The reported rates for depression in Malaysia vary widely. A national large scale study using validated tool will be helpful to refine or determine a more accurate rate of depression in the country. There is also the need to study the prevalence of depression in some subgroup population such as children, adolescents, medically ill or cancer patients and their caretakers. In addition, there is no study on depression among the male population in Malaysia.

The psychometric properties of some depression screening tools were studied in previous research. The results were more academically relevant than practical, as all of the scales were designed by Western researchers; while the Malaysian population is multi-ethnic with different religious and cultural backgrounds. The presentation of depressive symptoms could be varied. As a result, items of existing scales need to be examined in detail to develop a locally applicable scale to increase the sensitivity of screening of depression among the Malaysian population.

Local treatment guidelines have recommended pharmacotherapy and psychotherapy. However, primary prevention such as public education, awareness programmes and screening activities are crucial and should be implemented regularly for all levels of the population. Collaboration between the media, private practices and the government are important to achieve these objectives and disseminate the information. Psychoeducation, community services and compliance therapy ensure the maintenance of psychological well-being among the depressed patients.

Local research findings are important to provide information about the current depression situation in the country and the efficacy of the treatment options. However, as there are many unpublished thesis and research projects on this topic in the local universities, the setting up of an online repository of all these publications would be helpful so that the information can be effectively disseminated to all relevant parties.

ACKNOWLEDGEMENT

I would like to sincerely thank the Director General of Health, Malaysia for his permission to publish this paper. I wish to thank the Clinical Research Centre team for their contribution and support.

REFERENCES

1. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997; 349(9063): 1436-42.
2. American Psychiatric Association (2013) The Diagnostic and Statistic Manual of Mental Disorders (5th ed.).
3. World Health Organization (2008) The global burden of disease 2004. Geneva, Switzerland.
4. Institute of Public Health. The Second National Health and Morbidity Survey 1996 (NHMS II). Kuala Lumpur: Ministry of Health Malaysia, 1999.
5. Institute of Public Health. The Third National Health and MorbiditySurvey (NHMS III) 2006. Vol 1. Kuala Lumpur: Ministry of Health Malaysia, 2008.
6. Institute for Public Health (IPH) (2011) National Health and Morbidity Survey 2011 (NHMS 2011). Vol. II: Non- Communicable Diseases.
7. Firdaus M, Tian PSO. A Review on the Prevalence of Depression in Malaysia. Current Psychiatry Reviews, 2011, 7 (3).

8. Kader Maideen SF, Mohd. Sidik S, Rampal L, Mukhtar F (2014) Prevalence, Associated Factors and Predictors of Depression among Adults in the Community of Selangor, Malaysia. PLoS ONE 9(4): e95395. doi:10.1371/journal.pone.0095395.
9. Sherina MS, Rampal L, Mustaqim A. The prevalence of depression among the elderly in Sepang, Selangor. Med J Malaysia 2004; 59: 45-49.
10. Sherina MS, Arroll B, Goodyear-Smith F, Ahmad R. Prevalence of depression among women attending a primary urban care clinic in Malaysia. Singapore Med J 2012; 53(7) : 468-73.
11. Tan KL, Yadav H. Depression among the urban poor in Peninsular Malaysia: A community based cross-sectional study. Journal of Health Psychology 18(1) 121– 127.
12. Wong SY, Lua PL. Anxiety and Depressive Symptoms among Communities in the East Coast of Peninsular Malaysia: A Rural Exploration. MJP 2011; 20(1): 59-71.
13. Groer MW, Morgan K. Immune, health, and endocrine characteristics of depressed postpartum mothers. Psychoneuroendocrinology 2007; 32(2): 133–139.
14. Omar Din M, Mohd Noor N. Prevalence and factors associated with depressive symptoms in Malay women. Women and Health 2009; 49: 573-591.
15. Azidah AK, Shaiful BI, Rusli N, Jamil MY. Postnatal Depression and Socio-Cultural Practices Among Postnatal Mothers in Kota Bahru, Kelantan, Malaysia. Med J Malaysia 2006; 61(1): 76-83.
16. Klainin P, Arthur DG. Postpartum depression in Asian cultures: A literature review. International Journal of Nursing Studies 2009;46: 1355–1373.
17. O'Hara MW. Postpartum Depression: Causes and Consequences. 1995 Springer–Verlag, New York.
18. Beck AT. Depression: Causes and Treatment. University of Pennsylvania Press, 1970 Philadelphia.
19. Abramson LY, Seligman MEP, Tresdale JD. Learned helplessness in humans: critique and reformulation. Journal of Abnormal Psychology 1978; 87 (11): 49–84.
20. Hairi NN, Bulgiba A, Mudla I, Said MA. Chronic diseases, depressive symptoms and functional limitation amongst older people in rural Malaysia, a middle income developing country. Preventive Medicine 2011; 53: 343–346.
21. Kaur G, Tee GH, Ariaratnam S, Krishnapillai AS, China K. Depression, anxiety and stress symptoms among diabetics in Malaysia: a cross sectional study in an urban primary care setting. BMC Family Practice 2013; 14:69.
22. Ng TK. Prevalence of depression among diabetic patients in an outpatient clinic in Hospital Sik: A rural hospital in Malaysia. Asian Journal of Psychiatry 2010; 3: 76-7.
23. Sulaiman AH, Zainal NZ, Tan KS, Tan CT. Prevalence and associations of psot-stroke depression, Neurol J Southern Asia 2002; 7: 71-75.
24. Glamcevski II MT, Pierson J. Prevalence of and Factors Associated with Poststroke Depression: A Malaysian Study. Journal of Stroke and Cerebrovascular Diseases 2005; 14(4): 157-161.
25. Khoo KF, Tan HJ, Rosdinom R, Raymond AA, Norlinah MI, Shamsul A, Nafisah WY. Prevalence of Depression in Stroke Patients With Vascular Dementia in Universiti Kebangsaan Malaysia Medical Center, Med J Malaysia2013; 68(2): 105-110.
26. Zuraida NZ, Parameswaran R. Prevalence of depression among patients with headache in Kuala Lumpur, Malaysia. Malaysian Journal of Psychiatry 2007; 16:2.
27. Firdaus M, Tian PSO. A Review on the Assessment and Treatment for Depression inMalaysia. Depression Research and Treatment 2011. doi:10.1155/2011/123642.
28. Wan Mahmud WMR, Awang A, Herman I, Mohamed MN. Analysis of the psychometric properties of the Malay version of Beck Depression Inventory II (BDI-II) among postpartum women in Kedah, North West of Peninsular Malaysia. Malaysian Journal of Medical Sciences 2004; 11(2): 19-25.
29. Ramli M, Salmiah MA, Nurul Ain M. Validation and psychometric properties of Bahasa Malaysia version of the Depression Anxiety and Stress Scales (DASS) among diabetic patients. MJP 2009; 18 (2): 40-5.
30. Sherina MS, Arroll B, Goodyear-Smith F. Criterion Validity of the PHQ-9 (Malay Version) in a Primary Care Clinic in Malaysia. Med J Malaysia 2012; 67(3): 309-315.
31. Yusoff N, Low WY, Yip CH. Psychometric Properties of the Malay Version of the Hospital Anxiety and Depression Scale. Asian Pacific J Cancer Prev2011; 12: 915-917.
32. Ng CG, Boks MP, Roes KC, Zainal NZ, Sulaiman AH, Tan SB, de Wit NJ. Rapid response to methylphenidate as an add-on therapy to mirtazapine in the treatment of major depressive disorder in terminally ill cancer patients: a four-week, randomized, double-blinded, placebo-controlled study. Eur Neuropsychopharmacol. 2014; 24(4): 491-8.
33. Ministry of health, Malaysia. Clinical Practice Guidelines. Management of Major Depressive Disorder. Available at: http://www.moh.gov.my/attachments/3897.pdf.

A Review of Schizophrenia Research in Malaysia

Chee Kok Yoon, MMed(Psych), Salina Abdul Aziz, MMed(Psych)

Department of Psychiatry & Mental Health, Kuala Lumpur Hospital, Jalan Pahang, 50586 Kuala Lumpur.

SUMMARY

Research in schizophrenia has advanced tremendously. One hundred and seventy five articles related to Schizophrenia were found from a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. This project aims to examine published research articles, in local and international journals in order to provide a glimpse of the research interest in Malaysia with regards to schizophrenia. Single case study, case series report, reviews and registry reports were not included in this review. Medication trial, unless it concerned a wider scope of psychopharmacology was also excluded from this review. A total of 105 articles were included in this review. Despite numerous genetics studies conducted and published, a definitive conclusion on the aetiology or mechanism underlying schizophrenia remains elusive. The National Mental Health - Schizophrenia Registry (NMHR) proved to be an important platform for many studies and publications. Studies stemmed from NMHR have provided significant insight into the baseline characteristic of patients with schizophrenia, pathway to care, and outcomes of the illness. International and regional collaborations have also encouraged important work involving stigma and discrimination in schizophrenia. Ministry of Health's hospitals (MOH) are the main research sites in the country with regards to schizophrenia research. Numbers of schizophrenia research are still low in relation to the number of universities and hospitals in the country. Some of the weaknesses include duplication of studies, over-emphasising clinical trials and ignoring basic clinical research, and the lack of publications in international and regional journals.

KEY WORDS: schizophrenia, registry, Malaysia

INTRODUCTION

Research in schizophrenia has advanced tremendously. This project aims to examine the published research articles, in local and international journals in order to provide a glimpse of the research interest involving schizophrenia in Malaysia. Single case study, case series report, reviews and registry reports were not included in this review. Medication trial, unless it concerned a wider scope of psychopharmacology was also excluded from this review. Therefore only 105 of the 175 articles found on schizophrenia were included in this review.

SECTION 1: REVIEW OF LITERATURE

The formation of the National Mental Health Registry (NMHR) for schizophrenia was one the important milestone of local schizophrenia research. On 1 January 2003, the NMHR was formed by the Ministry of Health (MOH) Malaysia to collect information about people with mental disorders in Malaysia. Schizophrenia was the first mental disorder targeted by the NMHR. The registry collects information about patients with schizophrenia in Malaysia to evaluate the risk factors and treatment in the country, which will facilitate the planning and evaluation of mental health services in the country. In 2003, all 29 departments of psychiatry from the MOH and four local university hospitals participated in data collection. This was a coverage rate of 90.6%. By 2005, 74 primary health-care centres and hospitals throughout the country participated in data collection. The Mental Health Registry Unit (MHRU) was established to monitor the process of data collection throughout the country, which includes data entry, analysis and reporting. The NMHR for schizophrenia published its first paper in 2008 in the Medical Journal of Malaysia. The paper provided detailed information about the profile of person with schizophrenia presented for the first time to various psychiatry and mental health providers throughout Malaysia. The incidence rate reported in the paper was 7.7-43.0 per 100,000 population. Unemployment rate was as high as 70%. Duration of untreated illness was at a median of 12 months and 20% of them suffered from at least one form of comorbidity[1].

In 2012, NMHR for schizophrenia published its first paper on the one-year outcome of patients who were registered in 2004 and 2005. Of the 2604 registered patients with FES, only 37.7% had their outcomes successfully assessed. Among those assessed, 25.5% were lost to follow-up and 45.8% were followed-up in different centres. Only two patients committed suicide. Comparison of types of antipsychotic medications use between baseline and at one-year follow-up is shown in Fig. 1. Increases in weight gain and body mass index were major concerns. On a positive note, employability improved. Forty percent of the patients had their antipsychotics changed over the one-year period but about 20% of patients were on polytherapy at baseline and after one year. The use of anticholinergic medication dropped remarkably after the one-year treatment period[2].

In 2005, Esther et al from University Malaya Medical Centre (UMMC) reported an outcome study of early onset schizophrenia, defined as the onset of illness before 18 years old. About half of the subjects had an unfavourable outcome, with significantly younger (<15 years old) age of onset of illness, longer duration of symptoms prior to their first contact, and impaired functioning[3].

GENETICS RESEARCH

Genetics research in schizophrenia is relatively new in Malaysia and all the publications in this area occurred within the last five years. The Department of Chemical Engineering of Tunku Abdul Rahman University (UTAR) had published a

Corresponding Author: cheekokyoon@yahoo.com

substantial number of papers in genetic research in schizophrenia. Tee *et al.* from UTAR found a possible association between genotype distribution dopamine receptor (DRD3) polymorphism and schizophrenia in a Malay sample population[4]; they also found that tryptophan hydroxylase 2 gene (TPH2) was not associated with schizophrenia in the same ethnic population[5], and there was no significant association between DRD3 Ser9Gly polymorphisms and cathecol-o-methyltransferase (COMT) and schizophrenia in Malays[6]. The same research group, however, found highly significant association between the COMT gene and schizophrenia[7]. Another research group from UTAR led by Loh et al. failed to demonstrate the association between neuregulin-1 with schizophrenia in Malays, Chinese and Indians in Malaysia[8]. The same group also found no association between AKT1 gene variants and schizophrenia[9], and brain-derived neurotrophic factor (BDNF) and dopamine- and cAMP-regulated phospoproterin (DARPP-32) genes were not risk factors for schizophrenia in the Malay population[10].

Zahari *et al.* from the Institute for Research in Molecular Medicine, Universiti Sains Malaysia (USM) looked into the influence of the dopamine D2 receptor (DRD2) polymorphisms on the clinical outcomes of people with schizophrenia. DRD2 polymorphism might have implications for the symptoms of schizophrenia and a predictor of treatment outcomes. Patients with Cys311 allele were found to have more severe symptoms of schizophrenia and worse treatment response[11]. Zalina et al from USM studied the relationship between CYP2D6 polymorphisms on symptomatology in patients with schizophrenia; and it was found that CYP2D6 polymorphisms were significantly associated with negative symptoms of schizophrenia but not with the motor side effect of antipsychotics[12]. Zain et al. from the Department of Pharmacy, University Malaya (UM) found significant association between rs7690296 single nucleotide polymorphism and schizophrenia for Malays and Indians[13]. Wan *et al.* from the same department in UM demonstrated that COMT functional polymorphism of Val158Met had a weak association with schizophrenia and did not play a major role in susceptibility to schizophrenia[14].

ACCESS TO CARE

The pathway to care in schizophrenia is important because it gives us an understanding on how a patient eventually obtains mental health care from the moment symptoms occur. With this knowledge, providing optimal care to reduce the duration of untreated psychosis (DUP) or illness is possible. Almost all the information in this area came from the NMHR for schizophrenia and schizophrenia patients from Kuala Lumpur Hospital (HKL). Phang *et al.* found that even though consultation from traditional healers was common and popular prior to mental health consultation, it was not associated with treatment delay and traditional healers in an urban setting may even be a potential collaborator to manage patients with schizophrenia[15]. Half (54%) of the patients had at least one contact with traditional healer but only 7.4% of them reported beneficial effects from it[16]. He also found the commonest reason for treatment delay was lack of knowledge by patients and family members that the mental state changes were due to mental illness[17]. A study in Kota Kinabalu by Swami *et al* from the University of Westminster, London, UK, Sabah reported that the public believed schizophrenia was sinful and mental hospitals could not provide effective treatments[18].

In a larger scale, Chee *et al.* who examined DUP using data from NMHR found the mean DUP in Malaysia was 37.6 months and the indigenous community had the shortest DUP compared to Malays, Chinese and Indians. Being a female, having less education, and having comorbidities were related to longer DUP[19].

CLINICAL FEATURES

The symptoms profile of schizophrenia has been extensively researched in Malaysia for the last 10 years. McLean et al from the Queensland Centre for Mental Health Research in Australia published two articles on schizophrenia symptoms among the Iban community of Sarawak. They found distinct symptom profile in this community, in which they exhibited less thought disorders but more hallucinations and disorganised behaviours. Ibans also demonstrated shorter prodrome, higher use of substance, and older age for the onset of psychosis compared with Australian and Indian populations[20,21]. Gill et al from the UMMC in Malaysia studied the characteristics of first episode psychosis among the Malaysian Chinese and found the most common symptoms were functional decline, sleep disturbance and dysphoric mood. The drawback of this study was that there was no comparison with other ethnic groups[22]. Nor Zuraida *et al* from the same centre reported no gender differences in terms of psychopathology and functionality among patients with schizophrenia[23].

Lack of insight has been a common feature in schizophrenia and it has been one of the most significant factors contributing to medication non-adherence. Ting et al from UMMC studied schizophrenia patients in Permai Hospital, one of the largest mental institutions in Malaysia, and found 54% of them had moderate to poor insight[24]. Sharmilla and Hatim from the same centre who later compared insight among patients with schizophrenia and other mood disorders with psychosis found that schizophrenia patients had the worst insight. The level of impairment of insight was associated with functionality of patients[25].

Rusdi *et al* from UMMC studied schizophrenia patients with regards to substance use in Hospital Bahagia Ulu Kinta (HBUK), the largest mental institution in Malaysia. Based on the admission registry in HBUK, 24% of schizophrenia patients had a history of substance use. Those on cannabis had the highest prevalence for schizophrenia and male patients with a history of substance use were also more likely to exhibit aggression[26]. Abdul Hamid and Abdul Razak from the National University Hospital and Kuala Lumpur Hospital reported that 15% of schizophrenia outpatients had second diagnosis of obsessive-compulsive disorder (OCD). They did not find any differences in demographic and neurocognitive function for schizophrenia with and without OCD[27]. Ong *et al* from the USM in 2013 reported high prevalence of sexual dysfunction (ranging from 78.4% to 97.1%) among schizophrenia outpatients in Taiping Hospital; with orgasmic dysfunction being least impaired and satisfaction during intercourse as the worst impaired[28].

Cognitive impairment in schizophrenia, specifically verbal memory performance among schizophrenia patients were studied by Zahiruddin *et al* and Hazura *et al* from USM. Using the Malay version of the Auditory Verbal Learning Test, they were able to demonstrate that schizophrenia patients had significantly worse verbal memory and this was significantly correlated with occupational status, educational level, and negative symptoms of schizophrenia. Depressive symptoms and smoking were not found to be correlated with verbal memory performance[29,30]. Zakaria *et al* from National University of Malaysia (UKM) examined motor neurological soft signs among schizophrenia patients, and found 68.8% of them had motor neurological soft signs and this was associated with a wide range of clinico-demographic and neurocognitive factors[31].

Among the forensic patients with schizophrenia, Surina *et al* from USM studied the forensic patients in Hospital Bahagia in terms of the relationship between psychopathology and the offenders' characteristic. They showed that the offenders with schizophrenia received treatment at a later age. Those who were considered to be of unsound mind at the time of offence had significantly more positive symptoms[32].

Roseliza-Murni *et al* from the UKM studied the relationship between expressed emotion (EE) among the caregivers and relapse rate of patients. They found that high EE was associated with eight times the risk of illness relapse. Critical comments and the caregivers' extraversion personality trait were the strongest predictors[33].

OBESITY & METABOLIC SYNDROME

Obesity and metabolic syndrome are among the major medical comorbidities in schizophrenia. Several hospital-based studies were carried out to address the issue of obesity in schizophrenia. Salmi *et al* from the UKM did a cross-sectional study on schizophrenia patients and found 35.1% of them were categorised as obese and 39.2% as overweight. There were more Malays and Indians who were overweight. The risk factors were being male and having a lower total income[34]. Norlelawati *et al* carried out a similar study in Tengku Ampuan Afzan Hospital, Kuantan and found schizophrenia patients were twice as likely as the general population to develop obesity and this was seen across all the main ethnic groups in Malaysia[35]. Ainsah *et al* from UKM studied the possible relationship between binge eating, lifestyle and obesity in schizophrenia but could not establish any such associations[36]. Fairuz *et al* from the same centre examined the prevalence of insulin resistance among schizophrenia patients in UKM and found 68% of them had insulin resistance. Univariate analysis found body-mass index (BMI) and waist circumference to be associated with insulin resistance although this significance disappeared in multivariate analysis[37].

The relationship between weight gain or metabolic syndrome and antipsychotic medications were widely studied in Malaysia. Using the National Mental Health Registry for schizophrenia, Chee *et al* reported on weight changes among first-episode schizophrenia one year after the initiation of antipsychotic medications. At the time of diagnosis, mean weight for patients being treated with first-generation antipsychotics (FGAs) was 57.5±12.3 kg, and mean weight for patients with second-generation antipsychotics (SGAs) was 61.0±22.0 kg. The mean weights did not differ significantly at the time of diagnosis (P = 0.110). Patients treated with FGAs and SGAs gained significant amount of weight after one year (P < 0.001 for both groups). Mean weight gain for FGAs (6.6±8.5 kg; median, 5 kg) was slightly less than that for SGAs (9.7±9.3 kg; median, 7 kg). Body mass index for FGAs at diagnosis was 21.4±4.0 kg/m2 (median, 20.8 kg/m2), and that for SGAs was 23.0±7.0 kg/m2 (median, 21.6 kg/m2). Body mass index had increased significantly in both groups after one year of treatment but did not differ significantly at baseline (P = 0.594) and after treatment (P = 0.105) between the two groups. Patients treated with olanzapine had the biggest mean weight gain with treatment (ie, 14.3±10.1 kg)[38].

Mas Ayu et al from UMMC studied the prevalence of metabolic syndrome among schizophrenia patients on monotherapy antipsychotics. The prevalence of metabolic syndrome was 46.7% and more were taking SGAs. They found patients treated with the antipsychotics trifluoroperazine, flupenthixol decanoate, and clozapine to be associated with the highest prevalence of metabolic syndrome[39,40]. Ruzanna *et al* from UKM who studied the association between dyslipidaemia and types of antipsychotics failed to identify a significant difference between FGAs and SGAs although 66% of patients with chronic schizophrenia developed dyslipidaemia[41]. Ainsah et al from the same centre who studied the relationship between obesity and types of antipsychotic use also failed to find a significant difference between FGAs and SGAs. In this study, 71.4% of SGAs and 79.4% of FGAs were at least overweight[42].

Various genetic polymorphisms have been implicated in antipsychotic-induced weight gain. Roffeei et al from UMMC found patients that carried the ADRA2A rs1800544 GG genotype and the MTHFR rs1801131 C were associated with BMI reduction when their treatment was switched to aripiprazole and ziprasidone[43].

MANAGEMENT

Psychopharmacology

A study on the prescription pattern of medication use in schizophrenia was carried out at the Tengku Ampuan Rahimah Hospital psychiatric outpatient unit. The commonest antipsychotic was haloperidol (16.3%), average daily dose was 342.06 mg chlorpromazine equivalent. Thirty-two percent of the entire patients sample was prescribed with second-generation antipsychotics. The commonest SGA was olanzapine, followed by risperidone and quetiapine. Only 3.2% of those patients given SGA received clozapine[44].

Since 2009, Kuala Lumpur Hospital, Malaysia has been part of the Research on Asia Psychotropic Prescription (REAP) study group. This group is an ongoing pharmaco-epidemiological investigation of psychotropic drug prescription trends in schizophrenia inpatients in Asia. The participating countries and regions include Mainland China, Hong Kong, Japan, Korea, Singapore and Taiwan. Each centre used the same standardised protocol and data collection procedure. Centres in India, Malaysia and Thailand joined the project in 2009. The three REAP surveys to date were conducted in July 2001, July 2004 and from October 2008 to March 2009. Below is a summary of the study's findings;

1. Univariate analyses in the use of antipsychotics found the following factors to be significantly associated with the male sex: a younger age, higher doses of antipsychotics, less prominent delusions and hallucinations, more prominent negative symptoms, less likelihood of a prescription for SGAs, greater use of antipsychotic polypharmacy, mood stabilisers (MS) and depot antipsychotics, more frequent tardive dyskinesia (TD), and less weight gain[45].

2. The frequency of tardive dyskinesia (TD) was 5.0% with wide variations between countries (0 – 14.9%). Malaysia's rate was 1.2%. Multiple logistic regression analysis showed that the following variables were independently associated with TD: study time, study site, older age, male gender, more severe negative and extrapyramidal symptoms and less anti- cholinergic drugs[46].

3. Adjunctive benzodiazepine treatment of in-patients diagnosed with DSM-IV or ICD-10 schizophrenia has been prevalent in Asia over the past decade, averaging 54% of over 6700 schizophrenia patients sampled at 12 centres in nine countries. Use of adjunctive benzodiazepines was associated with prominent positive psychotic symptoms (delusions and hallucinations), aggressive behaviour, and occupational or social dysfunction. Moreover,

benzodiazepines also were associated with use of other drugs, notably MS and antidepressants, in addition to common use of anti-parkinsonian agents. Prevalence of benzodiazepine (BZD) in Malaysia was 59%, daily diazepam-equivalent of 18.7±14.1 mg[47].

4. The frequency of reported sexual dysfunction (SD) in the whole sample, in women, and in men were 3.0%, 0.8%, and 4.6%, respectively, with variations across study sites. Twelve percent of patients in Malaysia reported SD. In the multivariate analyses, male sex, more SGA, BZD, and antidepressants were independently associated with higher likelihood of reported SD, whereas negative symptoms had an inverse association with reported SD[48].

5. MS were given to 20.4% (n=1377/6761) of hospitalised schizophrenia patients, with increased usage over time. MS use was significantly and independently associated in multivariate logistic modelling with aggressive behaviour, disorganised speech, year sampled (2008 vs. earlier), multiple hospitalisations, less negative symptoms, and younger age. There were regional variations (Japan, Hong Kong, Singapore, Taiwan or China)[49].

6. The proportion of antipsychotic polypharmacy (APP) prescription decreased from 46.8% in 2001, to 38.3% in 2004, and increased to 43.4% in 2009, with wide inter-country variations at each survey. Forty-nine percent of schizophrenia patients in Malaysia received APP prescription. Multiple logistic regression analysis of the whole sample revealed that patients on APP were younger, had a higher dose of antipsychotics in chlorpromazine equivalents, and more severe positive and negative symptoms. They were also more likely to receive depot and first-generation antipsychotic drugs[50].

7. The frequency of anticholinergic medication (ACM) prescription in older patients (65 years and older) was 64.6% in the pooled sample, with 72.4%, 61.9%, and 59.5% in 2001, 2004, and 2009, respectively. In Malaysia, 25% of the older patients were given ACM. Multiple logistic regression analysis of the whole sample revealed that patients on ACM had a higher dose of antipsychotic medications, and were more likely to have extrapyramidal side effects and receive first-generation antipsychotic medications[51].

8. The frequency of MS prescription in older Asian was 26.7 % in the pooled sample, with 25.5 % in 2001, 26.9% in 2004 and 27.7% in 2009. No prescriptions were found in the Malaysian sample. The corresponding figures for BZD were 20.7% (pooled sample), 20.2% (in 2001), 18.4% (in 2004) and 23.1% (in 2009). Multiple logistic regression analysis of the whole sample revealed that patients on MS were younger and more likely to be men and to have EPS and a longer duration of illness. Compared to patients in China, those in Japan were more likely to receive MS, while Korean patients were prescribed less MS. In contrast, there were no significant sociodemographic or clinical correlates of BZD use. Compared to patients in China, Korean and Singaporean patients were more likely to be on BZD[52].

9. The prescription frequency for low doses of antipsychotic medications (300 mg/day CPZeq or less) in older Asian was 40.9% in the pooled sample. Sixty-five percent was found in the Malaysian sample. Multiple logistic regression analysis of the whole sample showed that patients on low doses of antipsychotic medications were more likely to be female, older, have a shorter length of illness and less positive symptoms. Of patients in the six countries and territories that participated in all the surveys between 2001 and 2009, those in Japan were less likely to receive low doses of antipsychotics[53].

10. Prescribing patterns of several FGAs and SGAs medications administered to older Asian patients with schizophrenia during the period between 2001 and 2009 were studied. Of the 467 patients, 192 (41.1%) received FGAs only, 166 (35.5%) received SGAs only and 109 (23.3%) received a combination of FGAs and SGAs. Of the FGAs, haloperidol was the most commonly used (31.3%; mean 9.4 ± 6.7 mg/day), followed by chlorpromazine (15.4%; mean 126.4 ± 156.4 mg/day) and sulpiride (6.6%; mean 375.0 ± 287.0 mg/day). Of the SGAs, risperidone was the most commonly used (31.5%; mean 4.5 ± 2.7 mg/day), followed by olanzapine (13.1%; mean 13.6 ± 6.5 mg/day), quetiapine (7.3%; mean 325.0 ± 237.3 mg/day) and aripiprazole (1.9%; mean 17.6 ± 7.7 mg/day)[54].

11. Trends in the use of antidepressants and their demographic and clinical correlates in the treatment of schizophrenia in Asia between 2001 and 2009. The proportion of antidepressant prescription was 6.8% in the whole sample, 5.3% in 2001, 6.5% in 2004 and 8.7% in 2009. There were wide inter-country variations at each survey ranging from 0.9% in Hong Kong to 15.3% in Singapore in 2001; from 1.9% in Korea to 15.4% in Singapore in 2004; and from 2.7% in Japan to 22.0% in Singapore in 2009 and 7% in Malaysia. Multiple logistic regression analysis of the whole sample revealed that patients on antidepressants were younger, more likely to receive benzodiazepines and have significant extrapyramidal side effects and less likely to have significant positive symptoms[55].

12. The use of APP in older Asian patients with schizophrenia was studied. The frequency of APP prescription was 51.6% in the pooled sample with wide inter-country variations. Multiple logistic regression analysis of the whole sample showed that patients on APP had higher antipsychotic doses and also were more likely to receive first-generation antipsychotics[56].

13. The use of clozapine and its demographic and clinical correlates in older patients with schizophrenia in East Asia during the period between 2001 and 2009 was researched. Clozapine was prescribed for 20.6% of the pooled sample, 19.0% in 2001, 19.4% in 2004 and 22.9% in 2009. Multiple logistic regression analysis of the whole sample revealed that patients taking clozapine had a longer duration of illness, more negative symptoms and were less likely to receive first generation antipsychotic and anticholinergic drugs, but more likely to report weight gain compared to those not receiving clozapine. Compared to those in other sites, older patients in China were more likely to receive clozapine[57].

14. The REAP researchers examined the use of high doses of antipsychotic medications (≧ 600mg/day chlorpromazine equivalent) in older Asian patients with schizophrenia and its demographic and clinical correlates. The frequency for high-dose antipsychotic medications was 36.0% overall, with 38.4% in 2001, 33.3% in 2004 and 36.0% in 2009. Multiple logistic regression analysis of the whole sample showed that compared to patients receiving low-medium antipsychotic doses, those on high doses had a longer illness duration (odds ratio (OR): 2.0, 95% confidence interval (CI:1.2-3.3, p=0.008), were more likely to be in the

50-59 year age group (OR: 0.95, 95% CI: 0.94-0.97, p<0.001), had more often current positive (OR: 1.5, 95% CI: 1.2-1.8, p<0.001) or negative symptoms (OR: 1.3, 95% CI: 1.03-1.6, p=0.03), and more commonly received antipsychotic polypharmacy (OR: 5.3, 95% CI: 4.1-6.7, p<0.001). Extrapyramidal symptoms (p=0.25) and tardive dyskinesia (p=0.92) were not more frequent in the high-dose group[58].

Community Psychiatry & Rehabilitation

Hospital-based community psychiatric service has been practiced in Malaysia for several years. Rahima *et al* studied patients with schizophrenia in Kuala Lumpur Hospital who received this service and found 90% of them had low rate of hospital admission with significant reduction in hospitalisation within one year of being enrolled in this service[59]. Among these patients, 74% achieved functional remission and 20% gained employment[60]. In terms of assertive community treatment, good remission outcome (76% remained in remission) was found[61].

Tan *et al* from UMMC studied patients from Bahagia Hospital, and found that community based patients were significantly less depressed, and had higher functional capability than chronic schizophrenia inpatients[62]. Marhani et al from UKM studied the cognitive function of patients with schizophrenia and examined the correlation with employment. The result supported the role of cognitive function, especially attention, working memory and executive function on attaining and maintaining employment in patients with schizophrenia[63].

Psychotherapy

Psychoeducation is one of the commonest and most important non-pharmacological treatment of schizophrenia. Paranthaman *et al* from Jelapang Health Clinic provided structured psychoeducation to caregivers in a controlled interventional environment. Caregivers that were given structured psychoeducation showed significant improvement in knowledge, reduced burden in caring for patients and reduced default rate among patients[64]. Ruzanna *et al* from the UKM also established the role of psychoeducation in improving the insight of patients with schizophrenia. It was also found that a shorter duration of illness and having no previous history of admission to mental institution were significantly related to improvement of insight[65].

Alwi *et al* from USM studied cognitive remediation therapy. They found this therapy to have good prospect as promising preliminary results revealed improvement in cognitive function of patients with schizophrenia[66]. Azhar carried out an open trial using cognitive psychotherapy to treat chronic drug resistant delusion in patients with schizophrenia, and found a positive response in all patients[67].

QUALITY OF LIFE AND SOCIAL LIVING

Quality of life has been emphasised in the management of schizophrenia, yet data from developing countries are lacking. Using the data from the NMHR for schizophrenia, the differences in subjective quality of life between FGAs and SGAs was explored. Patients with first-episode schizophrenia and related psychosis were recruited from Kuala Lumpur Hospital. There were no significant statistical differences between groups concerning subjective quality of life, extrapyramidal side effects and employment status at the end of a one-year regular treatment. Significant less benzhexol usage was reported among SGAs (P < 0.001) compared to FGAs and sulpiride. Overall, the results are in line with other major pragmatic clinical trials[68].

Determinants of quality of life in schizophrenia were looked into using the same database from NMHR. Gender, positive and disorganised symptoms of schizophrenia, and cognitive and physical impairments appeared to be the most important predictors of subjective quality of life among the patients from this centre in Malaysia[69]. Mohd Bahli *et al* from the UKM found employment and task-oriented coping style to be positively correlated with better quality of life, while emotion-oriented coping style was not[70]. Hasanah and Razali from USM compared quality of life between patients with diabetes mellitus and schizophrenia who were well controlled with antipsychotics. They found no significant difference in the psychological well-being and level of independence between the two groups. However, it was revealed that the most impaired aspect of well being in the schizophrenia group was social relationship[71].

Osman *et al* from UKM found 14% of care-givers of schizophrenia patients from Permai Hospital had psychological distress and 6% had depressive disorder. They found significant association between depressive disorders and family functioning dimensions in terms of communication and roles[72]. Both Lua and Zanariah from the Universiti Sultan Zainal Abidin, Terengganu and Ruzanna et al from UKM found significantly better quality of life experienced by care givers who were young, male, adequately educated, had regular income, physically healthy and employed[73,74]. Mubarak and Barber from the Flinders University of South Australia studied the quality of life of community-based chronic schizophrenia patients in Penang; and their research showed that emotional involvement of key caregivers significantly improved quality of life[75].

The patient's capacity to function is another important element in the recovery process of schizophrenia. Norlelawati et al from the International Islamic University of Malaysia studied the relationship between psychological symptoms, medications and social demographic and the psychosocial function of schizophrenia patients. They found positive, negative and disorganised symptoms of schizophrenia to be negatively correlated with psychosocial function. Patients treated with FGAs (except sulpiride) had poorer psychosocial function[76].

STIGMA & DISCRIMINATION

Many people with schizophrenia experience stigma caused by other people's knowledge, attitudes, and behaviour; and this can lead to impoverishment, social marginalisation, and a low quality of life. As a result, the Department of Psychiatry and Mental Health, Kuala Lumpur Hospital (HKL) collaborated with 26 countries to form the INDIGO network (International Study of Discrimination and Stigma Outcomes). Discrimination was measured with the newly validated discrimination and stigma scale (DISC), which produces three sub scores: positive experienced discrimination; negative experienced discrimination; and anticipated discrimination. Three hundred and forty four (47%) of the 729 participants experienced negative discrimination when they tried making or keeping friends, 315 (43%) of 728 from their family members, 209 (29%) of 724 when finding a job, 215 (29%) of 730 when keeping a job, and 196 (27%) of 724 during intimate or sexual relationships. Positive experienced discrimination was rare. Anticipated discrimination affected 469 (64%) when applying for work, training, or education and 402 (55%) who were looking for a close relationship; 526 (72%) felt the need to conceal their diagnosis. Over a third of participants had anticipated discrimination when seeking a job or during close personal relationships when no discrimination was experienced. From the study, it was obvious the discrimination

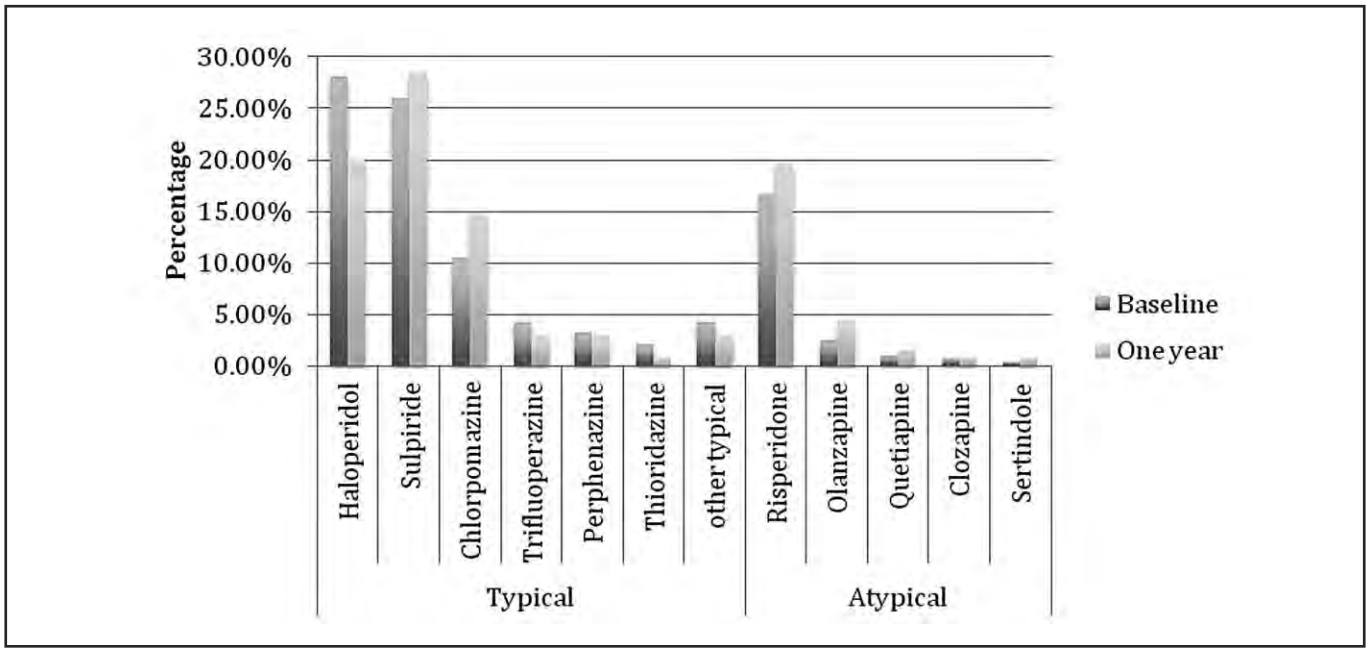


Fig. 1: Comparison of types of antipsychotic medications usage between baseline and at one-year follow- up.

experienced by schizophrenia patients in Malaysia was no different from the rest of the world[77]. Mubarak *et al* from the Flinders University of South Australia studied the quality of life of community-based chronic schizophrenia patients in Penang, Malaysia and found the patients experienced social isolation, discrimination and exploitation at the workplace[78].

With regards to anticipated discrimination, 64% of the participants reported that they had stopped themselves from applying for work, training or education because of the anticipated discrimination. Many (72%) of them reported that they felt the need to conceal their diagnosis. The expectation of being avoided by others who knew about their diagnosis was highly associated with decisions to conceal their diagnosis. Those who concealed their diagnosis were younger and more educated. The participants who perceived discrimination by others were more likely to stop themselves from looking for a close relationship. Anticipated discrimination in finding and keeping work was more common in the absence than in the presence of experienced discrimination. Similar findings were found for intimate relationships[79].

Private general practitioners have always been encouraged to manage schizophrenia patients but the response was disappointing. Ahmad Hatim and Hussain Habil from University Malaya Medical Centre (UMMC) looked into this issue and from the 15.6% that responded to the survey, most of them felt they need more training in managing even stable schizophrenia[80].

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Incidence of schizophrenia in Malaysia was reported to be 7.7-43.0 per 100,000 population and majority of them was unemployed. Long DUP (mean 37.6 months) was documented and it was associated with low educational background, the female gender and co-morbidity. Contact with traditional healer was common but not associated with treatment delay. On the contrary, ignorance of illness by patient and family member was the main reason for the delay. Substance-use comorbidity was commonly found among people with schizophrenia.

High rate of treatment discontinuation was found after one year of treatment and weight gain and metabolic syndrome were the major adverse events for those who were on treatment, particularly SGAs. Majority of the patients had insulin resistance. Frequency of TD was low compared to the other Asia countries. Twelve percent of patients reported sexual dysfunction.

Almost half of the patients received more than one antipsychotic medication. Although the use of anticholinergic medication declined over the years, there was still a substantial amount of such prescription among the elderly patients. Community psychiatric service had shown definite benefit in terms of reducing hospitalisations, improving remission outcome, and increasing functional capability and employment.

Different domains of self-rated quality of life correlated with different sociodemographic and clinical characteristics. Some of the characteristics were malleable such as positive symptoms of schizophrenia and depressive illness. Stigma and discrimination were still prevalent among the patients and most of them would conceal their diagnosis from employers. There were no significant difference between Malaysia and other parts of the world with regards to anticipated and experienced discrimination by the patients with schizophrenia.

SECTION 3: FUTURE RESEARCH DIRECTION

After 10 years of schizophrenia research in Malaysia, the time has come to shift from merely presenting local data to establishing hypothesis. There is a lot of replication of studies mostly done in treatment and clinical areas. There also seems

to be a lack of research in basic science involving genetics and other biological areas. In Malaysia presently, there is a need for more research that examines the relationships among genetic, neuroimaging (functional and structural), behavioral, developmental, social, and other factors in greater depth. This is important to understand the causes of the disorder and how it can be predicted and prevented.

The constraints that researchers in Malaysia face are numerous. The lack of resources, lack of research interest among psychiatrists and overwhelming clinical work are just some of the challenges. Another major factor is the over-emphasis in industrial-initiated studies by some centres including universities; thus resulting in less effort on investigator-initiated studies. A concerted effort by the Ministry of Health and the Universities is needed to meet this demand through research initiatives. Collaboration among centres may be one of the ways to overcome limited resources within a single centre. In the past, universities have been carrying out research in Ministry of Health hospitals due to the fact that these hospitals have more types of illnesses and more patients. For more meaningful collaborations, the previous practice of not getting Ministry of Health teams actively involved in research or as co-authors should be remedied.

Despite the availability of government funding, there were few takers by the Mental Health Services in the Ministry of Health. This is partly due to the lack of awareness and the reluctance to put in the effort in securing the grant.

In the long term, research in this area can be stimulated through the combined efforts of all involved with each complimenting the other. For more fruitful research, we have to move from merely presenting some data from a single hospital to conducting research that can be translated into clinical practice. It is hoped, that we can utilise available resources to be the world renowned research centre in schizophrenia.

ACKNOWLEDGEMENT

I would like to sincerely thank the Director General of Health, Malaysia for his permission to publish this paper. I wish to thank Clinical Research Centre team for their contribution and support.

REFERENCES

1. Aziz AA, Salina AA, Abdul Kadir AB, *et al.* The National Mental Health Registry (NMHR). Med J Malaysia 2008; 63 (Supplement C); 15-17.
2. Chee KY, Muhammad Dain NA, Abdul Aziz S, *et al.*Outcomes of patients with first-episode schizophrenia at one-year follow-up: Findings from the National Mental Health Registry in Malaysia. Asia- Pacific Psychiatry (2012);4(1): 30-39.
3. Esther E, Gill JS, Aili Hanim H. Outcome study of early onset schizophrenia. Malaysian Journal of Psychiatry 2005; 13(1): 20-26.
4. Tee S, Tang P, Loh H. Genetic association analysis of dopamine DRD3 Ser9Gly polymorphism and schizophrenia in Malay population. Iran J Public Health 2011; 40(2): 6-10.
5. Tee SF, Chow TJ, Tang PY, *et al.* Linkage of schizophrenia with TPH2 and 5-HTR2A gene polymorphisms in the Malay population. Genet Mol Res 2010; 9(3): 1274-1278.
6. Tee SF, Tang PY, Loh HC. No evidence for association between DRD3 and COMT with schizophrenia in a Malay population. Genet Mol Res 2011; 10(3): 1850-1855.
7. Tee SF, Tang PY, Loh HC. COMT haplotype analyses in Malaysians with schizophrenia. Psychiatry Res 2012; 195(1-2): 83-84.
8. Loh HC, Tang PY, Tee SF, *et al.* Neuregulin-1 (NRG-1) and its susceptibility to schizophrenia: a case-control study and meta-analysis. Psychiatry Res 2013; 208(2): 186-188.
9. Loh HC, Chow TJ, Tang PY, *et al.* No association between AKT1 gene variants and schizophrenia: A Malaysian case-control study and meta-analysis. Psychiatry Res 2013; 209(3): 732-733.
10. Loh HC, Tang PY, Tee SF, *et al.* BDNF and DARPP-32 genes are not risk factors for schizophrenia in the Malay population. Genet Mol Res 2012; 11(1): 725-730.
11. Zahari Z, Teh LK, Ismail R, *et al.* Influence of DRD2 polymorphisms on the clinical outcomes of patients with schizophrenia. Psychiatr Genet 2011; 21(4): 183-189.
12. Zalina Z, Mohd Razali S, Teh LK, *et al.* Influence of CYP2D6 polymorphisms on symptomatology and side-effects of patients with schizophrenia in Malaysia. Malays J Med Sci 2009; 16(3): 12-20.
13. Zain MA, Roffeei SN, Nor Zuraida Z, *et al.* Nonsynonymous polymorphisms of the PDLIM5 gene association with the occurrence of both bipolar disorder and schizophrenia. Psychiatr Genet 2013; 23(6): 258-261.
14. Wan CL, Nor Zuraida Z, Lian LH, *et al.* Association of the functional polymorphism in the catechol-O-methyltransferase gene with schizophrenia in the three ethnic groups of the Malaysian population. Psychiatry Res 2011; 189(1): 67-71.
15. Phang C, Marhani M, Salina AA. Traditional healers are causing treatment delay among patients with psychosis in Hospital Kuala Lumpur: fact or fallacy? ASEAN Journal of Psychiatry 2010; 11(2): 206-215.
16. Phang CK, Marhani M, Salina AA. Prevalence and experience of contact with traditional healers among patients with first-episode psychosis in Hospital Kuala Lumpur. Malaysian Journal of Psychiatry 2010; 19(2): 41-45.
17. Phang C, Marhani M, Salina A. Help-seeking pathways for in-patients with first-episode psychosis in Hospital Kuala Lumpur. Malaysian Journal of Medicine and Health Sciences 2011; 7(2): 37-44.
18. Swami V, Furnham A, Kannan K, *et al.* Beliefs about schizophrenia and its treatment in Kota Kinabalu, Malaysia. Int J Soc Psychiatry 2008; 54(2): 164-179.
19. Chee KY, Muhammad Dain N, Abdul Aziz S, *et al.* Duration of untreated psychosis, ethnicity, educational level, and gender in a multiethnic South-East Asian country: report from Malaysia schizophrenia registry. Asia Pac Psychiatry 2010; 2(1): 48-54.
20. McLean D, Barrett R, Loa P, *et al.* Comparing schizophrenia symptoms in the Iban of Sarawak with other populations to elucidate clinical heterogeneity. Asia Pac Psychiatry 2013.
21. McLean D, John S, Barrett R, *et al.* Refining clinical phenotypes by contrasting ethnically different populations with schizophrenia from Australia, India and Sarawak. Psychiatry Res 2012; 196(2-3): 194-200.
22. Gill JS, Koh OH, Jambunathan ST. First episode psychosis in a Malaysian Chinese population. Hong Kong Journal of Psychiatry 2005; 15(2): 54-59.
23. Nor Zuraida Z, Gill JS, Koh OH, *et al.* Gender influences on psychopathology and functionality in schizophrenia in University Malaya Medical Centre, Kuala Lumpur, Malaysia. Malaysian Journal of Psychiatry 2009; 18(1): 23-26.
24. Ting JH, Chan BTM, Ahmad HS. Assessment of insight in patients with schizophrenia in Hospital Permai. 2002; MJP; 12(1) 32-37.
25. Sharmilla K, Ahmad Hatim S. A comparison of insight in schizophrenia, bipolar affective disorder with psychosis and major depressive disorder with psychosis. Malaysian Journal of Psychiatry 2006; 14(1): 35-40.
26. Rusdi AR, Noor Zurani, Md Haris Robson, Ahmad Hatim S, *et al.* Schizophrenia, substance use and aggressions: What are the relationships? ASEAN Journal of Psychiatry 2010; 11(1): 72-78.
27. Abdul Hamid AR, Abdul Razak O. Obsessive-compulsive disorder in schizophrenia: clinical and neurocognitive correlates. Malaysian Journal of Psychiatry 2010; 19(2): 50-58.
28. Kheng Yee O, Muhd Ramli ER, Che Ismail H. Remitted Male Schizophrenia Patients with Sexual Dysfunction. J Sex Med 2013.
29. Zahiruddin O, Ruzita J, Muhammad Najib MA, *et al.* Demographic and clinical factors associated with verbal memory performance in patients. ASEAN Journal of Psychiatry 2011; 12(2): 148-156.
30. Hazura H, Wan Norhaida W, Ruzita J, *et al.* Verbal working memory in schizophrenia: relationship to cigarette smoking and psychopathology. Malaysian Journal of Psychiatry 2012; 21(1): 44-53.
31. Zakaria H, Jaafar NRN, Baharudin A, *et al.* Motor neurological soft signs among patients with schizophrenia: A clinical significance. Sains Malaysiana 2013; 42(3): 381-388.
32. Surina Z, Zahiruddin O, MohdAzhar M, *et al.* Offenders with schizophrenia: relationship to psychopathology. Malaysian Journal of Psychiatry 2013; 22(1): 3-8.

33. Roseliza-Murni A, Oei TPS, Fatimah Y, *et al.* Schizophrenia relapse in Kuala Lumpur, Malaysia: Do relatives' expressed emotion and personality traits matter? Compr Psychiatry 2013; 55(1); 188-198.
34. Salmi R, Ainsah O, Osman CB, *et al.* Obesity among patients with schizophrenia, attending outpatient psychiatric clinic, Hospital Universiti Kebangsaan Malaysia. ASEAN Journal of Psychiatry 2007; 8(2): 90-96.
35. Norlelawati AT, Kartini A, Ramli M, *et al.* Obesity in multiracial schizophrenia patients receiving outpatient treatment in a regional tertiary hospital in Malaysia. East Asian Arch Psychiatry 2012; 22(2): 49-56.
36. Ainsah O, Salmi R, Osman CB. Binge eating and lifestyle factors in relation to obesity in schizophrenia. Malaysian Journal of Psychiatry 2008;17(1):13-22
37. Fairuz AR, Maniam T, Khalid BA. Prevalence of insulin resistance in schizophrenia in HUKM. Med J Malaysia 2007; 62(4): 290-293.
38. Chee, K. Y. (2008). Weight gain and first-generation antipsychotics: experience from a developing country. Journal of Clinical Psychopharmacology, 28(5), 574–576.
39. Mas Ayu S, Ahmad Hatim S, Mohd Hussain H, *et al.* Metabolic syndrome and antipsychotic monotherapy treatment among schizophrenia patients in Malaysia. Prev Med 2013; 57 Suppl:S50-3.
40. Mas Ayu S, Ahmad Hatim S, Mohd Hussain H, *et al.* Metabolic syndrome and cardiovascular risk among patients with schizophrenia receiving antipsychotics in Malaysia. Singapore Med J 2012; 53(12): 801-807.
41. Ruzanna ZZ, Ong LY, Cheah YC, *et al.* The association between dyslipidaemia and types of antipsychotic medications among patients with chronic schizophrenia. Med J Malaysia 2012; 67(1): 39-44.
42. Ainsah O, Salmi R, Osman CB, *et al.* Relationships between antipsychotic medication and anthropometric measurements in patients with schizophrenia attending a psychiatric clinic in Malaysia. Hong Kong Journal of Psychiatry 2008; 18(1): 23-27.
43. Roffeei, S. N., Reynolds, G. P., Zainal, N. Z., Said, M. A., Hatim, A., Aida, S. A., & Mohamed, Z. (2014). Association of ADRA2A and MTHFR gene polymorphisms with weight loss following antipsychotic switching to aripiprazole or ziprasidone. Human Psychopharmacology: Clinical and Experimental, 29(1), 38–45.
44. Ponto T, Ismail NI, Abdul Majeed AB, *et al.* A prospective study on the pattern of medication use for schizophrenia in the outpatient pharmacy department, Hospital Tengku Ampuan Rahimah, Selangor, Malaysia. Methods Find Exp Clin Pharmacol 2010; 32(6): 427-432.
45. Xiang, Y.-T., Wang, C.-Y., Si, T.-M., Lee, E. H. M., He, Y. L., Ungvari, G. S., *et al.* (2011). Sex differences in use of psychotropic drugs and drug-induced side effects in schizophrenia patients: Findings of the Research on Asia Psychotropic Prescription (REAP) studies. Australian and New Zealand Journal of Psychiatry, 45(3), 193–198.
46. Xiang, Y.-T., Chee, K. Y., Wang, C.-Y., Si, T.-M., Lee, E. H., He, Y.-L., *et al.* (2011). Tardive dyskinesia in the treatment of schizophrenia: the findings of the Research on Asian Psychotropic Prescription Pattern (REAP) survey (2001 - 2009). International Journal of Clinical Pharmacology and Therapeutics, 49(6), 382–387.
47. Tor, P.-C., Ng, T. P., Yong, K.-H., Sim, K., Xiang, Y.-T., Wang, C.-Y., *et al.* (2011). Adjunctive benzodiazepine treatment of hospitalized schizophrenia patients in Asia from 2001 to 2008. The International Journal of Neuropsychopharmacology, 14(6), 735–745.
48. Xiang, Y.-T., Wang, C.-Y., Si, T.-M., Lee, E. H. M., He, Y. L., Ungvari, G. S., *et al.* (2011). The low frequency of reported sexual dysfunction in Asian patients with schizophrenia (2001-2009): low occurrence or ignored side effect? Human Psychopharmacology.
49. Sim, K., Yong, K.-H., Chan, Y. H., Tor, P.-C., Xiang, Y.-T., Wang, C.-Y., *et al.* (2011). Adjunctive mood stabilizer treatment for hospitalized schizophrenia patients: Asia psychotropic prescription study (2001-2008). The International Journal of Neuropsychopharmacology, 14(9), 1157–1164.
50. Xiang, Y.-T., Chee, K. Y., Wang, C.-Y., Si, T.-M., Lee, E. H., He, Y.-L., *et al.* (2011). Antipsychotic Polypharmacy in Inpatients with Schizophrenia in Asia (2001–2009). Pharmacopsychiatry, 45(01), 7–12.
51. Xiang, Y.-T., Dickerson, F., Kreyenbuhl, J., Ungvari, G. S., Wang, C.-Y., Si, T.-M., *et al.* (2012). Common use of anticholinergic medications in older patients with schizophrenia: findings of the Research on Asian Psychotropic Prescription Pattern (REAP) study, 2001–2009. International Journal of Geriatric Psychiatry, 28(3), 305–311.
52. Xiang, Y.-T., Dickerson, F., Kreyenbuhl, J., Ungvari, G. S., Wang, C.-Y., Si, T.-M., *et al.* (2012). Adjunctive Mood Stabilizer and Benzodiazepine Use in Older Asian Patients with Schizophrenia, 2001-2009. Pharmacopsychiatry, 45(6), 217–222.
53. Xiang, Y.-T., Dickerson, F., Kreyenbuhl, J., Ungvari, G. S., Wang, C.-Y., Si, T.-M., *et al.* (2012). Prescribing patterns of low doses of antipsychotic medications in older Asian patients with schizophrenia, 2001–2009. International Psychogeriatrics, -1(-1), 1–7.
54. Xiang, Y.-T., Kreyenbuhl, J., Dickerson, F. B., Ungvari, G. S., Wang, C.-Y., Si, T.-M., *et al.* (2012). Use of first- and second-generation antipsychotic medications in older patients with schizophrenia in Asia (2001-2009). Australian and New Zealand Journal of Psychiatry.
55. Xiang, Y.-T., Ungvari, G. S., Wang, C.-Y., Si, T.-M., Lee, E. H. M., Chiu, H. F. K., *et al.* (2012). Adjunctive antidepressant prescriptions for hospitalized patients with schizophrenia in Asia (2001-2009). Asia-Pacific Psychiatry.
56. Xiang, Y.-T., Dickerson, F., Kreyenbuhl, J., Ungvari, G. S., Wang, C.-Y., Si, T.-M., *et al.* (2012). Common Use of Antipsychotic Polypharmacy in Older Asian Patients With Schizophrenia (2001–2009). Journal of Clinical Psychopharmacology, 32(6), 809–813.
57. Xiang, Y.-T., Buchanan, R. W., Ungvari, G. S., Chiu, H. F. K., Lai, K. Y. C., Li, Y.-H., *et al.* (2013). Use of clozapine in older Asian patients with schizophrenia between 2001 and 2009. PLoS ONE, 8(6), e66154.
58. Xiang, Y.-T., Li, Y., Correll, C. U., Ungvari, G. S., Chiu, H. F. K., Lai, K. Y. C., *et al.* (2013). Common use of high doses of antipsychotic medications in older Asian patients with schizophrenia (2001-2009). International Journal of Geriatric Psychiatry.
59. Rahima D, Marhani M, Hatta S, *et al*. Hospital-based community psychiatric service for patients with schizophrenia in Kuala Lumpur: A 1-year follow-up study of re-hospitalization. Asia Pac Psychiatry 2013; 5 Suppl 1: 127-133.
60. Rahima D, Marhani M, Shamsul AS, *et al.* Functional remission and employment among patients with schizophrenia in Malaysia. Compr Psychiatry 2014; 55(Suppl 1) S46-51
61. Dahlan R, Marhani M, Hatta S. Remission of symptoms among schizophrenia patients receiving assertive community treatment (act) in Malaysia: One year follow-up. Sains Malaysiana 2013; 42(3): 389-397.
62. John Tan JT, Nor Zuraida Z, Mohamad Omer H, *et al.* Depression and functional level in schizophrenia: A comparison between chronic hospitalised in-patients and community care patients. JUMMEC 2007; 10(2): 31-36.
63. Marhani M, Rosdinom R, Ruzanna ZZ, *et al.* Clinical and cognitive correlates of employment among patients with schizophrenia: a cross-sectional study in Malaysia. Int J Ment Health Syst 2011; 5: 14-4458-5-14.
64. Paranthaman V, Satnam K, Lim JL, *et al.* Effective implementation of a structured psychoeducation programme among caregivers of patients with schizophrenia in the community. Asian J Psychiatr 2010; 3(4): 206-212.
65. Ruzanna ZZ, Marhani M, Parveen K, *et al.* Does psychoeducation improve insight of patients with schizophrenia? Malaysian Journal of Psychiatry 2010; 19(2): 27-40.
66. Alwi MNM, Ismail HC, Harris A, *et al.* Prospect of computerised cognitive remediation therapy in Malaysia: results of a pilot study in Kota Bharu, Kelantan. Malaysian Journal of Psychiatry 2007; 16(2): 41-49.
67. Azhar MZ. Comparison of risperidone and other neuroleptics in the management of chronic schizophrenia using cognitive therapy. Med J Malaysia 2000; 55(1): 7-13.
68. Chee, K. Y. (2009). Outcome study of first-episode schizophrenia in a developing country: quality of life and antipsychotics. Social Psychiatry and Psychiatric Epidemiology, 44(2), 143–150.
69. Chee, K. Y. (2010). Determinants of subjective quality of life in first-episode schizophrenia: perspective from Malaysia. Early Intervention in Psychiatry, 4(2), 111–118.
70. Mohd Badli M, Osman CB, Ainsah O. Coping style and clinical factors in relation to quality of life among patients with schizophrenia. Med Health 2008; 3(1): 14-21.
71. Hasanah CI, Razali MS. Quality of life: an assessment of the state of psychosocial rehabilitation of patients with schizophrenia in the community. J R Soc Promot Health 2002; 122(4): 251-255.
72. Osman CB, Alipah B, Tuti Iryani MD, *et al.* Depressive disorders and family functioning among the caregivers of patients with schizophrenia. East Asian Arch Psychiatry 2010; 20(3): 101-108.
73. Lua PL, Zanariah AB. Health-related quality of life profiles among family caregivers of patients with schizophrenia. Fam Community Health 2011; 34(4): 331-339.
74. Ruzanna ZZ, Marhani M, Hooi LS, *et al.* Schizophrenia in Malaysian families: A study on factors associated with quality of life of primary family caregivers. Int J Ment Health Syst 2011; 5(1): 16-4458-5-16.

75. Mubarak AR, Barber JG. Emotional expressiveness and the quality of life of patients with schizophrenia. Soc Psychiatry Psychiatr Epidemiol 2003; 38(7): 380-384.

76. Norlelawati AT, Kartini A, Norsidah K, *et al.* Relationship of psychological symptoms, antipsychotics and social data with psychosocial function in schizophrenia patients in Malaysia. Asia Pac Psychiatry 2013. DOI 10.1111/appy.12089

77. Thornicroft G, Brohan E, Rose D, Sartorius, *et al.* Global pattern of experienced and anticipated discrimination against people with schizophrenia: a cross-sectional survey. Lancet. 2009; 373(9661):408-15. doi: 10.1016/S0140-6736(08)61817-6.

78. Mubarak AR, Baba I, Chin LH, *et al.* Quality of life of community-based chronic schizophrenia patients in Penang, Malaysia. Aust N Z J Psychiatry 2003; 37(5): 577-585.

79. Üçok A, Brohan E, Rose D, *et al.* Anticipated discrimination among people with schizophrenia. Acta Psychiatrica Scandinavica 2012; 125, 77–83.

80. Ahmad Hatim S, Mohd Hussain H. General practitioners' view about treating schizophrenic patients in general practice settings. Malaysian Journal of Psychiatry 2001; 9(1): 43-47.

A Review of Substance Abuse Research in Malaysia

Norliza Chemi, MMed*, Norni Abdullah, MMed*, Anandjit Singh, MPM*, Mohd Fadzli Mohamad Isa, MPM**

*Department of Psychiatry, Hospital Kuala Lumpur, Jalan Pahang, 50586 Kuala Lumpur, **Department of Psychiatry, Hospital Tuanku Ja'afar, Jalan Rasah, 70300 Seremban

SUMMARY

This is a review of research done in the area of substance abuse in Malaysia. There were 109 articles related to substance abuse found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. Only 39 articles were reviewed, and case series, case report, reviews and reports were excluded. Research reviewed include the epidemiology of substance abuse, genetics, treatment and its relation to health behaviour, and health management. Studies have shown that more males than females use drugs. There was also a high prevalence of blood-bourne virus diseases and sexually transmitted diseases among drug users. Two studies showed some genetic polymorphism (Cyp 3a4 gene and FAAH Pro129Thr) among heroin and amphetamine users respectively that may contribute to drug dependence. Study on pharmacological treatment for substance abuse were limited to methadone and it was shown to improve the quality of life of heroin dependant patients. Alternative treatments such as acupunture and spiritual approach play a role in the management of substance abuse. Data also showed that treatment centres for substance abuse are lacking facilities for screening, assessment and treatment for medical illness related to substance use, e.g. Hepatitis C and tuberculosis. Studies on the effectiveness of current drug rehabilitation centres were inconclusive.

KEY WORDS: *Substance abuse, Malaysia, review, genetics, treatment, outcome,rehabilitation*

INTRODUCTION

There is a great concern over drug addiction in Malaysia. The most commonly abused drugs in the country include heroin, methamphetamine and amphetamine type stimulants, kratom, cannabis and ketamine. The growing popularity of methamphetamine was of particular concern. Seizures as a result of this substance abuse were the highest on record over the last few years. However, opioid continues to be the most widely abused drug in the country but the abuse of other substances are also increasing.

Drug addiction has huge consequences to the individuals involved and their family. It has a devastating impact on the individuals' physical and mental health, as well as their psychosocial well-being. Drug addiction is also a heavy burden for the government because it needs a lot of enforcement from the authorities and drains available health care resources.

Until the late 1990s, treatment of drug addiction in Malaysia was mainly through the enforcement of rehabilitation in detention centres. However, the success of these programmes remains controversial due to the high post-detention relapse rate. Treatment of opioids dependence with substitution therapy were started in 2001 with buprenorphine and subsequently Methadone Replacement Therapy was introduced in 2005. The Methadone Replacement Therapy has been expanded and upscaled yearly to cover almost all health care centres throughout Malaysia by 2015.

Studies on addiction cover epidemiology, treatment, and health behaviour. In this review, single case studies, case series reports, reviews and registry reports were excluded.

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY

The history of Malaysia's battle with its drugs problems are long. Various measures were introduced and this included the legislation of the Dangerous Act 1952[1].

A cross-sectional study to determine drug abuse among the youth found an unexpectedly high prevalence of depression among secondary school children in Selangor[2]. Children who abused drugs were also prone to medical issues such as blood and genitourinary complications among solvent (glue) abusers[3]. The drugs issue is aggravated as even students of higher institution have low knowledge regarding the effects of drugs and a significant number of respondents have been exposed to an environment of rampant drug abuse[4]. This possibly explains the 0.22% of public university students who were abusing methamphetamines; a significant number of them have already been exposed to this environment, were of Malay origin, and have low to moderate incomes[5]. Mahmood Nazar and colleagues (2008) found that there was no significant difference in the level of substance and drug misuse between Malay and non-Malay youths; but males showed a higher tendency than females[6].

Although the drug problem among women in Malaysia was comparably lower than among men, the state of Sabah had the most serious drug problems involving women. This was studied by Sabitha and colleagues (2007)[7]. Earlier, Rusli and colleagues (2001) who completed a study on sexually transmitted diseases (STDs) among female drug abusers in a rehabilitation centre in Kelantan, found a high prevalence of diseases such as syphilis. They suggested that female drug abusers go thorough screening for STDs[8].

Corresponding Author: norliza_chemi@hotmail.com

In terms of medical complications, Vicknasingam and colleagues (2009) found that drug users who were not in treatment had a high prevalence of contracting the Hepatitis C virus and this prevalence was higher in those who injected drugs. The most significant risk factors for contracting HIV among drug users who were not in treatment were the sharing of needles and lifetime homosexuality/bisexuality[9].

Among the genetic studies conducted in Malaysia was a study on the polymorphism of Cyp 3a4 gene in heroin-dependant individuals and a mutation of the gene was noticed[10]. FAAH Pro129Thr polymorphism may contribute to methamphetamine dependence among Malay and Chinese in Malaysia[11].

With the rapid evolution of synthetic drugs, Ahmad Hatim and colleagues (2013) found high risks of psychotic and non-psychotic disorders in methamphetamine-dependant patients[12]. Non-psychotic psychiatric co-morbidities were highly prevalent in patients with methamphetamine dependency especially among polysubstance abusers, those who have abused drugs for longer period, and those who have used a higher amount of drugs[13].

There were also several studies on the epidemiology of traditional and cultural substance of abuse. In the Asian Betel-quid Consortium (ABC) study, Lee and colleagues (2012), found that betel quid abuse were high in regions where it has become a customary practice and this abuse correlates highly with oral premalignant disorders (OPDs)[14]. The betel quid chewing behaviour in Malaysian adults was affected by gender, age, ethnicity and past smoking history, as well as the frequency and type of quid chewed[15]. The rates of men who chew betel quid were significantly higher than the rates among women in most Asian countries studied but the reverse was true in Malaysia and Indonesia. However, diverse cultural and demographic differences have contributed to the pattern of betel quid chewing in Asian region[16]. In another study, it was found that people who are dependent on betel quid had a higher pre-malignant risk compared to those who are not dependent[17]. Meanwhile, Ahmad and Aziz (2012) conducted a research on the characteristics of mitragyna speciosa in the northern states of Malaysia especially regarding its pattern of use, its effects and its potential for addiction[18].

TREATMENT AND OUTCOME

Treatment of addiction in general includes pharmacological and psycosocial approaches. The only illicit substance with established pharmacological treatment is opioid. The main approach of treament for other substances such as amphetamine and marijuana inhalants are mainly psychosocial using matrix module, motivational interviewing technique, 12 steps approach, etc.

Ahmad H *et al* studied the efficacy and safety of aripiprazole for treatment of psychosis, retention and abstinence in patients with methamphetamine dependence. The study showed that aripiprazole was no more effective than placebo in maintaining abstinence from methamphetamine use. However, it facilitated treatment retention and reduced the severity of psychotic symptoms. Aripiprazole was found to be generally safe and well tolerated[19].

Studies on the pharmacological treatment of opiods involved methadone and acupunture. Lua *et al* studied the clinical outcomes of methadone maintenance treatment (MMT) alone and MMT plus AA (MMT+AA) in terms of the daily methadone dose, number of cigarettes smoked/week, relapse rates, and withdrawal symptoms. The findings implied that AA could be beneficial as an adjunct to MMT in managing addiction, but the effectiveness of AA still requires further extensive investigation20. In another study, Lua et al looked into patient satisfaction level and preferred coping strategies among MMT patients in addition to AA intervention; and found that addition of of AA did not influence patient satisfaction and their coping ways[21].

Mahmood Nazar M *et al* studied drug substitution therapy; the success and limitations of the methadone and buphrenorphine maintenance programmes. The study looked at GPs' adherence to the Ministry of Health-prescribed maintenance protocols, the number of clients/patients under the Drug Substitution Therapy (DST), psychosocial intervention given and record keeping. They found more than 50% of the respondents reported benefits of the therapy; however incidences of non-adherence among the GPs were also identified. More importantly, almost half of the respondents reported abusing the substitute therapy by injecting and mixing with other substances[22].

A study on the perception of residents who were currently undergoing the drug rehabilitation programme at the Serenti Centre revealed that there was no correlation between the age of the residents and the perception of the effectiveness of the counselling sessions offered to them. However, there was a significant correlation between the number of counselling hours and the effectiveness of the counselling sessions. In addition, this study revealed that respondents who had high self respect perceived the counselling sessions to be effective[23].

STUDIES WITH CLINICAL OUTCOME

Clinical Studies

Chan KB, Pakiam C and Rahim RA used the gas-chromatography method to definitively identify the presence of mitragynine as the principle psychoactive component in suspected substances[24]. Opium addicts with clinically significant biliary symptoms should not be excluded for Endoscopic Retrograde Cholangiopancreatography (ERCP) although Common Bile Duct (CBD) dilatation is common among them[25]. In a cross-sectional study involving 26 drug rehabilitation centres in Malaysia, the prevalence of HIV was high among those who used drugs intravenously, shared needles, and had sexual exposure with prostitutes[26].

Health Behaviour

Motivation to change the drug dependent behavior is important but this is affected by the severity of psychopathological symptoms. As confirmed in a study by Wan Shahrazad and colleagues (2011), high level of psychopathology among in-treatment drug addicts may compromise their motivation to change[27]. Lua, Talib and Selamat (2011) found that drug abusers were ready to adopt positive behavioural changes regardless of their socio-economic backgrounds[28]. A study about personality traits for readiness to change was done by Wan Shahrazat and colleagues (2010)[29]. Saedah and colleagues (2008) did a study to look at the functions of family to improve the self-esteem of drug addicts[30]. Stressful home environment and peer influence were some of the external factors influencing youngsters into sniffing glue[31]. Mohd (2007) did a study to investigate the relationship between the age of onset for delinquent behavior and chronic drug abuse among adolescents[32]. The results show that the majority of chronic drug abusers began their involvement in delinquent behaviours at a significantly early age than the non-chronic

abusers. There was a study by Chan, Maniam and Suriati (2013) to look at the association between substance abuse and suicidal behavior[33]. They found that illicit drug use was associated with suicidal ideation, suicidal plan and deliberate self harm. Muhammad Muhsin and colleagues (2010) from Universiti Malaya attempted a study of the association between HIV infection and psychiatric disorders among prisoners in whom mental illness, substance abuse and HIV were disproportionately represented[34]. The readiness for change among female drug users admitted to drug treatment and rehabilitation centres was studied by Najwa, Sabitha and Mahmood Nazar (2008)[35]. Meanwhile, a study in the district of Tampin, Negeri Sembilan, found that there was a significant short-term improvement in the quality of life among MMT clients who stayed in the programme for at least 6 months[36].

Health Management

Management of addiction problems in Malaysia was introduced decades ago; and these are run by governmental and non-governmental agencies. The management includes treatment, rehabilitation and relapse prevention programmes. The programmes include interventions in the rehabilitation centres and among the community. The programmes are voluntary and involuntary. However, there are not many studies on the effectiveness of addiction treatment in rehabilitation centres in Malaysia.

In 2011, Fauziah et al studied the effectiveness of narcotics rehabilitation programme in Malaysia. They looked at the functionability, productivity and relapse rate of the addicts after the treatment and rehabilitation. They concluded that to improve the effectiveness of a rehabilitation centre in Malaysia, drug counsellors need to strengthen their modules, activities and programs and also to have more trained counsellors in every district. The extended care program and supervisions should also involve the community to ensure the effort to eradicate relapsed addictions were successful[37].

Many of the detainees in Malaysian rehabilitation centres were identified to have chronic infection and infectious diseases such as HIV, and Hepatitis B and C. Al-Darrajj *et al*, conducted a study on 196 patients in one drug treatment centre in Malaysia in 2013, and found 4.6% of them were HIV-infected and the prevalence of positive tuberculin skin test (TST) was 86.9% [38]. The actual prevalences of both latent TB infection (LTBI) and active disease in drug treatment centres in Malaysia were unknown. Therefore, there is an urgent need to establish TB screening and treatment programs in substance abuse treatment centres. Continuation of care for infectious disease in rehabilitation centres is also important.

In 2012, Fu et al, identified a lack of access to antiretroviral therapy in two of the six compulsory drug detention and rehabilitation centres in Malaysia. The found significant, unmet health needs among detainees with HIV. Individuals under such conditions are at a considerably high risk for morbidity and mortality[39].

Syed *et al.* (2009), studied chronic infections and management setting in drug addicts of MMT programme in Penang, Malaysia. They looked at the prevalence of blood-borne chronic infections, the quality of health of respondents active in the MMT program and possibly predict the risk reduction of relapse during treatment. They found that 2.3% were positive for HIV/AIDS, 76.3% for Hepatitis C, and 3.3% for Hepatitis B. About 38% of respondents had impaired liver function. The risk combination of Hepatitis C with impaired liver function involved 39.5% of respondents. None of them received any supportive management treatment for their current chronic infections. With these findings, the authors highly recommended producing necessary resources for the management treatment of drug addicts for such chronic infection. Further delay can possibly increase the risk of transmitting the infection within the society[40].

In addition, spirituality also play an important role in the treatment of addiction in Malaysia. Dara *et al* (2013), studied the implementation and effectiveness of drug treatment and rehabilitation programmes at Pondok Inabah, a legally set up establishment of the Anti-Drug Association of Malaysia or Persatuan Mencegah Dadah Malaysia (PEMADAM). They found the spiritual approach in the drug addiction treatment and rehabilitation to be one of the best component implemented by this centre. The holistic approach in the management of addiction in Malaysia is very important to improve the outcome of the treatment. More specific research in this area are needed[41].

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Most of the studies published in Malaysia during the last decade focused on illegal substances. Unfortunately, the issue and problem regarding cannabis was not addressed. However, at the same time, we must not forget the problems brought on through the use and abuse of 'legal' substances such as nicotine and alcohol. What is more pertinent was the lack of data on the prevalence and incidence of the substances being abused in the country. There was also a huge aperture in studies that addressed the outcomes of treatment for substance abuse. Most of the available studies on this were related to methadone for the treatment of opioid dependency.

SECTION 3: FUTURE RESEARCH DIRECTION

The changing trend of drug problems from traditional drugs of abuse such as cannabis and opioids towards synthetic drugs such as methamphetamine and Amphetamine-type Stimulants (ATS) reveals the need to move in that direction. Future studies should focus on these changes from opioid-based substances to recreational drugs such as MDMA (3,4-methylenedioxy-N-methylamphetamine) that is widely used socially, thus suggesting future epidemiological and clinical research studies addressing the prevalence of synthetic drugs. There should be more collaboration with law enforcement agencies such as the police and Agensi Anti Dadah Kebangsaan to establish data on prevalence of ATS, and other drugs abused in Malaysia. More attention should be given to studying special populations who abused drugs such as prison inmates, female drug abusers and homosexual/bisexual drug abusers, as well as the scope of issue covering drug abuse, HIV/AIDS and mental health problems. Outcomes of substance abuse treatment should be studied in detail to evaluate and ensure the effectiveness of current approaches. New treatment modalities are another aspect to be explored as drug problems become more complicated and are interwined with more biological and psychosocial factors. However, we should expand our knowledge on substance abused such as kratom and betel quid which are specific to our region. The possibility of using kratom as a drug replacement therapy for opioids dependency should be properly and extensively studied. Efforts to determine the co-morbid mental illness among drug abusers seeking treatment must be intensified.

ACKNOWLEDGEMENT

We would like to sincerely thank the Director-General of Health, Malaysia for his permission to publish this paper. We wish to thank the Clinical Research Centre team for its contribution and support.

REFERENCES

1. Abdul Rani K. The misuse of drugs in Malaysia: past and present. Malaysian Anti-Drugs Journal 2007; (1): 1-24.
2. Adlina S, Suthahar A, Ramli M, *et al.* Pilot study on depression among secondary school students in Selangor. Med J Malaysia 2007; 62(3): 218-222.
3. Zabedah MY, Razak M, Zakiah I, *et al.* Profile of solvent abusers (glue sniffers) in East Malaysia. Malays J Pathol 2001; 23(2): 105-109.
4. Kamarudin H, Abd Majid MI, Abdull Halim A, *et al.* A study of drug abuse among new students of institutions of higher learning. [Kajian pengaruh dadah dalam kalangan pelajar baru institusi pengajian tinggi.]. Malaysian Anti-Drugs Journal 2007; (2): 1-12.
5. Kamarudin H, Abd Majid MI, Abdul Halim A, *et al.* A study of drug abuse among students in the public institutions of higher learnng. [Kajian penyalahgunaan dadah bagi pelajar lama institusi pengajian tinggi awam.]. Malaysian Anti-Drugs Journal 2008; (3): 153-173.
6. Mahmood Nazar M, Sabitha M, Nadiyah E, *et al.* Pattern of substance and drug misuse among youth in Malaysia. Malaysian Anti-Drugs Journal 2008; (3): 1-56.
7. Sabitha M, Mahmood Nazar M, Rosnah I. Trend dan punca penggunaan dadah di kalangan penagih dadah wanita di negeri Sabah: implikasi kepada rawatan dan pemulihan dadah. Malaysian Anti-Drugs Journal 2007; (2): 111-136.
8. Rusli N, Abdul Rahman I, Mohamed Rusli A. Prevalence of sexually transmitted diseases among new female drug abusers in a rehabilitation centre. Malays J Med Sci 2001; 8(2): 9-13.
9. Vicknasingam B, Narayanan S, Navaratnam V. Prevalence rates and risk factors for hepatitis C among drug users not in treatment in Malaysia. Drug Alcohol Rev 2009; 28(4): 447-454.
10. Nasir M, Nurfadhlina M, Nazila T, *et al.* High frequency of CYP3A4* 1B among opiate dependent patients in Malaysia. Journal of Addiction Research & Therapy 2012; 3(3): 1000130.
11. Sim MS, Hatim A, Reynolds GP, *et al.* Association of a functional FAAH polymorphism with methamphetamine-induced symptoms and dependence in a Malaysian population. Pharmacogenomics 2013; 14(5): 505-514.
12. Ahmad Hatim S, Mas Ayu S, Mohd Hussain H, *et al.* The risk and associated factors of methamphetamine psychosis in methamphetamine-dependent patients in Malaysia. Compr Psychiatry 2013;
13. Ahmad Hatim S, Mas Ayu S, Gill JS, *et al.* Non-psychotic psychiatric co-morbidities in patients with methamphetamine dependence in Malaysia. International Medical Journal (Tokyo) 2013; 20(4).
14. Lee CH, Ko AM, Warnakulasuriya S, *et al.* Population burden of betel quid abuse and its relation to oral premalignant disorders in South, Southeast, and East Asia: an Asian Betel-quid Consortium Study. Am J Public Health 2012; 102(3): e17-24.
15. Ghani WM, Razak IA, Yang YH, *et al.* Factors affecting commencement and cessation of betel quid chewing behaviour in Malaysian adults. BMC Public Health 2011; 11: 82-2458-11-82.
16. Lee C, Ko AM, Warnakulasuriya S, *et al.* Intercountry prevalences and practices of betel-quid use in south, southeast and eastern Asia regions and associated oral preneoplastic disorders: an international collaborative study by Asian betel-quid consortium of south and east Asia. Int J Cancer 2011; 129(7): 1741-1751.
17. Lee CH, Ko AM, Yen CF, et al. Betel-quid dependence and oral potentially malignant disorders in six Asian countries. Br J Psychiatry 2012; 201(5): 383-391.
18. Ahmad K, Aziz Z. Mitragyna speciosa use in the northern states of Malaysia: a cross-sectional study. J Ethnopharmacol 2012; 141(1): 446-450.
19. Ahmad Hatim S, Gill JS, Mas Ayu S, *et al.* A randomized, placebo-controlled trial of aripiprazole for the treatment of methamphetamine dependence and associated psychosis.Int J Psychiatry ClinPract 2013; 17(2): 131-138.
20. Lua PL, Talib NS. Auricular acupuncture for drug dependence: an open-label randomized investigation on clinical outcomes, health-related quality of life, and patient acceptability. AlternTher Health Med 2013;19(4):28-42.
21. Lua PL, Talib NS, Ismail Z. Methadone Maintenance Treatment Versus Methadone Maintenance Treatment Plus Auricular Acupuncture: Impacts on Patient Satisfaction and Coping Mechanism. J Pharm Pract 2013.
22. MahmoodNazar M, Muhamad Dzahir K. Drug substitution therapy: success and limitations of the methadone and bephrenorphine maintenance programmes. Malaysian Anti-Drugs Journal 2007; (1): 25-72.
23. Zulkhairi A, Mahmood Nazar M. Effectiveness of counselling and drug rehabilitation programme: perspective of the inmates of PusatSerenti. Malaysian Anti-Drugs Journal 2007; (2): 13-28.
24. Chan KB, Pakiam C, Rahim RA. Psychoactive plant abuse: the identification of mitragynine in ketum and in ketum preparations. Bull Narc 2005; 57(1-2): 249-256.
25. Chuah SY, Leong CK, Pang CW. Dilated common bile duct in opium addicts with and without biliary symptoms --implication for research in AIDS cholangiopathy. Singapore Med J 2003; 44(5): 261-267.
26. Fauziah MN, Anita S, Sha'ari BN, *et al.* HIV-associated risk behaviour among drug users at drug rehabilitation centres. Med J Malaysia 2003; 58(2): 268-272.
27. Wan Shahrazad WS, Roselizamurni AR, Lukman ZM, *et al.* Psychopathological profile and readiness to change among drug addicts in Malaysia. World Applied Sciences Journal 2011; 12: 29-34.
28. Lua PL, Talib N, Selamat N. Readiness for behavioural change and its relation to health-related quality of life in opiod dependents patients. Malaysian Journal of Psychiatry 2011; 20(2): 15-29.
29. Personality traits and readiness to change among drug addicts in Malaysia. Research Journal of Applied Sciences 2010; 5(4): 263-266.
30. Saedah AG, Zainah AZ, Roselina Murni AR, *et al.* Family functioning and its relation with self-esteem among drug addicts. Malaysian Anti-Drugs Journal 2008; (3): 91-106.
31. Mohammad Shahid I, Mahmood Nazar M. Teenage glue sniffers: family and peer influence. Malaysian Anti-Drugs Journal 2007; (1): 131-152.
32. Mohd MS. The relationship between the age of onset for delinquent behavior and chronic drug abuse among adolescents. Malaysian Anti-Drugs Journal 2007; (2): 97-110.
33. Chan LF, Maniam T, Suriati MS, *et al.* Sexual abuse and substance abuse increase risk of suicidal behavior in Malaysian youth. Asia Pac Psychiatry 2013; 5Suppl 1: 123-126.
34. Muhammad Muhsin Z, Bae WH, Nor Zuraida Z, *et al.* Psychiatric and substance abuse comorbidity among HIV seropositive and HIV seronegative prisoners in Malaysia. Am J Drug Alcohol Abuse 2010; 36(1): 31-38.
35. Najwa MR, Sabitha M, Mahmood Nazar M. Motivation to change among drug dependent women undergoing rehabilitation. Malaysian Anti-Drugs Journal 2008;(3): 235-277.
36. Nizam B, Mohd Rohaizat H, Norsiah A, *et al.* Improvement of quality of life following 6 months of methadone maintenance therapy in Malaysia. Subst Abuse Treat Prev Policy 2012; 7: 32-597X-7-32.
37. Fauziah I, Bahaman AS, Subhi N, *et al.* The effectiveness of narcotics rehabilitation program in Malaysia. World Applied Sciences Journal 2011; 12: 74-79.
38. Al-Darraji HA, Wong KC, Yeow DG, *et al.* Tuberculosis screening in a novel substance abuse treatment center in Malaysia: Implications for a comprehensive approach for integrated care. J Subst Abuse Treat 2014 Feb; 46(2): 144-9.
39. Fu JJ, Bazazi AR, Altice FL, *et al.* Absence of antiretroviral therapy and other risk factors for morbidity and mortality in Malaysian compulsory drug detention and rehabilitation centers. PLoS One 2012; 7(9): e44249.
40. Syed Wasif G, Syed Azhar SS. Chronic infections and management setting in drug addicts of MMT program in Pinang, Malaysia. International Journal of Collaborative Research on Internal Medicine & Public Health 2009; 1(2): 48-54.
41. Dara Aisyah, H.M. Ali Puteh, Ibrahim M, Norizan AG, *et al.* Drug addict treatment and rehabilitation programme at Pondok Inabah, Kuala Terengganu, Terengganu, Malaysia (1998-2011). British Journal of Social Sciences 2013; 1(5): 37-46.

A Review of Dengue Research in Malaysia

W K Cheah, MRCP*, K S Ng, MRCP, Abd-Rahman Marzilawati, MMed**, Lucy C S Lum, MRCP*****

*Department of Medicine, Hospital Taiping, 34000 Perak, **Department of Medicine, Hospital Kuala Lumpur, 50586 Kuala Lumpur, ***Department of Paediatrics, Faculty of Medicine, University Malaya, 50603 Kuala Lumpur.

SUMMARY

Dengue infection is a major cause of morbidity and mortality in Malaysia. To date, much research on dengue infection conducted in Malaysia have been published. One hundred and sixty six articles related to dengue in Malaysia were found from a search through a database dedicated to indexing all original data relevant to medicine published between the years 2000-2013. Ninety articles with clinical relevance and future research implications were selected and reviewed. These papers showed evidence of an exponential increase in the disease epidemic and a varying pattern of prevalent dengue serotypes at different times. The early febrile phase of dengue infection consist of an undifferentiated fever. Clinical suspicion and ability to identify patients at risk of severe dengue infection is important. Treatment of dengue infection involves judicious use of volume expander and supportive care. Potential future research areas are discussed to narrow our current knowledge gaps on dengue infection.

KEY WORDS: *Dengue, Malaysia, serotypes, epidemiology, economic burden, diagnosis, prevention, vaccine*

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY

Demographic

The incidence of dengue has increased dramatically around the world in recent decades. World Health Organization (WHO) estimated about 2.5 billion people (two-fifths of the world's population) were at risk for dengue. Today, the disease is endemic in more than 100 countries, including Africa, America, Eastern Mediterranean, South East Asia, and the Western Pacific. Among these regions, South East Asia and the Western Pacific are the most seriously affected[1]. Prior to 1970, there were only nine countries in the world that experienced dengue epidemics. By 1995, this increased four-fold[1]. In Malaysia, dengue cases have increased since the first major outbreak in 1973[1].

There were several published papers recording the number of dengue cases and dengue incidence rate since 1982[2-9]. From the unpublished data from dengue surveillance system, Vector Borne Disease Section, Ministry of Health (MOH) Malaysia, there is a trend of increasing cases of dengue from 16,368 cases in 2001 to 46, 171 cases in 2010. The sudden drop of cases in 2011 could be due to the methodology difference in case reporting and need further exploration (Fig I).

Dengue infections affected all age groups, gender and ethnicity. In a one-year retrospective study in Negeri Sembilan in 2010, involving 1,466 cases of dengue infection, the youngest affected was 8 months old and the oldest was 89 years old. The mean age was 32.2 ± 15.8 years old. In terms of ethnic groups, majority who were affected were Malays, followed by Chinese and Indians (Ratio of 4.1:1.5:1). More males were affected than females (Ratio 1.4:1.0)[10]. The pattern of male predominance was observed consistently over several years across six culturally and economically diverse countries in Asia[11]. In Malaysia, as in Singapore[12] the incidence of dengue among the paediatric population has been declining while the incidence in the adult population has been on the rise. In 2006, about 80% of reported dengue cases in Malaysia were in the > 15 years age group Ministry of Health (MOH). Dengue became one of the leading causes of hospital admission among adults.

Distribution of reported dengue cases were more concentrated in urban areas. As shown in a Negeri Sembilan study in 2010, the highest number of dengue cases (81.9%) was reported from Seremban, its largest city. Of these, 8.3% were dengue haemorrhagic fever[10]. Since most reported dengue cases were from urban areas, the seropositivity rate of dengue IgG in healthy volunteers would be expected to be higher in subjects from urban areas compared to those from the rural regions. A cross-sectional epidemiological study of dengue IgG seroprevalence in 1000 Malaysian adult population (35 to 74 years), showed a high prevalence of up to 91.6%[13]. Among these subjects, however, the seroprevalence rates between urban and rural areas were similar. Chen WS et al. reported a lower prevalence of seropositivity (76.5%) in a smaller study (39 females, 46 males, with mean age of 42.8 years, from Dec 2000 to Dec 2001)[14].

Dengue virus and serotypes

Dengue virus is a single stranded RNA virus. It belongs to the family of *Flaviviridae*, which comes from the genus of Flavivirus. It contains three structural proteins, namely capsid protein C, membrane protein M, and envelope protein E. Seven nonstructural proteins: NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5. At the time of writing of this article, five serotypes of dengue viruses have been identified. However, for the purpose of this review article, only four serotypes will be discussed.

All four dengue serotypes (DEN 1, 2, 3 & 4) could be isolated in Malaysia at any point of time. The simultaneous presence of all four serotypes indicates that Malaysia is "hyperendemic" for dengue. However different serotypes have predominated throughout the years. From 1992 to 1995, and in 2001-2002 DEN 3 predominated[15]. DEN 2 and then DEN 1 predominated

Corresponding Author: drcheah.moh@1govuc.gov.my

over the period of 1998-2000 and 2004-2006 respectively[4]. DEN 4 was once the predominant serotype in Malaysia from 1967-1969. After that period, DEN 4 occurred at low levels (less than 5%) for many years until 2001, when there was a slight increase[16]. The latest publication from the Institute of Medical Research (IMR) showed that DEN 3 was once again the predominant serotype for the years 2008 and 2009[17].

In a phylogenetic study of the DEN 2 strains that caused two major outbreaks in the country in 1990s, two different DEN 2 genotypes were identified: DEN 2 Asian 1 and DEN 2 Cosmopolitan. Eighty percent of the isolates were DEN 2 Cosmopolitan, which was further divided into Clade I and Clade II. The latter was responsible for two major outbreaks in the 1990s. These strains originated from the same ancestral lineage, suggesting that both came from the same DEN 2 gene pool[18] .

A surveillance data analysis of dengue serotypes in Negeri Sembilan over a 1-year period in 2010 showed the presence of all serotypes. DEN 3 the predominant serotype in January, co-existed with DEN 2 until May. Thereafter, DEN 1 was the predominant serotype[10] .

Other than circulation of the viruses from within the locality, one study showed that there were multiple entries of DEN 2 and DEN 4 into Sarawak. These isolates were closely linked to those circulating in different localities in South East Asia from 1997 to 2002, based on phylogenetic analysis. Nonetheless, there was little exportation out of Sarawak[19].

PATHOGENESIS

The pathogenesis underlying the wide spectrum of clinical presentations of dengue is not well understood. The risk of Dengue Hemorrhagic Fever (DHF) was higher in situations of hyperendemicity when two or more virus serotypes were circulating simultaneously. The presence of pre-existing dengue antibodies, either by prior infection or passive immunity via maternal antibodies, would in fact, enhance viral infectivity and multiplication leading to a higher viral load. In primary dengue infection, dengue virus attaches to the target cell via highly sulphated glycosaminoglycan heparin sulfate, from which it penetrates target cells via high affinity receptor. In contrast, in secondary dengue infection, dengue virus mediates its entry into target cells via Fcγ-receptors. This phenomenon is called antibody-dependent enhancement (ADE). The virus combines with specific antibody, creating a complex that is taken up by mononuclear cells, dendritic cells and B-lymphocytes via a FcR mediated endocytosis[20].

A post-mortem study by Jessie K *et al.* reported that viral antigens but not viral RNA were found in Kupffer and sinusoidal endothelial cells of the liver, alveolar macrophages, multinucleated cells, vascular endothelial cells, macrophages and vascular endothelium in the lung and kidney tubular cells. The absence of strongly positive immunohistochemistry signals in these cells indicated absence of replication activities. There was no evidence of the involvement of megakaryocytes in the bone marrow at the time of death. Therefore thrombocytopenia during the later acute phase of dengue is probably not related to failure of platelet production[21]. Another post-mortem study demonstrated that dengue RNA was not retrievable from the brain tissue, suggesting that dengue virus replication in the central nervous system is rare in the later stages of disease[22]. In another work, Fong MY *et al.* analysed four encephalitogenic DEN 3 isolated in 1996, and compared them with five non-encephalitogenic DEN 3 viruses. Their envelope protein E showed high degree of similarity, suggesting that the neurovirulence of encephalitogenic dengue virus was not attributed to their envelope protein[23].

To further understand the pathophysiology of dengue infection, the investigation of various immune parameters, cytokines and antibody was reviewed by Shamala D[20]. Seventeen different peptides, C, E, NS2B, NS3, NS4A, NS4B and NS5 regions were found to evoke significant response in T cells of patients with dengue infections. Indeed, at the defervescence stage, viral load falls abruptly. It could be the response of the T cells to various stimuli that lead to tissue damage and severe immune response, followed by vascular leakage, bleeding and shock[24]. A study on the effect of active cytokines in the serum of DHF patients on human umbilical vein endothelial cells demonstrated changes in the vascular endothelium. The authors suggested that the production of cytokines during dengue significantly enhanced vascular permeability. However, this vascular permeability effect was transient[25]. At the febrile phase, IP-10 and MIP-1b were significant in dengue patients, with and without warning signs. At this stage, only MIP-1b was found to be significant in patients with warning signs. The IP-10 together with MIP-1b, G-CSF and MCP-1 were significant in patients during defervescence. Significant correlations between different cytokines group and the level of blood leukocytes, platelets and liver enzymes could be seen[26].

Genetic markers might be implicated in predicting susceptibility and/or protection to severe clinical manifestation of dengue infection. HLA-B*53 probably conferred susceptibility to DHF, while the HLA-A*03 and HLA-B*18 might confer protection from progression to severe disease. Interestingly, in the Malay subgroup, HLA-B*13 and B*18 were probably associated with disease susceptibility and protection, respectively[27].

PRESENTATIONS

The clinical presentation in the early febrile phase of illness is that of an undifferentiated fever. The prevalence of individual symptoms varied from one report to another. The most common symptoms were fever (100.0%), followed by headache (27% - 100%), myalgia and athralgia (39%- 99%), and nausea and vomiting (38%- 54%). Less common symptoms were rash (18-24%), petechiae and bleeding tendencies (7.0%-62%), and neurological deficits (1.2%). Abdominal pain and tenderness, gastrointestinal bleed, jaundice, hepatomegaly and ascites were predictors of the need for intensive care as reported by Ooi ET *et al.*[28]. Additionally, hepatomegaly and liver dysfunction were more common in DHF than Dengue Fever (DF)[29].

The tourniquet test, recommended by the World Health Organization (WHO) had a sensitivity of 82.8% and a specificity of 23.5%[30]. The positive predictive value (PPV) was 70.7% and negative predictive value (NPV) was 28.6%[30,31]. The presence of atypical reactive lymphocytes was seen in 85% (23/27) of patients with dengue fever[32]. However, the full blood picture was not a routinely requested investigation in the management of dengue, neither was laboratory confirmation of dengue.

In an outpatient setting in a dengue endemic area, thrombocytopenia in the context of an undifferentiated acute febrile illness (AFI) had a sensitivity of 88% and specificity of 71% to predict acute dengue infection. Thrombocytopenia was more useful to exclude than to diagnose dengue infection[33-35]. On the other hand, there was considerable overlap in clinical features of those with dengue infections with those with other AFI[36].

A cross-sectional retrospective study of 121 DHF children admitted to Hospital Kuala Lumpur from January 1999 to May 2001 reported fever in all patients. Vomiting and mild bleeding were observed in almost half of the children. Severe gastrointestinal bleeding was observed only in those with profound shock. Evidence of plasma leakage (pleural effusion and/or ascites) was present in 57% of the cases. Lowest mean platelet count was 41,785 /uL on the 6th day of illness. Hyponatraemia was a significant electrolyte imbalance seen in 65.9% of the cases[37].

In a single-centre outpatient-based prospective observational cohort study enrolling 214 patients >16 years with < 72 hours of undifferentiated fever, 65% eventually had a laboratory confirmed diagnosis of dengue, the rest were classified as other febrile illnesses (OFI)[38]. Of the 140 dengue patients, 11.4% developed DHF, no patients developed Dengue Shock Syndrome (DSS) and 37.1% required hospitalisation. In addition to a recent history of dengue within the family or neighborhood, the three early clinical predictors of dengue at < 72 hours of fever were: nausea and/or vomiting, postural dizziness and lower total white cell count compared to patients with OFI. Symptoms frequently reported by dengue patients such as headache, myalgia, arthralgia and retro-orbital pain were also observed in patients with OFI, with no significant differences between the two groups.

Chikungunya infection is spread by the same vector *Aedes aegypti* mosquito. Both dengue and chikungunya cause similar clinical features such as fever, myalgia, headache, arthralgia, and rash. Compared to patients with chikungunya infection, dengue patients were generally younger. A retrospective study of 60 patients with chikungunya and 120 patients with dengue from April 2008 to July 2009 in University Malaya Medical Centre, showed that the former was independently associated with arthralgia and rash, while latter was associated with myalgia, raised aspartate transaminase and leucopaenia. Arthralgia was seen in about 96% of chikungunya and 30% of dengue. Hence arthralgia is a strong predictor for chikungunya infection; self-reported arthralgia (22.5%) was reported for up to 1 year of follow up[39].

Tan PC *et al.* in their study involving 411 patients presenting with miscarriage, found 11 of the subjects to have dengue IgM or NS-1 Ag positive. The sample size was, however, too small to support the correlation between recent dengue infection and early pregnancy outcome[40]. Maternal and neonatal outcomes in dengue IgM seropositive women at delivery were not affected by subclinical recent dengue infection. Rates of preterm birth, mode of delivery, postpartum haemorrhage, low birth weight, and neonatal outcomes were not increased. The prevalence of the maternal seropositive rate was 2.5% (63/2531) with one case of vertical transmission rate, 1.6% (1/64)[41].

Several studies have attempted to describe clinical predictors of severe dengue[42,43].All of the ten dengue deaths reported by UMMC from June 2006 till October 2007, had secondary dengue infection (dengue IgG positive and dengue NS-1 positive, or dengue IgG positive in less than two weeks of infection). Clinical and laboratory warning signs of severe dengue included vomiting (90%), diarrhoea (60%), bleeding (80%), and evidence of vascular permeability (60%). Five patients had severe bleeding (gastrointestinal, lungs, brain or per vaginal) (50%), elevated liver enzymes (ALT>1000 IU/L) (50%) and hypoalbuminaemia (70%)[42].

Haemophagocytic syndrome has been reported in patients whose duration of fever, cytopenia and multi-organ dysfunction were prolonged beyond the plasma leakage phase of illness. This under-recognised phenomenon is most probably due to a "cytokine storm", caused by activated macrophages that secrete large amount of inflammatory cytokines. Diagnosis should be confirmed by bone marrow examination. Treatment should be supportive; however in severe cases, may include high dose immunosuppressive therapy such as IV methylprednisolone[44] and intravenous immunoglobulin. Other rare presentation of dengue infections include prolonged thrombocytopenia[45], myositis[46] and maculopathy[47,48].

Rare complications of dengue fever have been described. Most of these are believed to be immune-mediated. Three main mechanisms have been postulated to explain atypical neurological manifestations: direct neurotropic invasion, systemic complication and post infectious immune mediation[49]. Post-dengue associated Parkinsonism was reported by Azmin *et al.*[50] in which an 18-year-old man with NS-1 positive dengue developed Parkinson-like features, multiple cranial neuropathies, cerebellar ataxia and brachial plexopathy at day 9 of the illness. He was treated with IV methylprednisolone 500mg daily for 3 days. At one-month review, his symptoms of Parkinsonism and cerebellar ataxia had resolved but weakness in the right deltoid and infraspinatus muscles remained, together with marked muscle atrophy. Electromyogram (EMG) revealed chronic denervation changes involving the right deltoid and right trapezius muscle, which points to right brachial plexopathy. This is the second reported case of dengue-fever associated brachial plexopathy. Cerebellar ataxia following dengue fever has also been reported[50]. In the absence of dengue viral antigen in the cerebrospinal fluid coupled with CSF pleocytosis, the mechanism points towards immune mediation[50]. Other complications include dengue encephalitis[51] and atrial fibrillation[52].

DIFFERENTIAL DIAGNOSIS

The nonspecific clinical features of dengue may mimic many acute febrile illnesses such as acute flu-like syndrome, acute rash syndrome, acute diarrhoeal syndrome and acute neurological syndrome. On the other hand, during the critical phase when fever subsides, dengue may mimic acute abdominal conditions, acute respiratory conditions, septicaemic shock and any condition with leucopenia, thrombocytopenia and bleeding.

A multicentre prospective study identifying the causes of acute febrile illness in the paediatric group (2-14 years old) in South East Asia found the most common causes in Malaysia to be dengue fever, chikungunya and influenza A. Other tested illnesses included S. Typhi, rickettsia and hepatitis A[53]. Hamidon BB *et al.* reported a case of Seoul hantavirus infection that presented with haemorrhagic fever mimicking dengue infection. Seoul hantavirus is carried by domestic rats. This condition should be considered in dengue-sero-negative patients with clinical haemorrhagic features mimicking dengue[54].

A single positive dengue IgM should not be considered confirmatory as illustrated by a case[55] of a 47-year-old man from Pakistan, who was reported to have a mixed infection of leptospirosis and *vivax* malaria, despite a positive dengue IgM which could be explained by a recent dengue infection in the past 3 months. On the other hand, confirmed co-infection of dengue with other infection such as chikungunya has also been described[56].

DIAGNOSIS

The WHO case classification (1997) for dengue was used to differentiate DF from DHF/DSS. The DHF cases must fulfil all four of the following criteria:

1) Fever or history of acute fever lasting 2–7 days.
2) Haemorrhagic tendencies evidenced by at least one of the following:
   a) A positive tourniquet test. The test may be negative or mildly positive during the phase of profound shock. It usually becomes positive, sometimes strongly positive, if the test is conducted after recovery from shock (this limits its clinical usefulness);
   b) Petechiae, purpura, ecchymoses;
   c) Bleeding from mucosa, gastrointestinal tract, injection sites or other location haematemesis or melena.
3) Thrombocytopaenia (100,000 platelets/µl or less)
4) Haemoconcentration (20% or more rise in the haematocrit value relative to baseline average for the same age, sex and population) or evidence of plasma leakage (i.e. pleural effusion, ascites and/or hypoproteinaemia).

Ng CF *et al.* studied clinicians' ability to classify dengue using the WHO 1997 classification in a university hospital. They observed that DHF/DSS was under-recognised by clinicians. Out of the 520 adult and 191 paediatric hospital records that were reviewed, thrombocytopenia and evidence of plasma leakage were present in 8% of adult and 19% of paediatric patients. Of these patients who fulfilled the criteria for DHF, 93% and 49% respectively, were discharged with a diagnosis of DF[57].

A retrospective study by Tee *et al.* in Hospital Tengku Ampuan Afzan Kuantan between October 2004 and March 2005 involving 183 cases of confirmed dengue was conducted to evaluate the clinical and laboratory findings that correlated with the development of DHF or DSS. Seventy nine percent (145 cases) were classical dengue, 19% (35 cases) were DHF and 2% (3 cases) were DSS[42]. Table I is a summary of risk factors identified in this study.

Risk factors for haemorrhage in 114 children with DSS were hypotension, mottling, encephalopathy, organ failure, prolonged duration of shock, abnormal glycaemia, normal-low haematocrit at the diagnosis of shock, and abnormal coagulation ($P < 0.05$). However, the independent risk factors for haemorrhage in this cohort of DSS children were duration of shock (OR, 2.11; 95% CI, 1.13 to 3.92; $P = 0.019$) and normal-low haematocrit at the time of shock (OR, 0.72; 95% CI, 0.55 to 0.95; $P = 0.020$). On the other hand, platelet counts were not predictive of bleeding[58].

Bandyopadhyay S *et al.* in their review of 37 articles, reported that most clinicians reported difficulties in meeting all four WHO criteria for DHF/DSS and used a modified classification[59].

The positive tourniquet test representing the minimum requirement of a haemorrhagic manifestation did not distinguish between DHF and DF. In cases of DHF, thrombocytopenia was observed in 8.6–96%, plasma leakage in 6–95% and haemorrhagic manifestations in 22–93%. The low sensitivity of classifying DHF could be due to failure to repeat the tests or physical examinations at the appropriate time, early intravenous fluid therapy, and lack of adequate resources in an epidemic situation and perhaps a considerable overlap of clinical manifestations in the different dengue entities.

Some of the limitations of WHO classifications are as follows[59]:

1) Dengue with shock without fulfilling all four criteria of DHF
2) Severe organ impairment with or without shock are not captured
3) Haemoconcentration is hard to define in patients without prior baseline hematocrit.
4) Not useful in terms of clinical management

In view of the above limitations, a revised WHO classification in 2009 classifies dengue illness into dengue fever with/without warning signs and severe dengue. Severe dengue is characterised by severe plasma leakage, severe haemorrhage and/or severe organ impairment.

Faisal T *et al.* suggested an alternative risk criteria derived using the self-organised map (SOM) method. A patient fulfilling any two of the risk criteria is considered a high risk dengue patient. The criteria included:

a) Platelet count less than or equal 40,000 cells per mm^3,
b) Haematocrit concentration greater than or equal 25% rise, and
c) Aspartate aminotransferase (AST) rise of five times the normal upper limit for AST/alanine aminotranstansferase (ALT) rise of five times the normal upper limit for ALT[60]. The usefulness of SOM in clinical management has yet to be identified.

Diagnostic tests

The laboratory confirmation of dengue is a challenging issue. Fig.3 could be a guide on the most appropriate tests to diagnose the infection based on the day of illness and whether the infection is a primary or secondary. Research related to diagnostic tests, done locally or internationally are not reviewed and will not be further discussed here.

Other non-conventional test

Bioimpedance analysis (BIA) of water content in different body compartments of dengue patients and healthy subjects[61,62] was only able to explain approximately 42% of the variation in serum haemoglobin status, thus limiting its usage as a surrogate monitoring system for haemoglobin and haematocrit levels[62].

Another study used the multilayer feed-forward neural networks (MFNN) to predict dengue patients' defervescence phase which is solely based on clinical symptoms and signs. This system has a 90% prediction accuracy[63]. Combining BIA and artificial neural network (ANN), Ibrahim F *et al.* was able to show that ANN provided a system that was able to classify and diagnose patients with risk of severe dengue infection with an overall accuracy of up to 96.27%. The disadvantage of these systems is that they may appear too technical for clinicians[64].

Thayan R *et al.* showed that both alpha1-antitrypsin and NS1 proteins were overexpressed by two-fold in DHF patients compared with DF patients[65]. By analysing levels of protein expression in peripheral mononuclear cells, Thayan R et al. showed that alpha tubulin and thioredoxin peroxidase were over-expressed by 4.9 times in DHF patients and 3.3 times in DF patients, while aldolase was up-regulated by 2.2 times in DF patients compared to DHF patients[66]. The role of these biomarkers as indicators for DHF in dengue infected patients is worth exploring.

In short, management of dengue involves management of fever and adequate oral fluid intake during the febrile phase, usually the first 3 to 4 days of illness. For more details on

outpatient management, please refer to the following youtube videos:

http://www.youtube.com/watch?v=p6XPWAco958 – Patient-doctor encounter
http://www.youtube.com/watch?v=tPLLJ2Dka_k – dengue on the rise

After the first 3 to 4 days of illness, monitoring the patient for warning signs of plasma leakage, haemorrhage and shock becomes the main focus of management. Management of dengue shock involves judicious volume replacement with isotonic crystalloids and colloids and supportive care. In a randomised, double-blind comparison study done by Dung N.M. *et al.*[67], Dextran 70 (a colloid) gave the most rapid normalisation of haematocrit, with restoration of cardiac index, without adverse effect. There has been, however, no study on intravenous fluid management in adult patients with dengue shock.

The greatest challenge of intravenous therapy in dengue shock is to give "just enough" to maintain a "good enough" circulation without excessive fluid overload which leads to difficulties in breathing. Preventive transfusions of packed cells and fresh frozen plasma in paediatric patients with dengue shock syndrome with abnormal laboratory coagulation profile without bleeding are not necessary[68].

The study of Carica papaya leaves juice in patients with dengue infection shows a clinically modest but statistically significant rise of platelet count after 40 hours of ingestion of the juice[69]. This study was, however, not designed to address the two critical issues in dengue case management: its efficacy when used in the early febrile phase and whether drinking the papaya leaf juice could prevent the more critical complication of plasma leakage.

A case report of fulminant liver failure in an eight-month-old infant highlighted the potential of excessive dosing of paracetamol to cause this complication[70]. This should serve as a cautionary in adults too.

SPECIAL COMPLICATIONS

Acute liver failure is known to complicate severe dengue. However, the pathogenesis is not well understood. Acute liver failure could be a direct effect of severe dengue infection or a result of a secondary bacterial/fungal infection complicating the dengue infection. A retrospective case series of eight patients with DHF and acute liver failure (ALF) was reported by the national hepatology referral centre (Hospital Selayang, Department of Hepatology). Six of the eight cases had secondary bacterial / fungal infection in the blood and all had systemic inflammatory response syndrome (SIRS). All patients received broad spectrum antibiotics and some patients received fluconazole[71]. Although N-acetycysteine infusion was given as a routine in this report, it should be noted that this practice is not evidence-based.

POTENTIAL ANTI-VIRAL AGENTS

The development of antiviral therapy against dengue infection addresses targets that affect viral to host cell attachment, viral entrance or replication. Local research were restricted to laboratory tests on identifying potential candidates for antiviral development, such as NS5 MTase[72] (methyltransferase (MTase) enzyme which is responsible for assisting viral attachment to host cell via methylation of the viral RNA cap structure) and NS2B/NS3 protease[73] (enzyme responsible for viral life cycle via polyprotein processing).

HEALTHCARE SETTING AND ROLE

The role of primary care physician is important not only for early case detection and management, but also to promote preventive measures in the patients contact environment as well as notification for preventive measures to be taken by the state district health office. Ang KT *et al.* reported that 83.9% of hospitalised dengue patients have sought medical consultation at primary care facilities before admission to hospital and 68.7% had been seen on two or more occasions. The mean duration between first contact with primary care and hospitalisation was 1.4 days. Up to 98% of the patients reported that they had not been not advised on preventive measures even though 51.9% had been informed that they could be having dengue[74] .

A short stay in the emergency department could be an alternative to limit the burden of dengue inpatients while serving as a safety net for untimely discharge and unnecessary admissions. In a retrospective study done in University Kebangsaan Malaysia Medical Centre (UKMMC) from January to March 2010, patients with suspected dengue, who stayed in casualty, had a mean total length of stay of 32.2 hours. All patients were discharged well[75].

PUBLIC HEALTH MANAGEMENT AND CONTROL OF INFECTION

Research related to public health management and control of dengue infection, done locally or internationally were not reviewed and will not be further discussed here.

VACCINATION

The trend of dengue outbreak is likely to continue in Malaysia unless there is a breakthrough in the dengue vaccine development[76]. Vaccine introduction is a complex process[77]. The Dengue V2V initiative was established in 2009 to act as a global scientific expert's forum to lay the groundwork for rapid dengue vaccine introduction. The first Asia-Pacific meeting was held in Singapore at the end of 2010. The experts recommended few key important points which included documenting the actual human and economic costs of dengue, ensuring reliable surveillance of disease, identifying countries or regions for initial vaccine implementation based on data available, developing local logistical plans for dengue vaccine introduction, implementing holistic educational programmes (for health care workers, decision makers and the public), identifying sustainable source of funding and for each countries to take ownership of the disease and redefine the global view on dengue[78].

An effective vaccination program with effective dengue vaccine will be most welcomed. This is based on the fact that:

1) Dengue poses significant disease burden,
2) Current control measures have limited efficacy,
3) Disease treatment is limited to supportive care but the outcome is good if timely care is given.

The information regarding dengue vaccine in this article is limited as we only reviewed published data about the vaccine in Malaysia between 2000 and 2013. A Phase III Randomised Controlled Trial (RCT) on safety and immunogenicity of a tetravalent dengue vaccine in children showed that there were satisfactory safety profile and a balanced humoral immune response against all four DEN serotypes via three dose regimen. Most adverse events were of mild intensity and transient. There was no death. At third dose, seropositivity against all four DEN serotypes increased between 6.1-7.96 fold from baseline across all serotypes[79].

A study that was conducted in two cycles of outbreaks involving dengue virus DEN 2 of the same genotype found that sera of patients from the first outbreaks had poorer neutralisation activity against virus of the second outbreak. There were mild amino acid changes on the viral envelope protein between the same genotypic viruses from two separate outbreaks[80]. This, in part, could explain the eight years cyclical outbreaks of homogenotypic dengue virus in Malaysia. Additionally, effective vaccine should consider the potential subtle antigenic changes that can occur within a homogenotypic dengue virus. Furthermore, from our experience with pneumococcal vaccine introduction, there is the potential for serotype replacemenent with dengue vaccine.

Teoh BT *et al.* and Cardosa MJ *et al.* report on recent local isolation of ancestral sylvatic DEN 1 and DEN 2 from two separate cases of infected humans[81,82]. However, unless there is evidence that there are flare up of slyvatic strains, immunity against the existing four serotypes via vaccination may be good enough.

ANTIBODY DEPENDENT ENHANCEMENT (ADE THEORY) AND DENGUE

In the context of vaccination, two questions on the ADE theory should be addressed:

(i) Would an individual who has yet to complete the full vaccination regime develop a more severe disease?
(ii) Would an individual with waning antibody levels to sub-neutralising levels sometime after vaccination develop more severe disease?

To date, no evidence of ADE phenomenon has been observed. However, continuous monitoring well beyond vaccine introduction, for at least 5 years is necessary. This is to ensure that the vaccinated population will not succumb to increased risk of severe dengue.

MORTALITY

Case fatality rates for dengue cases is in a reducing trend from 0.31 in 2001 to 0.16 in 2012 (Fig. 2). A report of a tertiary referral hospital revealed a 4.1% mortality rate among DHF paediatric patients[83]. Since 2008, all dengue deaths were reviewed at hospital and state health departments and finally at the national level. To date, however, there has been no published literature that report on factors that contributed to the mortality.

QUALITY OF LIFE (QOL)

Lum LCS *et al.* in a prospective study showed that all the 207 participants experienced a drastic decrease in their QoL from the onset of symptoms. The QoL was the lowest (40% of healthy status) between the third and seventh day of illness. The duration of impaired QoL was longer than the duration of fever: nine days for ambulatory patients and 13 days for hospitalised patients[84].

ECONOMIC BURDEN

A large study involving eight countries in America and Asia looked at the economic burden of this disease. The estimated cost of dengue in Malaysia was a mean of USD 317 ± 105 for an ambulatory case and USD 947 ± 389 for a hospitalised case. The average illness lasted 8.6 days for ambulatory patients and 12.6 days for hospitalised patients. Among hospitalised patients, students lost 2.2 days of school, while those working lost on average 6.7 work days per dengue episode[85]. In another study, it was estimated that the economic burden of dengue illness was USD 56 million per year, which is approximately USD 2.03 per capita. The annual expenditure was higher ranging from USD 88 million to USD 215 million if additional cost of managing dengue such as vector control and research and development were included[86].

Economic studies may, however, underestimate the burden of cost if adjustment for under-reporting is not made. Undurraga Y *et al.* stressed the use of expansion factors (EF) to estimate a more accurate burden of dengue in Southeast Asia (SEA). They estimated EF of 7.6 for South East Asia in general and 3.8 for Malaysia[87,88]. None of these studies included costs associated with dengue prevention and control, disease surveillance and long term sequelae of dengue. If these were included, the economic burden will be even greater.

HEALTH ECONOMICS OF DENGUE VACCINE

In view of the high economic burden of a dengue epidemic[85], an effective dengue vaccine might be cost-effective. However, more studies will be required to study the particular age-group to be targeted for vaccination.

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Malaysia has all four dengue virus (DENV) serotypes that infect and circulate among humans.

There may be some genetic predisposition to or protection from severe dengue in certain patients. The findings of inflammatory markers both during the febrile phase and defervescence phase help us to understand the pathogenesis of dengue infection a little bit better. At present, the utility of genetic and biomarkers are still restricted to research purposes.

Clinicians should be aware of the non-specific nature and the wide spectrum of clinical presentation of dengue, and to consider it a possible or probable diagnosis in every case of undifferentiated fever. This has important implications on clinical management and anticipatory follow-up for severe disease and the clinical outcome. Tourniquet test has been shown to be neither sensitive nor specific. The revised WHO classification (2009) is more user-friendly in guiding management of a disease that not only has a diverse but evolving dynamic presentation. In this revised version, clinicians should look out for warning signs and risk factors and conditions known to be associated with severe disease. These include pregnancy, infancy, old age, diabetes mellitus, hypertension, chronic renal failure, chronic heart disease and chronic haemolytic conditions. The warning signs of severe vomiting, severe abdominal pain and lethargy may precede hemodynamic changes of significant plasma leakage.

The laboratory confirmation of dengue is a challenging issue. As Fig. 3 shows the most appropriate tests to confirm the infection which depends on the day of illness and whether the infection is primary or secondary. Dengue IgM is usually present between days 5 and 7 of illness. Therefore, a negative IgM earlier than day 7 does not exclude dengue infection while a positive test may not indicate a dengue infection. A negative IgM for dengue should be repeated during recovery phase. In primary and secondary dengue infection, dengue IgG can be detected in most patients after day 7of illness. Therefore, IgG is recommended after day 7 of illness if IgM is not detected and IgG done earlier was also negative. Dengue PCR is a useful diagnostic tool in early dengue infection, but the use is limited due to the cost and availability. NS 1 antigen is now increasingly used in the early phase of dengue infection.

Management of dengue infection currently focuses on fluid management but the treating physicians should be aware of the dangerous effects of fluid overload.

Table I: Risk factors associated with the development of DHF or DSS

Risk factors with DHF / DSS	OR (CI)
Patients aged > 30 years	2.37 (95% CI= 1.14-4.94)
Patients aged > 30 years with primary infection	4.24 (95% CI = 1.40-12.84)
Patients aged < 30 years with secondary infection	3.86 (95% CI = 1.29-11.58)
Diarrhoea	2.41 (95% CI = 1.04-5.57)
Patients with secondary dengue infections	2.27(95% CI= 1.08-4.78)
Platelet count < 35,000/mm3	2.73 (95% CI= 1.26-5.89)
Independent risk factors with DHF / DSS	
Haematocrit values of > 47% for male	13.22 (95% CI= 3.35-52.20)
Haematocrit values of > 40% for female	3.96 (95% CI =1.52-10.33)
Haematocrit fluctuation of more than 20%	39.71 (95% CI=13.90-113.48)
Activated partial thromboplastin time (APTT) ratio of > 1.25	2.82 (95% CI=1.15-6.90)

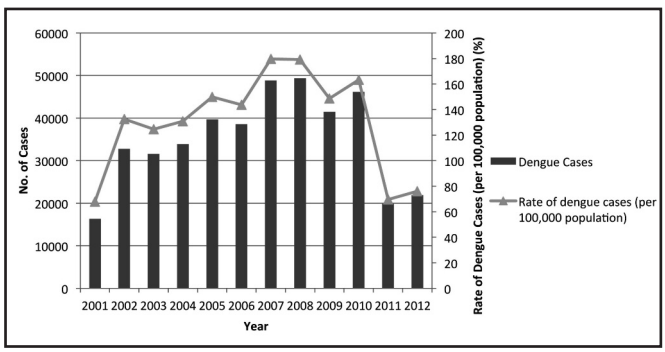


Fig. 1: Number of dengue cases and dengue incidence in Malaysia, 2001-2012.

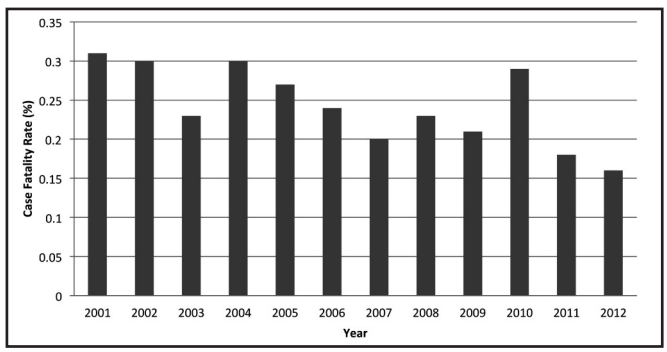


Fig. 2: Dengue Case Fatality Rate (CFR) in Malaysia, 2001-2012.

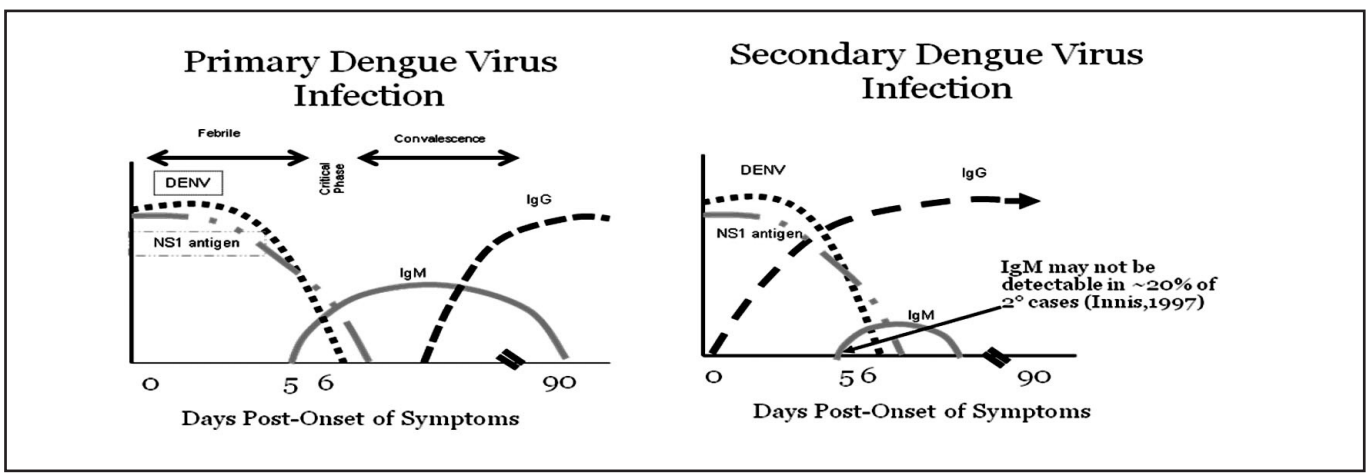


Fig. 3: Relationship between the phases during primary and secondary dengue infections with levels of dengue virus, NS1 antigen, IgM and IgG.

Unusual presentations should provoke considerations of secondary bacterial infections, co-infections with other pathogens, side-effects of drugs such as paracetamol or non-steroidal analgesics and the immune phenomena of haemophagocytosis and post viral infections. Unlike other viruses within the genus Flavivirus from the family Flaviviridae, dengue neurological complications whether due to encephalitis or encephalopathy appear to have good clinical outcome. However, on the rare occasion where dengue virus could be isolated from the brain tissue, the evidence does not support a direct virus invasion of the brain.

A therapeutic trial of the anti-viral effect of lovastatin in dengue infection is currently ongoing[89] and due to be completed in 2015. The phase 3 tetravalent dengue vaccine trial with a follow up period of 25 months[90] in children has an overall protection of 56.5%. Its protection in adults who bear the major burden of illness is still unknown. Other unanswered questions include the duration of protection and the effect of a new dengue serotype from the sylvatic cycle. The implementation of a vaccination programme requires thorough planning of logistics not least of which is a sustainable source of funding[79]. Unlike other arboviruses, dengue virus is maintained in the human cycle without replenishment from a zoonotic reservoir. Thus, wide spread use of dengue vaccine has the potential to eradicate human dengue infections. However, virus eradication by vaccination may provide an 'empty niche' which may eventually be filled by the adaptation of a related virus.

Both vector control and environmental planning may be the most effective methods to deal with the increasing number of dengue infection at this period of time. However the level of awareness of the environmental factors in dengue transmission among the public and their cooperation is still low.

Several local cohort studies showed that the level of awareness among the public with regards to dengue is still very low.

SECTION 3: FUTURE RESEARCH DIRECTION

The best way forward that will provide a more holistic understanding of the disease, clinical manifestations and pathogenesis is collaborative work among clinicians, epidemiologist, entomologist, primatologist and virologist.

The impact and cost-effectiveness of NS1 Ag in the evaluation of acute fever and the optimum outpatient management of dengue infection and admission criteria should be given priority by the primary care and emergency departments.

The effectiveness of and compliance to the current national guideline on acute management of dengue fever are topics of clinical importance. This includes studies looking at the appropriateness of fluid volume, type of fluids in different stages of dengue infection and the admission criteria. Effectiveness of oral fluid therapy in dengue patients should be evaluated. The effect of paracetemol on the liver function and the efficacy of N-acetycysteine in severe liver impairment due to dengue should be assessed. The potential effect of statin on dengue should be explored from a different perspective as we eagerly wait for the result form the Vietnam study[88].

The barriers to implementation of national dengue guidelines should be explored, particularly in view of the large percentage of deaths due to fluid overload. A comprehensive report of dengue deaths may alert clinicians of potential pitfalls in case management. By evaluating various training methods in dengue case management, effective teaching tools may be identified. A more sensitive method of staging the severity of dengue infection should be developed and validated to aid decision-making on outpatient or inpatient care.

ACKNOWLEDGEMENT

We would like to thank the Director-General of Health, Malaysia for his permission to publish this paper. We wish to thank the Clinical Research Centre team for its contribution and support.

REFERENCES

1. Wallace Hazel G, *et al.* Dengue haemorthagic fever in Malaysia 1973 epidemic. South East Asian J. Trop. Med. Pub. Health 1980; 11: 1-12.
2. Fang R, Lo E, Lim TW. The 1982 dengue epidemic in Malaysia: epidemiological, serological and virological aspects. Southeast Asian J Trop Med Public Health 1984; 15: 51-8.
3. Malaysia MoH. Clinical Practice Guidelines on Management of Dengue Infection in Adults. (revised 2nd ed)2010.
4. Malaysia MoH. Statement on dengue by director general of health. 2009.
5. Malaysia MoH. Annual report 1974,1980, 1984, 1998, 1999, 2000.
6. Mia MS, Begum RA, Er AC, *et al.* Trends of dengue infections in Malaysia, 2000-2010. Asian Pac J Trop Med 2013; 6(6): 462-6.
7. Arima Y, Matsui T. Epidemiologic update of dengue in the Western Pacific Region, 2010. Western Pac Surveill Response J 2011; 2(2): 4-8.
8. Arima Y, Edelstein Z, Han HK, *et al.* Epidemiologic update on the dengue situation in the Western Pacific Region, 2011. Western Pac Surveill Response J 2013; 4(2): 47-54.
9. Chew MH, Rahman MM, Sharifah Azura S. Dengue in Malaysia: An epidemiological perspective stud . Pak J Med Sci 2012; 28(4): 643-7
10. Ahmad Nizal MG, Rozita H, Mazrura S, *et al.* Dengue infections and circulating serotypes in Negeri Sembilan, Malaysia. Malaysian Journal of Public Health Medicine 2012; 12(1): 21-30.
11. Anker M, Arima Y. Male-female differences in the number of reported incident dengue fever cases in six Asian countries. Western Pac Surveill Response J 2011; 2(2): 17-23.
12. Ooi EE, Gubler DJ. Dengue in Southeast Asia: epidemiological characteristics and strategic challenges in disease prevention. Cad. Saúde Pública, Rio de Janeiro 2008; 25 Sup 1: S115-S124.
13. Nor Azila, MA Sharifah Azura S, Neoh HM, *et al.* Dengue epidemic in Malaysia: Not a predominantly urban disease anymore. BMC Res Notes 2011; 4(216): 0500-4-216.
14. Chen WS, Wong CH, Cillekens L. Dengue antibodies in a suburban community in Malaysia. Med J Malaysia 2003; 58(1): 142-3.
15. Ravindran T, MS, Fatimah S, *et al.* The role of virological surveillance of dengue serotypes for the prediction of dengue outbreak. Trop Biomed 2001; 18(2): 109-16.
16. Sazaly AB, Wong PF. Re-emergence of Dengue 4 virus. Med J Malaysia 2002; 57(2): 242-3.
17. Vinomarlini G, Rogayah T, Saraswathy TS, *et al.* Molecular typing of dengue viruses circulating on the East Coast ofPeninsular Malaysia from 2005 to 2009. Southeast Asian J Trop Med Public Health 2011; 42(1): 94-9.
18. Chee HY, Sazaly AB. Phylogenetic investigation of dengue virus type 2 isolated in Malaysia. Dengue Bulletin 2003; 27: 101-7.
19. Holmes EC, Tio PH, Perera D, *et al.* Importation and co-circulation of multiple serotypes of dengue virus in Sarawak, Malaysia. . Virus Res 2009; 143(1): 1-5.
20. Shamala D. Dengue: Breakbone fever, hemorrhagia or shock. JUMMEC 2008; 11(2):39-52. 21. Jessie K Fong MY, Shamala D, KC Sekaran, *et al.* Localization of dengue virus in naturally infected human tissues, by immunohistochemistry and in situ hybridization. J Infect Dis 2004; 189(8): 1411-8.
22. MJ. Cardosa. Dengue haemorrhagic fever: questions of pathogenesis. . Curr Opin Infect Dis 2000; 13(5): 471-5.
23. Fong MY, Yusup R, Yusof R, *et al.* Neurovirulence of four encephalitogenic dengue 3 virus strains isolated in Malaysia (1992-1994) is not attributed to their envelope protein. Trans R Soc Trop Med Hyg 2004; 98(6): 379-81
24. Appanna R, Tan LH, Lum LCS, *et al.* Cross-reactive T-cell responses to the nonstructural regions of dengue viruses among dengue fever and dengue hemorrhagic fever patients in Malaysia. Clin Vaccine Immunol 2007; 14(8): 969-77.
25. Appanna R, Wang SM, Ponnampalavanar SA, *et al.* Cytokine factors present in dengue patient sera induces alterations of junctional proteins in human endothelial cells. Am J Trop Med Hyg 2012; 87(5): 936-42.
26. Rathakrishnan A, Wang SM, Hu Y, *et al.* Cytokine expression profile of dengue patients at different phases of illness. PLoS One 2012; 7(12): e52215.
27. Appanna R, Sasheela P, Lum LCS, *et al.* Susceptible and protective HLA class 1 alleles against dengue fever and dengue hemorrhagic fever patients in a Malaysian population. PLoS One 2010; 5(9): 10.1371/journal.pone.0013029.
28. Ooi ET, Ganesananthan S, Anil R, *et al.* Gastrointestinal manifestations of dengue infection in adults. Med J Malaysia 2008; 63(5): 401-5.
29. S. Fadilah, Sahrir S, Mazlam MZ, *et al.* A comparison of the pattern of liver involvement in dengue hemorrhagic fever with classic dengue fever. Southeast Asian J Trop Med Public Health 2000; 31(2): 259-63.
30. Norlijah O, Khamisah A, Kamarul A, *et al.* Serial tourniquet testing in dengue haemorrhagic fever-How clinically useful is it?. Malaysian Journal of Paediatrics and Child Health 2005; 14:27-32.
31. Norlijah O, Khamisah A, Kamarul A, *et al.* Repeated tourniquet testing as a diagnostic tool in dengue infection. Med J Malaysia 2006; 61(1): 22-7.
32. Rusmawati I, Asma Hanim H, Naznin M, *et al.* A descriptive study of blood films of patients serologically positive for dengue in Hospital Tengku Ampuan Afzan, Kuantan. International Medical Journal (IIUM) 2010; 9(2): 35-8.
33. Tong SF, Aziz NA, Chin GL. Prevalence of non-dengue thrombocytopaenia among adult patients presenting with acute febrile illness in primary outpatient clinics. Medicine & health 2006; 1(1): 25-30.
34. Tong SF, Aziz NA, Chin GL, *et al.* Clinical features of acute febrile thrombocytopaenia among patients attending primary care clinics. Malaysian Family Physician 2006; 1(1): 15-8.
35. Tong SF, Aziz NA, Chin GL. Predictive value of thrombocytopaenia in the diagnosis of dengue infection in outpatient settings. Med J Malaysia 2007; 62(5): 390-3.
36. Mustafa B, Hani AW, Chem YK, *et al.* Epidemiological and clinical features of dengue versus other acute febrile illnesses amongst patients seen at government polyclinics. Med J Malaysia 2010; 65(4): 291-6.
37. Norlijah O, Kamarudin NB, Kamarul AR. Clinico-laboratory profile of dengue haemorrhagic fever in Malaysian children. Asian-Oceanian Journal of Pediatrics and Child Health 2004; 3(2).
38. Breen E *et al.*, Early Predictors of Dengue Infection in Adults (EPOD) – A Malaysian Outpatient Experience, Dengue Bulletin 2012, Vol 36.
39. Mohd Zim MA, Sam IC, Omar SF, *et al.* Chikungunya infection in Malaysia: comparison with dengue infection in adults and predictors of persistent arthralgia. J Clin Virol 2013; 56(2): 141-5.

40. Tan PC, Wang SM, Lay KS, *et al.* Dengue infection and miscarriage: a prospective case control study. PLoS Negl Trop Dis 2012; 6(5): e1637.
41. Tan PC, RajasingamG, Devi S, *et al.* Dengue infection in pregnancy: prevalence, vertical transmission, and pregnancy outcome. Obstet Gynecol 2008; 111(5): 1111-7
42. Tee HP, How SH, Jamalludin AR, *et al.* Risk factors associated with development of dengue haemorrhagic fever or dengue shock syndrome in adults in Hospital Tengku Ampuan Afzan Kuantan. Med J Malaysia 2009 64(4): 316-20.
43. Sam SS, Omar SF, Teoh BT, *et al.* Review of dengue hemorrhagic fever fatal cases seen among adults: a retrospective study. PLoS Negl Trop Dis 2013;7(5):e2194.
44. Tan LH, Lum LC, Omar SF, *et al.* Hemophagocytosis in dengue: comprehensive report of six cases. J Clin Virol 2012; 55(1): 79-82.
45. Kamil SM, Mohamad NH, Narazah MY, *et al.* Dengue haemorrhagic fever with unusual prolonged thrombocytopaenia. Singapore Med J 2006; 47(4): 332-4.
46. Rashidi A, Abdul Latiff AK, Salmi AR. Myalgia cruris epidemica: an unusual presentation of dengue fever. Southeast Asian J Trop Med Public Health 2007; 38(6): 1084-7.
47. Umi Kalthum MN, Wong HS. Dengue fever presenting as bilateral dengue maculopathy. Medicine & health 2012; 7(1): 57-61.
48. Tan SY, Kumar G, Surrun SK, *et al.* Dengue maculopathy: a case report. Travel Med Infect Dis 2007; 5(1): 62-3.
49. J M. K. Murthy, Neurological complications of dengue infection. Neurol India 2010; 58: 581-84.
50. Azmin S, S Ramesh, Suehazlyn Z, *et al.* Post-dengue parkinsonism. BMC Infect Dis 2013; 13(179): 2334-13-179.
51. Suhaimi A, Dengue encephalitis. International Medical Journal (IIUM) 2002; 1(2).
52. Masliza M, Noor Darinah MD, Ibtisam M, *et al.* Atrial fibrillation as a complication of dengue hemorrhagic fever: non-self-limiting manifestation. Int J Infect Dis 2009; 13(5): e316-8.
53. Capeding MR, Chua MN, Hadinegoro SR, *et al.* Dengue and Other Common Causes of Acute Febrile Illness in Asia: An Active Surveillance Study in Children. Neglected Trop Dis 2007; 7(7): 1-9.
54. Hamidon BB, Saadiah S. Seoul hantavirus infection mimicking dengue fever. Med J Malaysia 2003; 58(5): 786-7.
55. Yong LS, Koh KC. A case of mixed infections in a patient presenting with acute febrile illness in the tropics. Case Rep Infect Dis 2013; 2013: 562175.
56. Nayar SK, Noridah O, Paranthaman V, *et al.* Co-infection of dengue virus and chikungunya virus in two patients with acute febrile illness. Med J Malaysia 2007; 62(4): 335-6.
57. Ng CF, Lum LC, Noor Azina I, *et al.* Clinicians' diagnostic practice of dengue infections. J Clin Virol 2007; 40(3): 202-6.
58. Lum LC, Goh AY, Chan PW, *et al.* Risk factors for hemorrhage in severe dengue infections. J Pediatr 2002; 140(5): 629-31.
59. Bandyopadhyay S, Lum LC, Kroeger A. Classifying dengue: a review of the difficulties in using the WHO case classification for dengue haemorrhagic fever. Trop Med Int Health 2006; 11(8): 1238-55.
60. Faisal T, Taib MN, Ibrahim F. Reexamination of risk criteria in dengue patients using the self-organizing map. Med Biol Eng Comput 2010; 48(3): 293-301.
61. Faisal T, Ibrahim F, Taib MN. Analysis of significant factors for dengue infection prognosis using the self organizing map. Conf Proc IEEE Eng Med Biol Soc 2008; 2008: 5140-3.
62. Ibrahim F, Ismail NA, Taib MN, *et al.* Modeling of hemoglobin in dengue fever and dengue hemorrhagic fever using bioelectrical impedance. Physiol Meas 2004; 25(3): 607-15.
63. Ibrahim F, Taib MN, Abas WA, *et al.* A novel dengue fever (DF) and dengue haemorrhagic fever (DHF) analysis using artificial neural network (ANN). Comput Methods Programs Biomed 2005; 79(3): 273-81
64. Ibrahim F, Faisal T, Salim MI, *et al.* Non-invasive diagnosis of risk in dengue patients using bioelectrical impedance analysis and artificial neural network. Med Biol Eng Comput 2010; 48(11): 1141-8.
65. Thayan R, Huat TL, Lum LCS, *et al.* The use of two-dimension electrophoresis to identify serum biomarkers from patients with dengue haemorrhagic fever. Trans R Soc Trop Med Hyg 2009; 103(4): 413-9.
66. Thayan R, Huat TL, Lum LCS, *et al.* Differential expression of aldolase, alpha tubulin and thioredoxin peroxidase in peripheral blood mononuclear cells from dengue fever and dengue hemorrhagic fever patients. Southeast Asian J Trop Med Public Health 2009; 40(1): 56-65.
67. Dung N M, Day NP, Tam TH, Loan HT, Chau HTT, Minh LN, Bethell DB, Kneen R, Hien TT, White NJ, Farrar JJ. Fluid replacement in Dengue Shock Syndrome: A Randomized, Double-blind Comparison of Four Intravenous Fluid Regimens. Clinical Infectious Disease 1999; 29: 787-94.
68. Lum LCS, Abdel-Latif Mel-A, Goh AYT, *et al.* Preventive transfusion in Dengue shock syndrome-is it necessary? J Pediatr 2003; 143(5): 682-4.
69. Subenthiran S, Tan CC, Cheong KC, *et al.* Carica papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue haemorrhagic fever. Evid Based Complement Alternat Med 2013; 2013: 616737.
70. Gan CS, Chong SY, Lum LCS, *et al.* Regular paracetamol in severe dengue: a lethal combination? Singapore Med J 2013; 54(2): e35-7.
71. Tan SS, Bujang MA. The clinical features and outcomes of acute liver failure associated with dengue infection in adults: a case series. Braz J Infect Dis 2013; 17(2): 164-9.
72. Lim SV, Rahman MB,, Tejo BA. Structure-based and ligand-based virtual screening of novel methyltransferase inhibitors of the dengue virus. BMC Bioinformatics 2011; 12 Suppl 13: S24,2105-12-S13-S24. Epub 011 Nov 30.
73. Heh CH, Othman R, Buckle MJ, *et al.* Rational discovery of dengue type 2 non-competitive inhibitors. Chem Biol Drug Des 2013; 82(1): 1-11
74. Ang KT, Dengue cluster outbreak in Gombak. Journal of Health Management 2008; 5(2): 55-61.
75. Nasarudin NM, Mohd SI, Ismail AK. The role of an emergency department short-stay ward in the management of dengue fever: a case-control study in a university hospital. Eur J Emerg Med 2013; 20(5): 335-8
76. Sazaly AB, Shafee N. Outlook of dengue in Malaysia: a century later. Malays J Pathol 2002; 24(1): 23-7.
77. Lam SK, Challenges in reducing dengue burden; diagnostics, control measures and vaccines. Expert Rev Vaccines 2013; 12(9): 995-1010.
78. Lam SK, Burke D, Capeding MR, *et al.* Preparing for introduction of a dengue vaccine: recommendations from the 1st Dengue v2V Asia-Pacific Meeting. Vaccine 2011; 29(51): 9417-22.
79. Amar Singh HSS, Koh MT, Tan KK, *et al.* Safety and immunogenicity of a tetravalent dengue vaccine inhealthy children aged 2-11 years in Malaysia: A randomized, placebo-controlled, Phase III study. Vaccine 2013; 31(49): 5814-21.
80. Wong SS, Abd-Jamil J, Sazaly AB. Antibody neutralization and viral virulence in recurring dengue virus type 2 outbreaks. Viral Immunol 2007; 20(3): 359-68.
81. Teoh BT, Sam SS, Juraina AJ, *et al.* Isolation of ancestral sylvatic dengue virus type 1, Malaysia. Emerg Infect Dis 2010; 16(11): 1783-5.
82. Cardosa MJ, Ooi MH, Tio PH, *et al.* Dengue virus serotype 2 from a sylvatic lineage isolated from a patient with dengue hemorrhagic fever. PLoS Negl Trop Dis 2009; 3(4): e423.
83. Norlijah O, Booth A, Intan H, *et al.* Overt bleeding in dengue infection. Asian-Oceanian Journal of Pediatrics and Child Health 2006; 1:23-30.
84. Lum LCS, Suaya JA, Tan LH, *et al.* Quality of life of dengue patients. Am J Trop Med Hyg 2008; 78(6): 862-7.
85. Suaya JA, Shepard DS, Siqueira JB, *et al.* Cost of dengue cases in eight countries in the Americas and Asia: a prospective study. Am J Trop Med Hyg 2009; 80(5): 846-55.
86. Lee HL, Vasan SS, Birgelen L, *et al.* Immediate cost of dengue to Malaysia and Thailand: an estimate. Dengue Bulletin 2010; 34: 65-76.
87. Undurraga EA, Halasa YA, Shepard DS. Use of Expansion Factors to Estimate the Burden of Dengue in Southeast Asia: A Systematic Analysis. PLoS Negl Trop Dis 2013; 7(2): e2056.
88. Shepard DS, Lees RS, Ng CW, Undurraga EA, Halasa Y, Lum LCS. Burden of Dengue in Malaysia. Report from a Collaboration between Universities and the Ministry of Health of Malaysia. 2013.
89. Withehorn J, Van Vinh Chau N, *et al.* Lovastatin for adults patients with dengue: protocol for a randomized controlled trial. Trial 2012 doi: 10.1186/1745-6215-13-203.
90. Capeding M R, Tran N H, *et al.* Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomized, observer-masked, placebo-controlled trial. Lancet 2014 (online publication).

A Review of HIV/AIDS Research in Malaysia

Koh Kwee Choy, MMed

Department of Medicine, International Medical University, Clinical School, Jalan Rasah, Seremban, Negeri Sembilan.

SUMMARY

Two hundred fifty seven articles related to HIV/AIDS were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000–2013. One hundred seventy one articles were selected and reviewed on the basis of clinical relevance and future research implications. This review of literature has been divided into six sections, namely, epidemiology, risk behaviour, clinical features and opportunistic infections, management, diagnosis and discussion. Wherever possible, the reviewed articles have been presented in a chronological order to provide a historical perspective to the reader as many of the results of earlier publications, which are common knowledge now, were relatively unknown then. Since the early days of the HIV epidemic in Malaysia, there have been rapid advances in the understanding and the management of the epidemic in Malaysia based on the insights derived from the results of these research. These insights are invaluable tools for policy makers, advocators, healthcare providers, researchers and everyone and anyone who are involved in the care of individuals with HIV/AIDS. Attempts have been made to identify gaps in certain research areas with the hope of providing directions for future research in HIV/AIDS in Malaysia.

KEY WORDS: *HIV, AIDS, Review, stigma, discrimination, religion, knowledge, attitude, practice, prevalence, incidence, genotyping, phylogenetic studies, most-at-risk-populations*

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY

This year, 2014, marks the 30th year since the Human Immunodeficiency Virus (HIV) was identified as the causative agent of Acquired Immune Deficiency Syndrome (AIDS). Cure, however, remains elusive and HIV and AIDS have resulted in approximately 30 million deaths worldwide since the first few cases were reported in 1981[1]. In Malaysia, the numbers have increased dramatically from the initial three cases of HIV infections reported in 1986 to 91,362 cases of HIV-infections, 16,352 AIDS cases and 12,943 AIDS-related deaths by the end of 2010[2]. Nevertheless, the global scientific community has made great strides in the fight against the epidemic. The introduction of Highly Active Antiretroviral Therapy (HAART) in the early 1990s transformed HIV/AIDS infections from a death sentence to a chronic manageable condition. People living with HIV and AIDS (PLWHA) on HAART can now be expected to live a near normal or normal life.

Malaysia is home to one of the fastest growing HIV epidemics in the East Asia and Pacific regions. Although the disease was mostly confined within the circle of injecting drug users (IDUs) in the early years, it has since spread to every stratum of society. In 2010, 40% of new reported HIV cases were from heterosexual transmission, a dramatic increase from 27% in 2009. The proportion of women reported with HIV has increased from 4% of new cases in 1995 to 12% in 2005 and 18% in 2010. In 2010, the ratio of housewives and sex workers who tested HIV-positive was 13:1. A report in 2004 estimated that there were 19 new HIV infections per day in youths[3]. Gender inequity, silence, denial and ignorance continue to fuel the epidemic in Malaysia[4]. However, with several major national initiatives in place, there is evidence to suggest the increase of HIV and AIDS cases in Malaysia may at last be slowing[5].

The most-at-risk-populations (MARPs) for HIV transmission in Malaysia are the IDUs, sex workers, men-who-have-sex-with-men (MSM), women, transgender people and migrant workers. The estimated prevalence of HIV infections in some of these groups and other important groups of people are shown in Table I.

A systematic review of published and unpublished articles between 1998 and 2003 in developing countries including Malaysia, estimated the prevalence of HIV infection among IDUs was more than 20%[20]. Roshan *et al*[21], reported that only 46% of Malaysian blood donors whose blood tested positive for HIV responded to calls from the transfusion medicine units which is a cause for concern; while Tan *et al*[22], discussed the cost-effectiveness screening for HIV in the general population with special reference to the mandatory premarital screening for Muslims.

RISK BEHAVIOUR

The risk behaviours attributable to HIV acquisition in several at-risk groups such as sex workers, IDUs, pregnant women, fishermen and MSM are summarised in Table II. Three main survey tools were used in most of these studies: self-administered structured or semi-structured questionnaires or face-to-face interview using a structured questionnaire. The risk behaviours of each group were distinctly different. Among the IDUs, injecting drug use, sharing of injection apparatus, substance abuse at young age, sex with prostitutes, and high risk sexual behaviours were the common denominators[7,8,23-25]. Among MSM, unprotected anal sex was identified as risk behaviour in all three studies[12,13,23]. Among fishermen, poor social and parental guidance were identified as significant risk behaviours in addition to drug use and high risk sexual behaviours[19,26]. Huang *et al*[27], discussed the vulnerability of partners of fishermen. In a majority of HIV-infected pregnant women, the only risk factor identified was sexual intercourse with their partners[15,16,28].

Corresponding Author: kweechoy_koh@imu.edu.my

Table I: Prevalence of HIV in selected groups in Malaysia

Authors	Group	Setting (year)	N	HIV prevalence
Anonymous[6]	IDU	National HIV Screening Program (2002)	NA	9.67% to 41.19%
Chawarski[7]	IDU	Treatment seeking subjects in a clinical drug abuse treatment trial	177	19.2%
Chawarski[8]	IDU	Opiate IDU not-in-treatment in 3 urban areas (2006–2008)	732	27.6%
Fauziah[9]	IDU	Drug users in 26 rehabilitation centres in Malaysia	6324	12.1%
Anonymous[10]	SW	National HIV Sentinel Surveillance Survey (1996)	NA	6.3%
Anonymous[11]	SW	Ad hoc survey (2000)	208 females 136 male transsexuals	6.9% 14.0%
Kanter[12]	MSM	MSM sex soliciting sites (2011)	517	3.9%
Koh[13]	MSM	Community based voluntary counselling and testing centre (1998)	433	9.2%
Anonymous[14]	PW	National Surveillance (1998–2002)	NA	0.02–0.04%
Balkis[15]	PW	National Antenatal HIV Screening Programme in healthcare centres in Terengganu (1998–2001)	57,882	0.052%; VT 6.25%
Japaraj[16]	PW	National Antenatal HIV Screening Programme in healthcare centres in Perak and Negeri Sembilan (1997–1999)	26,195 (Perak) 22,524 (Negeri Sembilan)	0.08%; VT 14% (3/21) 0.03%; VT 20% (6/29)
Zahariyah[17]	PW	National Antenatal HIV Screening Programme in healthcare centres in Kedah (1992–2002)	53,380	0.07%; VT 15.8% (3/19)
Khebir[18]	PMS	Premarital HIV screening programme in Johor (2002–2004)	74,210	0.17%
Anonymous[14]	BD	National HIV screening programme for blood donors (2002)	418,118	0.034%
Anonymous[14]	STI	National Surveillance of STI patients diagnosed at health clinics (2002)	1183	6.09%
Anonymous[14]	LDTD	National Surveillance (1999)	NA	1.7%
Anonymous[14]	FM	National Surveillance (2002)	NA	2.7%
Fauziah[19]	FM	Selected fishermen in Terengganu (1997)	542	1.7%

Abbreviations: NA, not available; IDU, intravenous drug user; SW, sex workers; MSM, men-who-have-sex-with-men; PW, pregnant women; VT, vertical transmission; PMS, premarital screening; BD, blood donors; STI, sexually transmitted infections; LDTD, long distance truck drivers; FM, fishermen.

KNOWLEDGE, ATTITUDE AND PRACTICE

Most of the studies on knowledge, attitude and practice related to HIV/AIDS were focussed on MARPs such as MSM, IDUs and pregnant women. Several such studies on other vulnerable groups such as adolescents, students, fishermen, indigenous people (orang asli), factory workers, and healthcare workers were also reported.

Men-Who-Have-Sex-With-Men (MSM)

Kanter *et al*[12] reported 20% of MSM did not believe that HIV is transmissible through insertive or receptive anal sex. Koh *et al*[13] reported that most MSM practiced oral and anal sex (79.3%, 337/425), had multiple sexual partners (37.9%, 196/425 had between two to five male sex partners and 25,7%, 133/425 had more than six male sex partners in the last six months) and admitted to low rates of condom use during vaginal (20%), anal (13.5%) and oral sex (1.3%). Lim *et al*[29] reported alarming rates of unprotected receptive anal intercourse with internal ejaculation (URAIE) among Asian MSM in a large online survey of 10,413 MSM across Asia, including Malaysia.

Prisoners

Bachireddy *et al*[30] surveyed 102 opioid-dependent prisoners and reported alarmingly high rates of needle sharing (66%), unprotected sex before incarceration (30%), injecting drug use (77%) and low proportion of prisoners who believed they needed opioid substitution therapy (OST) after release to prevent relapse (33%). Gill *et al*[31] reported that knowledge of HIV status had no bearing on high risk sexual behaviours where 73.3% of IDUs continued to practice high risk sexual behaviours despite knowing their HIV status.

Pregnant women

Akmal *et al*[32] surveyed 158 pregnant women attending antenatal clinic in Hospital Muar and reported high rates of HIV screening (95%). Among those who declined to be screened, the most common reasons for refusal were feeling of wellbeing, the perception of not being at risk and apathy. Sharifa *et al*[33] surveyed 205 antenatal mothers in western Sabah and reported that a low proportion of them had good knowledge (32.3%), attitude and practice (56.4%) related to HIV/AIDS. These women were younger, better educated and had received health education from health staff. Vinothini *et al*[34] conducted a face-to-face survey of 100 pregnant women in an urban antenatal clinic in Malaysia in 1999 and reported good knowledge about HIV/AIDS was positively correlated with higher level of education. The issues of rising HIV infection rates among women and the feminisation of the HIV epidemic were discussed in an article produced by UNICEF and the Malaysian Ministry of Health[35].

Table II: Risk behaviours for HIV acquisition in at-risk groups

Authors	Group	Setting (year)	Significant risk behaviours
Chawarski[7]	IDU	Survey of 177 treatment seeking subjects in a clinical drug abuse treatment trial.	Malay ethnicity Lifetime IDU Needle sharing Lack of condom use during sex
Chawarski[8]	IDU	Survey of 732 opiate IDUs not-in-treatment in 3 urban centres. (2006– 2008)	Lifetime use of amphetamine type stimulants Lifetime use history of sharing needles
Fauziah[9]	IDU	Survey of 6324 drug users in 26 rehabilitation centres in Malaysia. (1998)	Injecting drug use Sharing needles Addiction at young age Had sexual exposures Had sex with prostitutes
Dokubo[23]	IDU	Systematic review of articles and abstracts in 13 countries, including Malaysia. (1983–2012)	Young age Frequent injections Sharing of needles or syringes
Vicknasingam[24]	IDU	Survey of 526 IDUs not-in-treatment from 5 cities in peninsular Malaysia.	Sharing injection equipment Multiple sexual partners
Juita[25]	IDU	Case control study of 87 HIV-positive vs 261 HIV-negative drug addicts in a drug rehabilitation centre in Selangor. (1994)	Needle sharing (OR 8.53) Sex with prostitutes (OR 3.7) Homosexuality (OR 4.05) Non-condom use during sex with prostitutes (OR 2.27)
Dokubo[23]	SW	Systematic review of articles and abstracts in 13 countries, including Malaysia. (1983–2012)	Brothel work
Kanter[12]	MSM	Survey of 517 MSM in sex solicitation sites in Kuala Lumpur. (2011)	Unprotected anal sex with casual partner (OR 2.99) Unprotected receptive anal sex (OR 2.71) Group sex (OR 3.7)
Koh[13]	MSM	Survey of 433 MSM in a community based voluntary counselling and testing centre in Kuala Lumpur.(1998)	Inconsistent condom use during anal sex (OR 3.7)
Dokubo[23]	MSM	Systematic review of articles and abstracts in 13 countries, including Malaysia. (1983–2012)	Multiple male sexual partners Receptive anal intercourse Syphilis
Balkis[15]	PW	National Antenatal HIV Screening Programme of 57,882 pregnant women in healthcare clinics in Terengganu. (1998–2001)	93% of HIV positive pregnant women's only risk factor was sexual contact. 66.7% of the husbands were HIV-positive
Japaraj[16]	PW	National Antenatal HIV Screening Programme of 48,719 pregnant women in healthcare clinics in Perak and Negeri Sembilan. (1997–1999)	Multiple sexual partners
Zahariyah[26]	PW	HIV antenatal screening programme in Kedah. (1999–2002)	Sexual contact with husbands. Risk factors for husbands include IDU and multiple sexual partners
Fauziah[19]	FM	Survey of 542 fishermen. (1997)	Drug use (marijuana, morphine, heroin) (OR 7.3) Regular and non-regular sex partners Sex with prostitutes
Niza[27]	FM	Focus group discussions with fishermen in East Coast of Malaysia.	Early involvement in substance abuse High risk sexual behaviours Poor parental support Lack of social support

Abbreviations: IDU, intravenous drug user; SW, sex workers; MSM, men-who-have-sex-with-men; PW, pregnant women; OR, odds ratio; FM, fishermen.

Table III: Case reports of HIV/AIDS-related conditions

Authors	Case report
Tan *et al*[128]	Reported the first 3 cases of disseminated histoplasmosis in patients with AIDS.
Jarmin *et al*[129]	Reported a rare case of spontaneous common bile duct perforation due to Mycobacterium tuberculosis in a HIV-positive man and its management.
Kenali *et al*[130]	Reported a rare case of concurrent mycobacterial infection and non-Hodgkin's lymphoma at the same site in a patient with AIDS.
Subha *et al*[131]	Reported a case of Nocardia infection of the mastoid in a patient with HIV.
Wong *et al*[132]	Reported the successful management of pulmonary hypertension using sildenafil in an 18-month old child.
Othman *et al*[133]	Reported a case of intra-abdominal mass due to Penicillium marneffei in a 7-year-old child with HIV which responded to conventional antifungal therapy.
Chow *et al*[134]	Highlighted the risk of fatal lactic acidosis secondary to ART in a report of two cases of HIV-positive patients receiving ART.
Khairy-Shamel *et al*[135]	Reported on a case of orbital rhabdomyoscarcoma with intracranial extension in a child with HIV that responded to surgery, chemotherapy and reinstitution of ART.
Ketan *et al*[136]	Reported a case of pancreatic TB in a HIV-positive patient that mimicked carcinoma.
Fong *et al*[137]	Reported a case of cutaneous toxoplasmosis in a HIV-positive patient whose anti-toxoplasma antibody was negative. Histopathological examination, electron microscopy and PCR confirmed the diagnosis.
Isa *et al*[138]	Reported a case of renal tubular acidosis in a patient with hepatitis C-HIV-tuberculosis lymphadenitis co-infections and its management.
Nimir *et al*[139]	Reported a case of toxoplasma encephalitis in a HIV-positive man who presented with seizure. The diagnosis was complicated by the presence of lung findings suggestive of pulmonary tuberculosis.
Nurfahzura *et al*[140]	Reported the successful treatment of syphilitic uveitis in several HIV-positive patients.

General public, adolescents and young adults

Jasvindar[36] surveyed 39,910 Malaysians in 2006 as part of the 3rd National Health and Morbidity Survey and reported high proportions of them were aware of the high risk of HIV transmission when not using condom. Those with the poorest knowledge were from the lower income group, had lower education levels and were rural dwellers. Siti *et al*[37], surveyed 520 adolescents aged 15–21 years and reported high scores for knowledge and positive attitude towards HIV/AIDS but also prevalence of misconceptions regarding HIV transmission and gender bias related to sexual behaviour and contracting the disease. Although 72% of the sexually-experienced did not use protection at first sexual intercourse, 80% did not perceive themselves to be at risk of contracting HIV. Jasvindar et al, advocated a critical review of existing HIV/AIDS prevention programmes to focus on adolescent risk taking behaviour and sexuality issues, including male-female negotiation skills. Wong *et al*[38], reported similar findings in a survey of 1075 young adults aged 15–24 years.

Students

Ahmed *et al*[39], reported serious misconceptions, negative attitudes and risk perceptions towards HIV/AIDS among 108 pharmacy students. Chew *et al*[40], surveyed 170 preclinical and 170 clinical medical students of a public university in Malaysia and reported the former were more stigmatising while the latter were less comfortable handling patients with HIV. Ibrahim *et al*[41], reported improvement of knowledge and attitude after intervention in the form of peer-led education among 276 university students. Jahanfar *et al*[42], reported similar improvement among 182 secondary school students who received a two-hour talk on sex education. However, in another study on 530 university students who received a four-hour education programme, Jahanfar *et al*[43], reported that improvement in knowledge and attitudes towards HIV did not translate into change in risk taking behaviour.

Koh *et al*[44], surveyed 1020 medical students from several public and private medical universities; and reported that less than 20% had received adequate training to care for PLWHA. Medical students from public universities had more prevalent negative beliefs regarding testing, confidentiality, disclosure and environment of care towards PLWHA compared to students from private universities. However, in providing care to PLWHA, the attitudes were largely positive and non-discriminatory in both cohorts of students. Ni *et al*[45], surveyed 155 medical students from a university in East Malaysia and reported relatively poor knowledge on HIV/AIDS. Rozina *et al*[46], surveyed 23,202 university students and reported unsatisfactory level of knowledge and low condom usage (29.8%) among sexually active students. In another survey of 1773 university students, Rozina *et al*[47], reported only 19.5% were willing to disclose their HIV status to partners or family if diagnosed with HIV infection and only 43% were willing to care for an HIV-infected person in the house.

Fishermen, *Orang Asli* and factory workers

Fauziah *et al*[19], surveyed 542 fishermen in 1997 and found high proportion of false beliefs such as the belief that HIV is transmissible through shaking hands (44.3%), insect bites (41.0%), and sharing public utilities (50.9%), and that it is curable (39.7%). Anita *et al*[48], surveyed 2706 *Orang Asli* and reported that although they made up only 0.5% of the population of Malaysia, they constituted 0.06% of total notified HIV cases. The HIV seroprevalence among them was 0.3%. Although knowledge regarding HIV/AIDS was fair (30–50%), they had negative attitudes towards the disease. In a survey of 3300 factory workers in Negeri Sembilan and Melaka, Anita *et al*[49], reported they had high levels of knowledge and positive attitude towards HIV/AIDS.

Healthcare providers

A small survey of 34 doctors and 52 nurses revealed that about half of them had fair knowledge regarding post-exposure

prophylaxis (PEP) against HIV[50]. A survey of 450 female surgical-based nurses in a teaching hospital in Kuala Lumpur found that senior nurses and nurses who had received training on universal precaution had higher level of knowledge and more positive attitude towards HIV/AIDS[51]. Hasnah *et al*[52], surveyed 222 healthcare workers and reported that good knowledge on universal precaution was not reflected in practice during a five-day observation in the ward.

Khan *et al*[53], surveyed 270 PLWHA regarding their knowledge, attitude and practice on oral hygiene and found most were ignorant about the oral manifestations of the disease and 1/3 of them had negative attitudes towards oral healthcare, and often resorted to various measures to manage oral lesions rather than seek professional care.

CLINICAL FEATURES AND OPPORTUNISTIC INFECTIONS

Opportunistic infections

Articles published in the early 2000s reported patterns of opportunistic infections (OIs) in Malaysian HIV-positive patients that were consistent with research findings from around the world. A retrospective survey of 419 patients in the Kuala Lumpur General Hospital (KLGH) from 1994–2001 found the preponderant age group to be 25–34 years. Half (53%) had CD4 < 200 cells/mm^3 at time of diagnosis of OI. The survey also revealed heterosexual contact as the leading risk for HIV transmission, HIV infection via IDU to be directly related to the incidence of tuberculosis (TB) infection, and HIV-related TB was dependently correlated with unemployment. The four main AIDS-defining diseases were TB (48%), pneumocystis carinii pneumonia (PCP) (13%), toxoplasma encephalitis (TE) (11%) and cryptococcal meningitis (7%)[54].

Another retrospective survey on the prevalence of pulmonary OIs in 406 AIDS patients in KLGH in May 2001 found that most of them had CD4 <200 cells/mm^3 (65.1%). Almost half, 40.9% (166/406) had pulmonary OIs with pulmonary tuberculosis (PTB) being the most common (30.1%). Cough (75.3%) and fever (34.3%) were common clinical manifestations. Oral candidiasis was the most common co-infection with AIDS-related pulmonary OIs (39.8%)[55]. Another survey of 205 HIV-infected patients in KLGH from 2001–2002 on the spectrum of OIs found an older preponderant age group of 34–45 years. The median CD4 count was 34 cells/mm^3 and sexual contact was the most frequent mode of transmission (78.5%) followed by injecting drug use (30%) and blood transfusion (5%). Oral candidiasis was the most common muco-cutaneous disease and there were significant co-infection with main OIs such as TB, PCP, TE, penicillosis, and cytomegalovirus (CMV) retinitis. A CD4 count < 100 cells/mm^3 at diagnosis of OI was significantly associated with major OIs[56]. A small retrospective study of 59 HIV-positive patients with OI admitted from 2000–2009 reported PCP and toxoplasmosis as the most common OIs[57].

Tuberculosis

HIV prevalence in patients with TB was estimated to be between 6.3% and 10.5%.[11,58] Nissapatorn *et al*[59], reported significant association between HIV-infected injecting drug users and PTB in a survey of 290 patients with HIV-related TB. They reported that 57% patients subsequently were lost to follow-up, 31.8% were successfully treated and 0.8% had died by the end of the study. In another report, Nissapatorn *et al*[60], found significant association between occupation or mode of HIV transmission and TB infection. Pulmonary tuberculosis was the most common manifestation of TB infection (84.6%, 104/123). The most common symptoms were fever, cough, sputum or haemoptysis. Narwani *et al*[61], compared 97 HIV-negative and 97 HIV-positive TB patients and reported dissimilarity between the two cohorts in terms of age, family members to room ratio, sex and marital status. Mohammad *et al*[62], reported that HIV-positive TB patients were less infectious to their contacts compared to HIV-negative TB patients.

Mohammad *et al*[63], explored the clinical features, radiological findings and outcomes of treatment in 149 HIV-positive TB patients and found that 80% (117/149) had PTB, 20% had extrapulmonary TB (ETB), 45% had cough, 51% had sputum smear positive, 55% had radiological findings (localised, military, diffused infiltrates, opacities) on chest radiograph, 5.4% had pleural lesions, 5.5% had mediastinal or hilar lesions. During the survey period, 38.9% died. The median survival time from treatment initiation was 13.5 weeks (range 1–56). Majority (74%) died without completing the six-months of anti-TB therapy.

Velaiutham *et al*[64], found no correlation between Mantoux test, sputum culture and CXR severity in HIV-positive TB patients. They also reported higher incidence of sputum smear negative, sputum culture positive and non-reactive tuberculin skin test in these patients. Pulmonary tuberculosis was the most common manifestation (63%) followed by ETB (22%), and PTB + ETB (15%). Tuberculosis adenitis was the most common ETB presentation. Chest radiograph findings ranged from moderate to severe in sputum acid fast bacilli (AFB) negative patients. Kooi *et al*[65], reported that AIDS patients with CD4 count < 200 cells/mm^3 were more likely to present with atypical radiographic appearance of PTB.

Nissapatorn *et al*[66] reported the similarities and differences between PTB and ETB in HIV-infected patients in a survey of 406 HIV-positive TB patients. Both groups had similar mean age and most had CD4 count < 200 cells/mm^3. For PTB, cough and haemoptysis (88%) were the most common symptoms; the lungs were most commonly affected (89%) and 42% were successfully treated with six months anti-TB therapy. For ETB, lymphadenopathy (33.5%) was the most common symptom; miliary TB was the most common disease location (55.6%) and 43% were successfully treated with nine months anti-TB therapy. Among patients who defaulted therapy, a higher proportion (87%) had PTB. No multidrug resistant (MDR)-TB or relapse cases were detected in this study. Naing *et al*[67], performed a meta-analysis study and found significant association between HIV and ETB (OR 1.3), and between CD4 count <100 cells/mm3 and ETB (OR 1.3).

Toxoplasmosis

Diagnosing *Toxoplasma* gondii infection in HIV-positive patients based on serological results can be challenging. Shamilah *et al*[68], reviewed the immunofluorescent antibody test (IFAT) results of 2554 sera of HIV-positive and HIV-negative patients between 1995–1997. The authors considered IgG titre cut-off point of 1:>64 by IFAT to be highly suggestive of current toxoplasmosis. They reported an overall prevalence of 26.3% with a significantly higher prevalence in HIV-positive (31.3%) compared with HIV-negative (24.3%) patients. Nissapatorn *et al*[69], compared the toxoplasma IgG serology results of 100 HIV-positive patients and 203 healthy blood donors. They reported toxoplasma IgG seroprevalence of 21% and 28.1% in HIV-positive patients and blood donors, respectively. There was no significant association between seroprevalence of toxoplasma IgG with possible risk factors such as contact with felines, consumption of undercooked meat, and history of blood transfusions in both groups. The mean CD4 count in HIV-

positive patients in this study was 202.23 cells/mm^3. The CD4 count was not associated with seropositivity for toxoplasma antibodies in HIV/AIDS patients.

Nissapatorn *et al*[70], determined the anti-toxoplasma IgG levels by ELISA technique in 301 sera of HIV/AIDS patients. They reported seroprevalence of 41.2% (124/301). Higher seroprevalence were found in Malays (57.9%) compared to Chinese (38.7%) and Indians (29.6%). No association between toxoplasma IgG seroprevalence and CD4 count was found.

Nissapatorn *et al*[71], reported toxoplasma IgG seroprevalence of 51.2% (208/416) in a survey of 406 HIV-infected patients and 14.9% (31/208) were diagnosed with active toxoplasma encephalitis (TE) while 10.6% (22/208) had chronic (latent) toxoplasma infection. The most common symptom was headache (67.7%). Computed tomography (CT) brain scan findings included multiple lesions (87.5%), hypodense lesion (66.7%) and frontal region (41.7%). Significant association was found between CD4 count and TE (PR 2.6, $p = 0.019$). After six weeks of anti-TE therapy, relapsing TE was detected in 9.7% cases.

Nissapatorn *et al*[72], surveyed 505 HIV-infected patients and reported a toxoplasma IgG seroprevalence of 44.8% (226/505). Out of the 88.7% (448/505) with no TE, 44.4% (199/448) showed toxoplasma seropositivity. In contrast, 11.3% (57/505) had TE; out of which 47.4% (27/57) showed toxoplasma seropositivity. Six-point-five percent (17/260) who received primary prophylaxis (cotrimoxazole) and 0.7% (1/137) who received HAART developed TE. The most common symptom was headache (56%). The CT findings included multiple lesions (96.4%), hypodense lesion (66.7%), and parietal region (39.3%). The median CD4 count was 25 cells/mm^3. The CD4 count of < 100 cells/mm^3 was significantly associated with development of TE.

A comprehensive review of toxoplasmosis in HIV/AIDS in 2009 reported the prevalence of latent toxoplasma infections in HIV-infected patients varied between 3–97%[73]. Prevalence was related to ethnicity, certain risk factors, and reactivation of toxoplasma infection. In the pre-HAART era, TE was the most common focal cerebral lesion in approximately half of toxoplasma-seropositive AIDS patient with toxoplasma infection. Infection of the eyes, lungs, heart and the spinal cord has been reported. The introduction of HAART resulted in marked decrease in overall incidence. Toxoplasma encephalitis was significantly associated with neurological immune restoration inflammatory syndrome (NIRIS)[73].

Parasitic infections

Asma *et al*[74], examined the stool samples of 346 HIV-infected individuals and reported the prevalence of intestinal parasitic infection (IPI) as 37.9% (18.8% protozoa and 7.5% helminths), and 50.4% had multiple parasitic infections. Low CD4 count of < 200 cells/mm^3 was associated with IPI. Lono *et al*[75], reported that HIV-positive individuals were three times at risk to acquire microsporidium infection compared to HIV-negative individuals (OR 3.2). The overall prevalence was 8.5% (21/247). Nissapatorn *et al*[76], produced a comprehensive review of the challenges in the diagnosis and therapy of parasitic infections in HIV-infected individuals.

Fungal infections

A survey of 96 patients with cryptococcal infections from 2003–2004 showed that HIV was the major underlying illness in 37.5% (36/96) of them. The predominant species were *Cryptococcus neoformans var grubii* followed by *C. gatti*. Cryptococcosis in children was uncommon[77]. Nor Hayati *et al*[78], reported the successful management of *Penicillium marneffei* infection in 20 AIDS patients. Forty-five percent had acquired HIV through heterosexual intercourse and 40% from IDU. Median CD4 count was 10 cells/mm^3. Diagnosis were made from blood cultures and four skin biopsy samples. Nine patients were aware of their HIV status at time of diagnosis, four were on HAART but were not compliant. All except one had other concurrent OIs, the most common being oral candidiasis (95%, 19/20) and TB (30%, 6/20). Common presenting features included typical skin lesions, fever, anaemia, and hepatomegaly. Median length of hospital stay was 19 days. All were successfully treated with intravenous amphotericin B at induction and switched to itraconazole (80%) or fluconazole as maintenance (20%). No relapses or mortality were reported at the end of scheduled therapy and at third month review.

Sexually transmitted infections (STI)

Choon *et al*[79], surveyed 132 HIV-positive individuals presenting with STI from 1992–1998 and reported males outnumbered females by 4.5 to 1, the preponderant group was 20–40 years (82.5%), 53.0% (70/132) were single, 34.1% married, 7.5% divorcees, 97.7% were heterosexuals, 53.3% male patients patronised prostitutes, 50 (37.9%) were IDUs; of which 24 had multiple sex partners, 48.2% (53/109) had one or more STIs, 31.9% had history of one STI and 3.6% had two STIs in the past. Fifty six (42.4%) had developed AIDS while 13 had passed away at the time of the study. The main mode of HIV transmission was heterosexual contact. The prevalence of STI was high.

Dermatological manifestations

Jing *et al*[80], surveyed 182 HIV-positive patients and reported prevalence of mucocutaneous disorders (MCD) of 71.4% (130/182). All had low CD4 cell counts and AIDS-defining illnesses. The common manifestations were generalised hyperpigmentation (35.7%), papular eruptions (29.1%), xerosis (27.5%), seborrhoeic dermatitis (19.2%) and psoriasis (7.7%). The most common infections were oral candidiasis (35.7%), tinea corporis and onychomycosis (9.9%) and herpes (4.3%). Kaposi sarcoma was rare. Mucocutaneous findings were useful clinical predictors of HIV infection or a sign of advanced HIV infection. Rosnah *et al*[81] reported that oral candidiasis was the most common mucocutaneous manifestation in children before starting ART. The frequency of mucocutaneous manifestations was proportionate to the severity of immune depletion.

Nissapatorn *et al*[82], surveyed 174 patients with AIDS-related skin diseases (mean CD4 count 100.5 cells/mm^3) and identified two main categories of skin conditions, namely the predominant group of infectious mucocutaneous manifestations such as seborrhoeic dermatitis (6.3%), icthyosis (0.6%), tumours (1.8%), sexually transmitted diseases (0.6%); and the minority group consisting of drug-related skin conditions (0.6%).

Progressive encephalopathy

Hamid *et al*[83], followed up 55 HIV-positive children and found the incidence of progressive encephalopathy to be 18.2% (10/55). All presented with hepatosplenomegaly, lymphadenopathy, and abnormal deep tendon reflexes while five had impairment of brain growth. Low CD4 count and percentage were associated with progressive encephalopathy.

Psychiatric disorders

Tung *et al*[84], surveyed 89 patients using the Patient Health Questionnaire-9 (PHQ-9) and the Hospital Anxiety and

Depression Scale (HADS); and reported lower depression rate among HIV-positive patients in Malaysia compared to countries in the West. Patients dependent on others for support, non-alcoholic drinkers and being a female were identified as significant predictors for depression. In contrast, Shane *et al*[85], surveyed 41 HIV-positive patients using the Mini International Neuropsychiatric Interview (MINI) questionnaire and the WHO Quality of Life (QOL) questionnaire; and reported 51% of them had psychiatric morbidity, 21% had depression associated with hepatitis B infection and poor social support. Depression was correlated with psychological wellbeing on WHOQOL. Psychiatric morbidity, including suicidality, was associated with CD4 count < 200 cells/mm^3. The Malay version of the survey tool developed by WHO specific for people infected with HIV to assess their quality of life, the WHOQOL-HIV BREF, was validated by Saddki *et al*[86].

Muhammad Muhsin *et al*[87], compared 200 HIV-positive and 200 HIV-negative prisoners using the Structured Clinical Interview for Diagnosis Statistical Manual of Mental Disorders-IV (SCID-1) and found extremely high prevalence of mental illness and substance use disorders, especially opioid dependence in HIV-positive prisoners. HIV infection was significantly correlated with age, ethnicity, marital status, history of injection drug use, lifetime duration of incarceration, substance abuse, polysubstance abuse and non-substance induced psychiatric disorders. Prisoners with triple diagnosis (psychiatric disorders, substance use disorders and HIV) spent 46.7 cumulative lifetime months in prison compared to those with only one psychiatric diagnosis. No difference was found between those with two psychiatric diagnoses and those with only one psychiatric diagnosis. HIV infection and triple diagnoses were not associated with violent offenses.

Hasanah *et al*[88], surveyed 271 HIV-positive patients using the Functional Assessment of HIV Infection (FAHI) and HADS to determine the socio-demographic, clinical and psychological factors influencing QOL in these patients. They reported that the psychological and social wellbeing of patients were more affected than their physical wellbeing. Heterosexual route of HIV transmission was associated with lower social wellbeing but not in IDUs. Lua *et al*[89], surveyed 30 caregivers of patients with HIV/AIDS using the Malay Caregiver Quality of Life (MCQoL) questionnaire and reported favourable psychometric properties among them.

Opportunistic pneumonias and hepatitis E

Tengku *et al*[90], conducted an extensive review of the common HIV-associated opportunistic pneumonias and the management of PTB, PCP and recurrent bacterial pneumonias. Ng *et al*[91], reported the seroprevalence of anti-HEV antibodies in 21/145 HIV-1 infected subjects was 14.4% (10.5% IgG and 4.1% IgM). The most likely route of transmission was faecal.

Predictors of death

Lubis *et al*[92], surveyed data of 845 HIV-positive patients from 1989–2009 and reported age 50 and older, secondary and tertiary education, unemployment, AIDS on presentation, single and double drugs antiretroviral (ART) regime, and inability to achieve viral load of ≤ 50 copies/ml despite being on ART were significant predictors of death.

MANAGEMENT

HIV-TB co-infection

Marzuki *et al*[93], reported the prevalence of drug-induced hepatitis in a survey of 473 patients with TB was 9.7% (46/473). HIV and ETB were significant risk factors for development of drug induced hepatitis. Ismail *et al*[94], in a survey of 219 HIV-TB patients, reported slightly more than half (53.4%) achieved successful outcomes (cure, completed therapy). Unsuccessful outcomes (death, default therapy, treatment failure) were associated with IDUs (OR 2.72), not being on HAART (OR 5.1), lymphadenopathy (OR 2.01) and poor nutritional status (OR 4.61). In another study of 227 HIV-TB patients, Ismail *et al*[95], reported 23.3% of them had died at the end of the study; out of which 40% died within 2 months of diagnosis. Survival at 2, 6, and 12 months after starting anti-TB therapy was 90.7%, 82.8% and 78.8%, respectively. Death was associated with Malay ethnicity, CD4 count < 200 cells/mm^3, presence of three or more OIs, not being on HAART and leucocytosis.

Injecting Drug Users (IDUs)

Several articles highlighted the failure of national drug rehabilitation programmes and punitive response to the drug problem in Malaysia and the successful piloting and implementation of the harm reduction policies and programmes including the drug substitution therapy and needle and syringe exchange programme (NSEP) in 2005[96-98]. The inclusion of the health aspects of illicit drug use in Malaysia's drug policies resulted in better access to HAART, reduction in HIV risk behaviour and greater social benefits including increased employment[98]. Nevertheless, tension between law enforcement and public health as overall drug policy is based on abstinence and zero tolerance remains a challenge[97]. Sarnon *et al*[99], reported favourable reception of the NSEP among IDUs. Degenhardt *et al*[100], discussed the positive impact of the shift from punitive law enforcement approach to evidence-based treatment in Malaysia, an effect not seen in other countries like Russia and the USA. A review by Mesquita *et al*[101], traced the course of development of the HIV/AIDS epidemic among people who inject drugs (PWID) in the Western Pacific and Asia and WHO's role in supporting these responses.

In a review of evidence for effectiveness, cost-effectiveness and coverage of ART for IDU with HIV in several countries with the very highest burden of IDUs, including Malaysia, Wolfe *et al*[102], reported disproportionately low access to ART among IDUs which was attributed to systemic and structural obstacles restricting treatment access. They highlighted the need for integration of ART with opioid substitution and TB treatment, increase peer engagement in treatment delivery and reform harmful policies to improve ART coverage of IDUs.

Chou *et al*[103], explored the responsibility attribution, defined as 'how an individual perceives the cause of their HIV/AIDS infection', and its relationship to coping styles of IDUs with HIV/AIDS. They identified four homogenous attribution groups among IDUs in Malaysia – external, fatalistic, internal and indeterminate. A combination of self-esteem, social support and religiosity mediate the relationship between responsibility attribution and coping behaviours. Suresh *et al*[104], highlighted the important role of non-governmental organisations (NGOs) in pushing for implementation of harm reduction policies and programmes in Malaysia through the formation of a state-NGO alliance to dialogue with opposition from mainly Muslim religious groups. A study by Koh *et al*[105], laid to rest a prevalent myth popular among IDUs in Malaysia that efavirenz ingestion can lead to a false positive urine cannabis test thus negating the need for letter-of-certification by healthcare providers to be used by IDUs in the event of a drug raid.

Prisoners

Choi *et al*[106], surveyed 102 HIV-infected prisoners within six

months of release from incarceration and reported four major concerns among them: staying out of prison (60.8%), remaining off drugs (39.2%), finding employment (35.3%) and obtaining HIV care (32.4%). High levels of stigma, including negative self-image and public attitudes-related stigma were independent barriers to obtaining HIV treatment. Factors associated with higher likelihood of identifying more re-entry challenges included previous incarcerations (OR 3.2), higher HIV-related symptoms (OR 2.0), and higher public attitudes-related stigma (OR 2.5). They pressed for more targeted interventions (effective drug treatment, HIV care and public awareness campaign) to stem the HIV epidemic and improve the health outcomes among HIV-infected prisoners in Malaysia. The same sentiment was echoed by Copenhaver *et al*[107], in their study involving interviews with HIV-positive prisoners and their healthcare providers. Wickersham *et al*[108], reported HIV-positive prisoners on higher dose of methadone at the time of release from prison were associated with greater retention on methadone-maintenance therapy (MMT) after release to the community. Optimisation of MMT doses with proper monitoring are required prior to re-entering the community from prisons.

Fu *et al*[109], evaluated 100 HIV-infected prisoners in two of the largest compulsory drug detention and rehabilitation centres in Malaysia. None of the prisoners had access to ART during detention, only 9% received HIV-related clinical assessment or care, nearly 25% had symptoms of TB but were not screened, 95% met criteria for opioid dependence, none had access to opioid substitution therapy (OST) during detention, 86% reported current craving, 87% anticipated relapsing to drugs after release and 14% had suicide ideation. There were significant unmet health needs and high risk of morbidity and mortality while in detention.

Transsexuals (*Mak Nyah*)

Teh *et al*[110], interviewed 15 *Mak Nyahs* from five major towns in Malaysia and reported HIV problem as critical in this group. Knowledge of HIV/AIDS was poor and the practice of safe sex was low. HIV/AIDS was not considered a primary problem. Finding employment and discrimination were more important issues. They faced constant harassment from enforcement authorities for prostitution. There were no HIV prevention activities in many parts of Malaysia to cater to their needs.

Health clinics and NGOs

Foong *et al*[111], interviewed healthcare providers in two major HIV/AIDS clinics in Malaysia and identified gaps in providing care to HIV-positive patients in primary care setting. The gaps included lack of treatment and consultation facilities, lack of availability and accessibility to information, lack of publicity on available facilities, lack of communication and inter-professional working, and the need for more effective coordinated efforts with clear leadership. It was suggested that nurses may have a greater role to play.

Azwa *et al*[112], conducted a comprehensive review of the management of HIV in pregnancy with special emphasis on ART strategies and obstetric care in a middle income country. Musa[113] discussed the successes and challenges faced in the running of a half-way home established for the care of women and children with HIV/AIDS.

Children with HIV

Mohd *et al*[114], surveyed 95 HIV-positive children on ART aged 1–18 years. They reported that almost all did not achieve the recommended energy intake for their age groups and almost half had vitamin A and selenium deficiencies. Nasir *et al*[115], reported that children on protease inhibitors had lower body weight, low HDL-C but less selenium deficiency. A comprehensive review of 1301 children in Asia in the TREAT Asia (Therapeutics Research, Education, and AIDS Training in Asia) report[116] reported 10% of Asian children were on second-line ART. The median age at second-line initiation was 120 months (range 78–145). Better use of current first-line regimens and broader access to heat-stable, paediatric second-line and salvage formulations were needed. Earlier diagnosis of treatment failure was of little use unless providers and patients had access to appropriate drugs for children to switch to.

HIV-positive refugees

Mendelsohn *et al*[117], compared the adherence to HAART in 153 refugees and 148 host community clients at a public clinic in Kuala Lumpur. Similar proportion between refugees and host community clients in terms of < 95% adherence and unsuppressed viral load was reported. Refugees in protracted asylum situations were able to sustain good treatment outcome and should be included in the HIV strategic plans of host countries.

Antiretroviral therapy (ART)

Hasan *et al*[118], asked 325 HIV-positive patients on ART to describe their experiences of adverse drug reactions (ADRs) and identify drug-drug-interactions. The common ART agents used were lamivudine (64.6%), zidovudine (40.6%) and efavirenz (42.5%). Common ADRs were fatigue, allergic reactions, weight loss, dry mouth and memory loss. Females, non-complementary and alternative medicine users and age younger than 50 years were associated with higher ADRs. Forty-four cases of category-D drug-drug-interactions were identified in the study. In another study, Hasan *et al*[119] reported 78.2% (254/325) had used complementary and alternative medicine but 68% did not disclose this to healthcare professionals. The most common complementary and alternative medicine used were vitamins and supplements, herbal products and massages.

Hejazi *et al*[120], surveyed 334 HIV-positive adults on ART and reported abdominal obesity prevalence of 36.5%. Risk factors associated with abdominal obesity included older patients (OR 1.05), higher fasting plasma glucose levels (OR 1.19) and higher body mass index (OR 1.43). In another survey of 2738 adult HIV-positive patients, Hejazi et al121, reported high prevalence of metabolic abnormalities, including elevated levels of serum triglyceride, LDL-C, total cholesterol and fasting plasma glucose levels. Protease inhibitors use (OR 2.3) and alcohol consumption (OR 2.7) were associated with elevated triglyceride levels in these patients.

Lian *et al*[122], surveyed 128 HIV-positive patients newly started on ART and reported AIDS-defining illnesses (ADIs) still occur especially in patients with CD4 count < 100 cells/mm^3 at HAART initiation. The most common ADIs were pulmonary tuberculosis, extra-pulmonary tuberculosis and Pneumocystis carinii pneumonia.

Yagoub *et al*[123], explored the key determinants of adherence to HAART in a survey of 925 HIV-positive patients on HAART. Poor adherence was associated with diarrhoea, vomiting, forgetfulness, use of herbal medications or religious treatment, and long travel distance to obtain medications. Good adherence was associated with the use of alarm clocks, acceptance of HIV status, self-efficacy, older age, higher education level, and higher income. Effective treatment of adverse effects, discouraging the use of alternative treatments, counselling, use of alarm clock and easier access to HAART were needed to improve adherence.

CULTURE AND RELIGION

In a 2005 editorial, Kamarulzaman[124] discussed the challenges of managing the HIV epidemic in a multicultural and predominantly Islamic Malaysia. Since then, the challenges have remained relatively unchanged. The success from implementing harm reduction strategies to curb HIV transmission in IDUs was not seen in MSM and sex workers[125]. Homosexuality is culturally frowned upon and is often hidden. Majority of MSM may be married adding to the challenge to design appropriate intervention strategies among MSM[126]. Wong *et al*[127], surveyed 2271 Malaysians aged 18–60 years and reported poor knowledge was not the root causes of HIV stigma and discriminatory attitudes but rather ethnicity was the strongest correlate of knowledge of HIV transmission, self-stigma, and public stigma attitudes.

CASE REPORTS

A handful of case reports of patients with rare HIV/AIDS-related conditions have been published including several case reports on the challenges in diagnosis and management. These are summarised in Table III.

DIAGNOSIS

Genotyping and Phylogenetic Studies

Circulating recombinant forms (CRF)

A fascinating picture of the evolution of the HIV epidemic in Malaysia at the molecular level was made possible through genotyping and phylogenetic studies with the discovery of various subtypes of the HIV-1 virus that spread from one at-risk population group to other groups and ultimately into the general population. In 2000, Saraswathy *et al*[141], reported HIV-1 B, C and E subtypes were identified among Malaysian IDUs with predominance of the B subtype. The CRF subtype B was also identified as the dominant subtype in IDUs by Tee *et al*[142]. They went on to describe the discovery of CRF33_01B disseminating widely among various risk populations in Kuala Lumpur between 2003 and 2005 as well as the discovery of the emergence of intersubtype recombinants CRF01_AE/B suggesting a new circulating form in Kuala Lumpur which had emerged as early as the mid-1990s, predominantly in IDUs. CRF01_AE/B were the progenitors of CRF33_01B1[43-146].

Lau *et al*[147], in 2007 reported the discovery of HIV-1 isolate 06MYKLD46, a possible second generation HIV-1 recombinant derived from CRF33_01B. A year later, Lau *et al*[148], and Wang *et al*[149], reported evidence of rapid and extensive HIV-1 evolution in the region with the discovery of several novel recombinant forms of HIV-isolates, namely 07MYKL47, 07MYKL48 and 07MYKL49. In 2010, Lau *et al*[133], reported evidence for possible biological advantages of the newly emerging HIV-1 CRF from Malaysia (CRF33_01B) compared to its progenitors (CRF01_AE and subtype B). In 2012, Ng *et al*[150], reported the discovery of novel HIV-1 CRF54_01B from three epidemiologically unlinked subjects of different risk groups in Malaysia suggesting that the new CRF may have potential in bridging HIV-1 transmission among different risk groups in South East Asia (SEA). Similarly, Chow *et al*[151], reported the discovery of a novel HIV-1 genotype phylogenetically linked to CRF33_10B identified in three epidemiologically unrelated persons in Malaysia. They suggested that the discovery may contribute to HIV-1 molecular surveillance and future vaccine development in the SEA region. In the same year, Mohamad *et al*[152], reported the emergence of CRF33_01B as the predominant subtype and a high frequency of primary mutations among HIV-1 infected children after failure of ART in Kelantan.

In 2013, Ng *et al*[153], reported that the HIV-1 subtype B and CRF01_AE were predominant and contributed to about 80% of total HIV-1 infections among MSM in Malaysia, of which 12 monophyletic clusters were identified. Bayesian coalescent analysis estimated that the divergence times for these clusters were mainly from 1995–2005. In the same year, Chow *et al*[154], reported that the founder lineages of CRF33_01B were likely to have first emerged among IDUs in the early 1990s before spreading exponentially to various high and low-risk populations (including children who acquired infections from their mothers) and became endemic later on during the early 2000s. Their findings provided notable genetic evidence indicating the widespread expansion of CRF33_01B among IDUs and into the general population.

Oyomopito *et al*[155], reported that patients infected with CRF01_AE have reduced immunologic response to therapy at 12 months compared to subtypes B infected counterparts. Clinical deterioration was associated with low baseline CD4 counts and older age. Major drug resistance mutations among antiretroviral (ARV) treated patients with detectable viral load was reported by Tee *et al*[156], in 2005. Resistance was greatest with non-nucleoside reverse transcriptase resistance and least with protease inhibitor. Ong *et al*[157], studied the molecular diversity of HIV-1 and surveillance of transmitted drug resistance among treatment naïve patients, five years after introduction of ART in Kuala Lumpur between 2008 and 2010. They found the predominant circulating HIV-1 genotypes were CRF-01_AE (51%; 51/100) and CRF33_01B (17%; 17/100). Transmitted drug resistance among ART-naïve patients was low five years after the introduction of HAART[157-159]. In 2011, Sungkanuparph *et al*[160], reported prevalence of patients with one or more drug resistance mutation was 13.8% in a multicentre HIV-1 drug resistance monitoring study suggesting that primary HIV drug resistance was emerging after rapid scaling-up of ART use in Asia. Chitra *et al*[161], reported that the increase of beta-2 microglobulin and reduced absolute CD4, CD8 count, CD4/CD8 ratio and leucocytes count in HIV patients who were non-adherent to HAART may have a contributory role in the immune progression of HIV with interruption of HAART. Beta-2 microglobulin plays an important role in the diagnosis of HIV and might indicate HIV progression.

Other genotyping studies

Tan *et al*[162], reported cryptococcal and Mycobacterium tuberculosis immune restoration disease (IRD) coincided with peaks in the proportion of activated T-cells, pathogen-specific gamma-interferon responses and reactive plasma IgG. However, Sumatoth *et al*[163], later reported that the level of antibody to mycobacterial antigens did not predict IRD.

Lim *et al*[164], and Iqbal *et al*[165], reported the predominance of Cryptosporidium parvum subgenotypes signified the possibility of zoonotic as well as anthroponotic transmissions of cryptosporidiosis in HIV-infected individuals. Lim *et al*, also reported the first detection of *C. hominis, C. meleagridis, C. felis* and Giardia in Malaysian HIV/AIDS patients.

Other Diagnostic Methods and Laboratory-Based Research

In 2000, Jayaram *et al*[166], reported the value of fine needle aspiration cytology (FNAC) in the diagnosis of bacterial, fungal and high grade lymphoma including phenotyping in HIV-positive patients who presented with lymph node enlargement. In 2008, Zaidah *et al*[167], reported the superiority of the polymerase chain reaction (PCR) over microscopy in identifying *C. parvum* infection and its usefulness in the determination of the true prevalence and epidemiology of *C. parvum*. Al-Darraji

et al[168], evaluated the single GeneXpert MTVB/RIF assay against the acid-fast bacilli (AFB) smear microscopy and the gold standard BACTEC MGIT 960 liquid culture in 125 HIV-positive prisoners. The single GeneXpert assay outperformed AFB smear microscopy but has low screening sensitivity of 53.3%. Lee *et al*[169], evaluated the use of the dried blood spot (DBS) method as a tool to detect HIV, hepatitis B and C infections. They concluded that although the DBS was an ideal choice as a screening tool, its use was restricted by the need to use different cut off values for validation of test positivity. Chew *et al*[170], reported the results of a longitudinal study exploring the role of chemokines in IRD and sensory neuropathy.

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Studies on the prevalence of HIV in many of the most-at-risk-populations in Malaysia have provided reliable insights into the magnitude of the problem in Malaysia (Table I). These statistics are useful to guide the implementation of prevention and treatment strategies in these groups, especially in a resource-limited setting. Logically, greater proportions of resources should be allocated to groups with higher HIV prevalence such as the injecting drug users, sex workers and MSM[6-13]. In practice, however, resources have often been allocated for programmes such as the premarital HIV screening for Muslims that have very low yield of HIV positive detection despite screening a large population[18,22]. This policy ought to be re-evaluated as it is not only potentially discriminative as the policy does not apply to non-Muslims, it is also clearly a policy borne out of political or religious expediency rather than evidence-guided use of limited resources. Incidence studies in various-at-risk groups are sorely lacking in Malaysia as are prevalence studies in other marginalised groups such as the transgender people, migrant workers and refugees.

Risk behaviours for injecting drug users in Malaysia have been well documented and they are consistent with the findings of studies conducted in other countries[7-9,23-25]. On the other hand, there is little or no data about the prevalence of HIV and risk behaviours in many of the marginalised communities in Malaysia such as sex workers, MSM, transgender people, migrant workers and refugees. Identifying risk behaviours in these groups can help guide the formulation of risk-reduction strategies tailored specifically for each of these groups. The successes of the opioid substitution therapy and needle and syringe exchange programmes among intravenous drug users are prime example of tailored strategies targetted at identified risk-behaviours[96-100]. The knowledge, attitude and practice studies in Malaysia have largely been focussed on students, adolescents and pregnant women[32-35,39-47].

Although at least 24 AIDS-defining illnesses have been identified[171], most of the research in Malaysia have largely focussed on only a few of the common conditions associated with HIV/AIDS such as tuberculosis, toxoplasmosis, and fungal infections. Case reports of patients with rare manifestations of conditions related to HIV/AIDS and the management strategies used for these conditions should be encouraged. A neglected area of research is the complex issue of managing HIV-hepatitis B and C co-infections especially with recent advances in the management of hepatitis B and C infections where cure is possible.

In conclusion, 30 years after the identification of HIV as the causative agent of AIDS and 28 years after the first few cases of HIV were reported in Malaysia, the HIV epidemic is here to stay and continue to be a major public health concern. Although we have achieved substantial success in slowing the epidemic, particularly among injecting drug users, a significantly large proportion of at-risk populations in Malaysia remain vulnerable to the epidemic.

SECTION 3: FUTURE RESEARCH DIRECTION

More incidence and prevalence studies should be conducted on marginalised groups such as the transgender people, migrant workers and refugees. Studies should also be conducted to identify the factors that help fuel the rise of heterosexual transmission of HIV infections in recent years in the population.

Future knowledge, attitude and practice studies should focus on less studied groups such as the injecting drug users, MSM, sex workers, transgender people, migrant workers, and refugees. Outcomes studies on the effectiveness of destigmatising strategies are needed.

Research on the management of HIV-HBV and HIV-HCV co-infections in Malaysian patients should be carried out since there is lack of data in this area. Studies on children living with HIV is also an important aspect to look into. Health economic studies are vital to assess the need for pre-marriage screening.

A large number of studies have identified problems in the management of specific groups of patients with HIV/AIDS such as those with HIV-TB co-infection, injecting drug users and prisoners[93-110]. Outcome studies based on strategies to address the identified problems should be done. The findings of outcome studies are vital to affect policy change. More research is needed to address the problem of access to ART, particularly among prisoners and refugees. Research in developing strategies to improve adherence to ART, the key to success in managing HIV infection, is needed to provide insight into what works and what does not in the local context.

Studies and case reports on the use of post-exposure prophylaxis (PEP) for HIV beyond the confines of healthcare personnel are needed in order to affect a policy change to extend PEP to people who are exposed to HIV in a non-healthcare setting such as condom failure, victims of sexual abuses and rape, and homosexual and bisexual men with multiple sex partners.

Another potential area for research is the use of ART as a pre-exposure prophylaxis (PrEP) strategy, particularly in MSM and sex workers. Pre-exposure prophylaxis may indeed prove to be the key to controlling the spread of HIV within these groups and the general population, just as harm reduction policies and programmes had done to control the HIV epidemic in IDUs. The use of PrEP may be a reasonable alternative to sperm-washing and child adoption for discordant couples who wish to conceive. As patients on ART are able to live longer, research on the long term effects of ART and other causes of morbidity and mortality in these patients should be conducted. Adverse effects associated with older ARTs should be highlighted in case reports in order to push for the availability of newer and safer drugs. Outcome studies on early intervention with ART and the short and long term benefits of ART are needed in order to widen the scope of coverage for treatment of HIV in the population.

Non-governmental organisations (NGOs) and advocacy groups working for people living with HIV/AIDS must publish articles describing their works and the successes from their works, not only for the sake of posterity but also as leverage in obtaining crucial funding and support as well as serve as guides for other NGOs and groups.

More laboratory-based research need to be done especially in the areas of diagnostics. A reliable biomarker to predict, diagnose and manage immune-reconstitution syndrome in HIV-positive patients newly started on ART remains elusive and requires more research. Although genotyping and phylogenetic studies have provided useful insight to the evolution of the HIV epidemic in Malaysia at a molecular level, studies must now focus on translating this knowledge from the bench to the bedside in a clinically relevant fashion, in terms of identifying potential drug-resistance based on viral genotyping, molecular surveillance and vaccine development[138,146].

More research is needed to provide solid and reliable evidence that can be used to affect policy changes and formulate workable treatment and prevention strategies.

ACKNOWLEDGEMENTS

The author wish to acknowledge the significant contribution from A/Prof. Lim Kean Ghee, Prof. Teng Cheong Lieng, Dr. Lim Ai Wei and the CRC team of Hospital Kuala Lumpur in the writing of this review. I would like to sincerely thank the Director-General of Health, Malaysia for his permission to publish this paper.

REFERENCES

1. Centers for disease control and prevention. HIV/AIDS. http://www.cdc.gov/hiv/statistics/basics/ (accessed on 29 April 2014).
2. Disease Control Unit, Ministry of Health Malaysia, 2010. http://www.mac.org.my/v3/?page id=792#sthash.XblzyqUO.dpuf (accessed on 29 April 2014).
3. Huang M, Hussein H. The HIV/AIDS epidemic country paper: Malaysia. AIDS Educ Prev 2004; 16(3 Suppl A): 100-109.
4. UNICEF. AIDS in Malaysia. http://www.unicef.org/malaysia/aids.html (accessed on 29 April 2014).
5. Ong HC, Soo KL. Backcalculation of HIV infection rates in Malaysia. Med J Malaysia 2006; 61(5): 616-620.
6. Anonymous Consensus report on HIV and AIDS epidemiology in 2004: Malaysia, 2004.
7. Chawarski MC, Mazlan M, Schottenfeld RS. Heroin dependence and HIV infection in Malaysia. Drug Alcohol Depend 2006; 82 Suppl 1: S39-42.
8. Chawarski MC, Vicknasingam B, Mazlan M, *et al.* Lifetime ATS use and increased HIV risk among not-in-treatment opiate injectors in Malaysia. Drug Alcohol Depend 2012; 124(1-2): 177-180.
9. Fauziah MN, Anita S, Sha'ari BN, *et al.* HIV-associated risk behaviour among drug users at drug rehabilitation centres. Med J Malaysia 2003;58(2):268-272.
10. Anonymous. STD prevalence among sex workers in Kuala Lumpur: Ministry of Health, Malaysia, 2001.
11. Anonymous. Consensus report on HIV and AIDS epidemiology in 2004: Malaysia, 2004.
12. Kanter J, Koh C, Razali K, *et al.* Risk behaviour and HIV prevalence among men who have sex with men in a multiethnic society: a venue-based study in Kuala Lumpur, Malaysia. Int J STD AIDS 2011; 22(1): 30-37.
13. Koh KC, Kamarulzaman A. Profiles of men-who-have-sex-with-men seeking anonymous voluntary HIV counselling and testing at a community-based centre in Malaysia. Med J Malaysia 2011; 66(5): 491-494.
14. Anonymous Consensus report on HIV and AIDS epidemiology in 2004: Malaysia, 2004.
15. Balkis AK, Zahari CD. HIV prevalence among antenatal mothers in Terengganu. Malaysian Journal of Public Health Medicine 2003; 3(2): 48-52.
16. Japaraj RP, Sivalingam N. The prevalence of HIV positive antenatal mothers in a routine screening programme in two states. Med J Malaysia 2001; 56(2): 180-185.
17. Zahariyah Y, Rohani I, Shahrul Bariyah A, *et al.* A review of HIV antenatal screening programme in selected district in Kedah (1999-2002). IMR Quarterly Bulletin 2003; (55): 39-43.
18. Khebir BV, Adam MA, Daud AR, *et al.* Premarital HIV screening in Johor--(2002-2004). Med J Malaysia 2007; 62(1): 19-22.
19. Fauziah MN, Anita S, Shaari N, *et al.* HIV infection among fishermen in Terengganu. Malaysian Journal of Public Health Medicine 2002; 2(1): 21-25.
20. Aceijas C, Stimson GV, Hickman M, *et al.* Global overview of injecting drug use and HIV infection among injecting drug users. AIDS 2004; 18(17): 2295-2303.
21. Roshan TM, Rosline H, Ahmed SA, *et al.* Response rate of Malaysian blood donors with reactive screening test to transfusion medicine unit calls. Southeast Asian J Trop Med Public Health 2009; 40(6): 1315-1321.
22. Tan HL, Koh KC. Is HIV screening in the general population cost effective? Malaysian Family Physician. 2008; 3(2): 96-97.
23. Dokubo EK, Kim AA, Le LV, et al. HIV incidence in Asia: a review of available data and assessment of the epidemic. AIDS Rev 2013; 15(2): 67-76
24. Vicknasingam B, Narayanan S, Navaratnam V. The relative risk of HIV among IDUs not in treatment in Malaysia. AIDS Care 2009; 21(8): 984-991.
25. Juita G, Osman A. Drug addiction and HIV infection amongst male in Malaysia, 1994. Jurnal Kesihatan Masyarakat 2006; 12(1).
26. Niza S, Aishah A, Mohd Aznan MA, *et al.* Social and HIV/AIDS risk behaviours in a fishing community, International Journal of Humanities and Social Science 2011; 1(21): 251-257. (26).
27. Huang M. HIV among fishers: vulnerability of their partners. In: Anonymous World Fish Center, 2002. (27).
28. Zahariyah Y, Rohani I, Shahrul Bariyah A, *et al.* A review of HIV antenatal screening programme in selected district in Kedah (1999-2002). IMR Quarterly Bulletin 2003; (55): 39-43. (28).
29. Lim SH, Guadamuz TE, Wei C, *et al.* Factors associated with unprotected receptive anal intercourse with internal ejaculation among men who have sex with men in a large internet sample from Asia. AIDS Behav 2012; 16(7): 1979-1987.
30. Bachireddy C, Bazazi AR, Kavasery R, *et al.* Attitudes toward opioid substitution therapy and pre-incarceration HIV transmission behaviors among HIV-infected prisoners in Malaysia: implications for secondary prevention. Drug Alcohol Depend 2011; 116(1-3): 151-157.
31. Gill JS, Norzuraida Z. HIV risk behaviours among intravenous drug users. Malaysian Journal of Psychiatry 2003; 11(1): 18-23.
32. Akmal MN, Lee CK, Neng EE, *et al.* Women's attitudes to HIV screening in Hospital Muar antenatal clinic. Hospital Muar Medical Journal 2003; 1(1): 15-19.
33. Sharifa Ezat WP, Mohammad J, Jamsiah M, *et al.* Knowledge, attitude and practice about HIV/AIDS and its influencing factors among pregnant mothers in west of Sabah, Malaysia. Malaysian Journal of Public Health Medicine 2012; 12(2): 15-23.
34. Vinothini A, Khoo EM, Adeeba K. Knowledge of HIV/AIDS among pregnant women in an urban health clinic - a preliminary study. Family Physician 2005; 13(1): 10-15.
35. Anonymous. Women and Girls. Confronting HIV and AIDS in Malaysia. Ministry of Health, Malaysia, 2008.
36. Jasvindar K. Knowledge of HIV transmission among Malaysians: a population based study. Journal of Health Management 2012; 10(2): 10-19.
37. Siti Norazah Z, Wong YL. Knowledge, attitudes and beliefs related to HIV/AIDS among adolescents in Malaysia. Med J Malaysia 2002; 57(1): 3-23.
38. Wong LP, Chin CK, Low WY, *et al.* HIV/AIDS-related knowledge among Malaysian young adults: findings from a nationwide survey. Medscape J Med 2008; 10(6): 148.
39. Ahmed SI, Hassali MA, Aziz NA. An assessment of the knowledge, attitudes, and risk perceptions of pharmacy students regarding HIV/AIDS. Am J Pharm Educ 2009; 73(1): 15.
40. Chew BH, Cheong AT. Assessing HIV/AIDS knowledge and stigmatizing attitudes among medical students in Universiti Putra Malaysia. Med J Malaysia 2013; 68(1): 24-29 http://www.e-mjm.org/2013/v68n1/knowledge-on-HIV-AIDS.pdf
41. Ibrahim N, Rampal L, Jamil Z, *et al.* Effectiveness of peer-led education on knowledge, attitude and risk behavior practices related to HIV among students at a Malaysian public university--a randomized controlled trial. Prev Med 2012; 55(5): 505-510.

42. Jahanfar S, Lim AW, Loh MA, *et al.* Improvements of knowledge and perception towards HIV/AIDS among secondary school students after two hours talk. Med J Malaysia 2008; 63(4): 288-292.
43. Jahanfar S, Lye MS, Rampal L. A randomized controlled trial of peer-adult-led intervention on improvement of knowledge, attitudes and behavior of university students regarding HIV/AIDS in Malaysia. Singapore Med J 2009; 50(2): 173-180.
44. Koh KC, Teh JR, Khan SA. Beliefs and attitudes of medical students from public and private universities in Malaysia towards individuals with HIV/AIDS. Scientific World Journal 2013; 2013: 462826.
45. Ni H, Htet A. Knowledge and attitude of HIV/AIDS infection among medical students. International Journal of Collaborative Research on Internal Medicine & Public Health 2012; 4(4): 317-326.
46. Rozina R, Lekhraj R, Lye MS, *et al.* Knowledge, attitude and practice related to HIV/AIDS among students in a local university (2007). Malaysian Journal of Medicine and Health Sciences 2009; 5(2): 27-41.
47. Rozina R, Rampal L, Lye MS, *et al.* Factors influencing students' attitude towards HIV/AIDS in a public university, Malaysia. Glob J Health Sci 2011; 3(1): 128-134.
48. Anita S, Zahir WM, Sa'iah A, *et al.* HIV/AIDS knowledge, attitudes and risk behaviours among Orang Asli in Peninsular Malaysia. Med J Malaysia 2007; 62(3): 227-233.
49. Anita S, Khatijah MY, Mahamin MY, *et al.* A cross-sectional study of knowledge, education, risk behaviour, attitude of HIV/AIDS among factory workers in three states. Malaysian Journal of Public Health Medicine 2004; 4(1): 40-46.
50. Bairy KL, Ganaraja B, Indira B, *et al.* Awareness of post-exposure prophylaxis guidelines against occupational exposure to HIV in Hospital Sungai Petani. Med J Malaysia 2005; 60(1): 10-14.
51. Gulifeiya A, Rahmah M. Nurses awareness and attitude towards HIV/AIDS and universal precautions: a cross-sectional study in UKMMC. Jurnal Kesihatan Masyarakat 2008; 14(2): 36-45.
52. Hasnah B, Mohd Hatta M. Knowledge, attitude and practice of prevention towards HIV/AIDS amongst health personnel in Tapah Hospital , Perak, 1996. Jurnal Kesihatan Masyarakat 2006; 12(1).
53. Khan SA, Moorthy J, Omar H, *et al.* People living with HIV/AIDS (PLWHA) and HIV/AIDS associated oral lesions; a study in Malaysia. BMC Public Health 2012;12: 850-2458-12-850.
54. Nissapatorn V, Lee CKC, Khairul AA. Impact of pulmonary opportunistic infections among AIDS patients in General Hospital Kuala Lumpur, Kuala Lumpur, 2001. Trop Biomed 2001; 18(2): 117-121.
55. Nissapatorn V, Lee C, Fatt QK, *et al.* AIDS-related opportunistic infections in Hospital Kuala Lumpur. Jpn J Infect Dis 2003; 56(5-6): 187-192.
56. Nissapatorn V, Lee CK, Rohela M, *et al.* Spectrum of opportunistic infections among HIV-infected patients in Malaysia. Southeast Asian J Trop Med Public Health 2004; 35 Suppl 2: 26-32.
57. Jamaiah I, Rohela M, Tok EL, *et al.* Pneumocystis carinii (jiroveci) pneumonia (PCP): the most common opportunistic infection observed in HIV/AIDS cases at the University Malaya Medical Centre, Kuala Lumpur, Malaysia. Southeast Asian J Trop Med Public Health 2012; 43(4): 825-831.
58. Jamalluddin AR. Review of pulmonary tuberculosis patients with positive culture in Kuala Terengganu, 1998-2001. International Medical Journal (IIUM) 2003; 2(2).
59. Nissapatorn V, Kuppusamy I, Init I, *et al.* Pulmonary tuberculosis in HIV/AIDS Patients. Trop Biomed 2002; 19(1): 49-53.
60. Nissapatorn V, Lee C, Ithoi I, *et al.* Tuberculosis in AIDS patients. Malays J Med Sci 2003; 10(1): 60-64.
61. Narwani H, Naing NN. Comparison of socio-economic and demographic characteristics of HIV and HIV-infected tuberculosis patients in Kota Bharu Hospital, Kelantan. Jurnal Kesihatan Masyarakat 2004; 10: 38-40.
62. Mohammad Z, Naing NN, Salleh R, *et al.* A preliminary study of the influence of HIV infection in the transmission of tuberculosis. Southeast Asian J Trop Med Public Health 2002; 33(1): 92-98.
63. Mohammad Z, Naing NN. Characteristics of HIV-infected tuberculosis patients in Kota Bharu Hospital, Kelantan from 1998 to 2001. Southeast Asian J Trop Med Public Health 2004; 35(1): 140-143.
64. Velaiutham S, Abdul Razak M, Khatijah B. Characteristics of pulmonary tuberculosis in HIV seropositive patients in Chest Clinic, Penang Hospital. Malaysian Journal of Pharmaceutical Sciences 2004; 2(2): 31-31.
65. Kooi ES, Mahayidin M. Pulmonary Tuberculosis in HIV Infection : The Relationship of the Radiographic Appearance to CD4 T-Lymphocytes Count. Malays J Med Sci 2001; 8(1): 34-40.
66. Nissapatorn V, Kuppusamy I, Sim BL, *et al.* Tuberculosis in HIV/AIDS patients: a Malaysian experience. Southeast Asian J Trop Med Public Health 2005; 36(4): 946-953.
67. Naing C, Mak JW, Maung M, *et al.* Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. Lung 2013;191(1):27-34.
68. Shamilah H, Lokman Hakim.S., Noor Azian MY, *et al.* Seroprevalence of Toxoplasma gondii antibodies in HIV positive and negative patients using the immunofluorescence antibody test (IFAT) methods. Trop Biomed 2001; 18(2): 137-141.
69. Nissapatorn V, Kamarulzaman A, Init I, *et al.* Seroepidemiology of toxoplasmosis among HIV-infected patients and healthy blood donors. Med J Malaysia 2002; 57(3): 304-310.
70. Nissapatorn V, Lee CK, Cho SM, *et al.* Toxoplasmosis in HIV/AIDS patients in Malaysia. Southeast Asian J Trop Med Public Health 2003; 34 Suppl 2: 80-85.
71. Nissapatorn V, Lee CK, Khairul AA. Seroprevalence of toxoplasmosis among AIDS patients in Hospital Kuala Lumpur, 2001. Singapore Med J 2003; 44(4): 194-196.
72. Nissapatorn V, Lee C, Quek KF, *et al.* Toxoplasmosis in HIV/AIDS patients: a current situation. Jpn J Infect Dis 2004; 57(4): 160-165.
73. Nissapatorn V. Toxoplasmosis in HIV/AIDS: a living legacy. Southeast Asian J Trop Med Public Health 2009; 40(6): 1158-1178.
74. Asma I, Johari S, Sim BL, *et al.* How common is intestinal parasitism in HIV-infected patients in Malaysia? Trop Biomed 2011; 28(2): 400-410.
75. Lono A, Kumar S, Chye TT. Detection of microsporidia in local HIV-positive population in Malaysia. Trans R Soc Trop Med Hyg 2011; 105(7): 409-413.
76. Nissapatorn V, Sawangjaroen N. Parasitic infections in HIV infected individuals: diagnostic & therapeutic challenges. Indian J Med Res 2011; 134(6): 878-897.
77. Tay ST, Rohani MY, Hoo TS, *et al.* Epidemiology of cryptococcosis in Malaysia. Mycoses 2010; 53(6): 509-514.
78. Nor Hayati S, Sahlawati M, Suresh Kumar C, *et al.* A retrospective review on successful management of Penicillium marneffei infections in patients with advanced HIV in Hospital Sungai Buloh. Med J Malaysia 2012; 67(1): 66-70.
79. Choon SE, Mathew M, Othman BS. Demographic characteristics and prevalence of other sexually transmitted diseases in HIV-positive patients seen in the Dermatology cum Genitourinary Clinic, Hospital Sultanah Aminah, Johor Bahru. Med J Malaysia 2000; 55(2): 174-179.
80. Jing W. A retrospective survey of mucocutaneous manifestations of HIV infection in Malaysia: analysis of 182 cases. J Dermatol 2000; 27(4): 225-232.
81. Rosnah T, Kamarul A, Mardziah A. Mucocutaneous manifestations of pediatric HIV/AIDS – their association with the 1994 revised CDC immunological classification and antiretroviral therapy. Malaysian Journal of Dermatology 2000; 13: 20-24.
82. Nissapatorn V, Lee CKC, Khairul AA. The prevalence of AIDS-related skin diseases in Hospital Kuala Lumpur. Trop Biomed 2002; 19(1): 55-60.
83. Hamid MZ, Aziz NA, Zulkifli ZS, *et al.* Clinical features and risk factors for HIV encephalopathy in children. Southeast Asian J Trop Med Public Health 2008; 39(2): 266-272.
84. Tung MY, Lee MHG, Ng CG, *et al.* Identifying depression among the human immunodeficiency virus (HIV) patients in University Malaya Medical Centre, Kuala Lumpur, Malaysia. ASEAN Journal of Psychiatry 2009; 10(2): 135-147.
85. Shane V, Koh KC, Cheah KS, *et al.* Psychiatric morbidity among HIV patients in Hospital Tuanku Jaafar, Seremban, Malaysia. HIV/AIDS Prevention, Treatment and Care: The Way Forward. Universiti Sains Malaysia, Penang, AIDS Action & Research Group. 2010; 85-101.
86. Saddki N, Noor MM, Norbanee TH, *et al.* Validity and reliability of the Malay version of WHOQOL-HIV BREF in patients with HIV infection. AIDS Care 2009; 21(10): 1271-1278.
87. Muhammad Muhsin Z, Bae WH, Nor Zuraida Z, *et al.* Psychiatric and substance abuse comorbidity among HIV seropositive and HIV seronegative prisoners in Malaysia. Am J Drug Alcohol Abuse 2010; 36(1): 31-38.
88. Hasanah CI, Zaliha AR, Mahiran M. Factors influencing the quality of life in patients with HIV in Malaysia. Qual Life Res 2011; 20(1): 91-100.
89. Lua PL, Norhayati M, Ahmad Kashfi A. HRQoL profile and psychometric properties assessment of caregiver quality of life instrument among HIV/AIDS family caregivers in Terengganu. Malaysian Journal of Psychiatry 2013; 22(1): 9-21.

90. Tengku Saifudin TI, Lee C. HIV associated opportunistic pneumonias. Med J Malaysia 2011; 66(1): 76-82.
91. Ng KP, He J, Saw TL, *et al.* A seroprevalence study of viral hepatitis E infection in human immunodeficiency virus type 1 infected subjects in Malaysia. Med J Malaysia 2000; 55(1): 58-64.
92. Lubis R, Bulgiba A, Kamarulzaman A, *et al.* Predictors of death in Malaysian HIV-infected patients on anti-retroviral therapy. Prev Med 2013; 57 Suppl: S54-6.
93. Marzuki OA, Fauzi AR, Ayoub S, *et al.* Prevalence and risk factors of anti-tuberculosis drug-induced hepatitis in Malaysia. Singapore Med J 2008; 49(9): 688-693.
94. Ismail I, Bulgiba A. Determinants of unsuccessful tuberculosis treatment outcomes in Malaysian HIV-infected patients. Prev Med 2013; 57 Suppl: S27-30.
95. Ismail I, Bulgiba A. Predictors of Death during Tuberculosis Treatment in TB/HIV Co-Infected Patients in Malaysia. PLoS One 2013; 8(8): e73250.
96. Razali SM. Drug substitution therapy: a new approach in preventing the spread of HIV/AIDS in Malaysia. Trop Doct 2008; 38(2): 109-110.
97. Reid G, Kamarulzaman A, Sran SK. Malaysia and harm reduction: the challenges and responses. Int J Drug Policy 2007; 18(2): 136-140.
98. Kamarulzaman A. Impact of HIV prevention programs on drug users in Malaysia. J Acquir Immune Defic Syndr 2009; 52 Suppl 1: S17-9.
99. Sarnon N, Baba I, Jusojf K, et al. Psychosocial reactions of injecting drug users' (IDU) towards needle syringe exchange program in Malaysia. World Applied Sciences Journal 2011; 12: 80-84.
100. Degenhardt L, Mathers BM, Wirtz AL, *et al.* What has been achieved in HIV prevention, treatment and care for people who inject drugs, 2010-2012? A review of the six highest burden countries. Int J Drug Policy 2014; 25(1): 53-60.
101. Mesquita F, Jacka D, Ricard D, *et al.* Accelerating harm reduction interventions to confront the HIV epidemic in the Western Pacific and Asia: the role of WHO (WPRO). Harm Reduct J 2008; 5: 26-7517-5-26.
102. Wolfe D, Carrieri MP, Shepard D. Treatment and care for injecting drug users with HIV infection: a review of barriers and ways forward. Lancet 2010; 376(9738): 355-366.
103. Chou CC, Chronister J, Chou CH, *et al.* Responsibility attribution of HIV infection and coping among injection drug users in Malaysia. AIDS Care 2013; 25(12): 1551-1558.
104. Suresh N, Balasingam V, Noor Zurani, Md Haris Robson. The transition to harm reduction: understanding the role of non-governmental organisations in Malaysia. Int J Drug Policy 2011; 22(4): 311-317.
105. Koh KC, Lee WY, Eh ZW, *et al.* Efavirenz does not cause false-positive urine cannabis test in HIV-infected patients on Highly Active Anti-Retroviral Therapy. Med J Malaysia 2013; 68(3): 249-252.
106. Choi P, Kavasery R, Desai MM, *et al.* Prevalence and correlates of community re-entry challenges faced by HIV-infected male prisoners in Malaysia. Int J STD AIDS 2010; 21(6): 416-423.
107. Copenhaver MM, Tunku N, Ezeabogu I, *et al.* Adapting an Evidence-Based Intervention Targeting HIV-Infected Prisoners in Malaysia. AIDS Res Treat 2011; 2011: 131045.
108. Wickersham JA, Zahari MM, Azar MM, *et al.* Methadone dose at the time of release from prison significantly influences retention in treatment: Implications from a pilot study of HIV-infected prisoners transitioning to the community in Malaysia. Drug Alcohol Depend 2013; 132(1-2): 378-382.
109. Fu JJ, Bazazi AR, Altice FL, *et al.* Absence of antiretroviral therapy and other risk factors for morbidity and mortality in Malaysian compulsory drug detention and rehabilitation centers. PLoS One 2012; 7(9): e44249.
110. Teh YK. HIV-related needs for safety among male-to-female transsexuals (mak nyah) in Malaysia. SAHARA J 2008; 5(4): 178-185.
111. Foong AL, Ng SF, Lee CK. Identifying HIV/AIDS primary care development needs. J Adv Nurs 2005; 50(2): 134-142.
112. Azwa I, Khong SY. Human immunodeficiency virus (HIV) in pregnancy: a review of the guidelines for preventing mother-to-child transmission in Malaysia. Ann Acad Med Singapore 2012; 41(12): 587-594.
113. Musa MN. Rumah Solehah-Malaysia: half way home for women and children with HIV/AIDS. Bangladesh Journal of Medial Science 2009; 8(1-2): 29-32.
114. Mohd NM, Yeo J, Huang MS, *et al.* Nutritional status of children living with HIV and receiving antiretroviral (ARV) medication in the Klang Valley, Malaysia. Malays J Nutr 2011; 17(1): 19-30.
115. Nasir MTM, Yeo J, Huang MSL, *et al.* Nutritional status and the use of protease inhibitors among HIV-infected children in Klang Valley, Malaysia. Malaysian Journal of Medicine and Health Sciences 2011; 7(2): 73-79.
116. TREAT Asia Paediatric HIV Observational Database (Typhoid), International Epidemiologic Databases to Evaluate AIDS (Idea) Southern Africa Paediatric Group. A bioregional survey and review of first-line treatment failure and second-line paediatric antiretroviral access and use in Asia and southern Africa. J Int AIDS Sock 2011; 14: 7-2652-14-7.
117. Mendelsohn JB, Schilperoord M, Spiegel P, *et al.* Is forced migration a barrier to treatment success? Similar HIV treatment outcomes among refugees and a surrounding host community in Kuala Lumpur, Malaysia. AIDS Behav 2013. http://researchonline.lshtm.ac.uk/id/eprint/967532 (accessed 1 May 2014).
118. Hasan SS, Keong SC, Choong CL, *et al.* Patient-reported adverse drug reactions and drug-drug interactions: a cross-sectional study on Malaysian HIV/AIDS patients. Med Princ Pract 2011; 20(3): 265-270.
119. Hasan SS, See CK, Choong CL, *et al.* Reasons, perceived efficacy, and factors associated with complementary and alternative medicine use among Malaysian patients with HIV/AIDS. J Altern Complement Med 2010; 16(11): 1171-1176.
120. Hejazi N, Rajikan R, Kwok Choong LC, *et al.* Metabolic abnormalities in adult HIV infected population on antiretroviral medication in Malaysia: a cross-sectional survey. BMC Public Health 2013; 13(1): 758.
121. Hejazi N, Huang MSL, Khor GL, *et al.* Factors associated with abdominal obesity among HIV-infected adults on antiretroviral therapy in Malaysia. Glob J Health Sci 2010; 2(2): 20-31.
122. Lian YL, Heng BS, Nissapatorn V, *et al.* AIDS-defining illnesses: a comparison between before and after commencement of highly active antiretroviral therapy (HAART). Curr HIV Res 2007; 5(5): 484-489.
123. Yagoub U, Awang B, Peramalah D, *et al.* Factors affecting adherence level to HAART (adherence predictors) in Kuala Lumpur, Malaysia. Life Science Journal 2012; 9(4): 3600-3603.
124. Kamarulzaman A. Taking stock of two decades of the HIV/AIDS epidemic in Malaysia. Med J Malaysia 2005; 60(1): 1-4
125. Adeeba K. Fighting the HIV epidemic in the Islamic world. Lancet 2013; 381(9883): 2058-2060.
126. Barmania S. Malaysia makes progress against HIV, but challenges remain. Lancet 2013; 381(9883): 2070-2071.
127. Wong LP. Prevalence and factors associated with HIV/AIDS-related stigma and discriminatory attitudes: A cross-sectional nationwide study. Prev Med 2013; 57 Suppl: S60-3.
128. Tan HJ, Cheong I, Muhaizan WM. Disseminated histoplasmosis in AIDS: a report of three patients. Med J Malaysia 2000; 55(2): 259-262.(128).
129. Jarmin R, Alwi RI, Shaharuddin S, *et al.* Common bile duct perforation due to tuberculosis: a case report. Asian J Surg 2004; 27(4): 342-344. (129)
130. Kenali MS, Fadzilah I, Maizaton AA, *et al.* Concurrent mycobacterial infection and non-Hodgkin's lymphoma at the same site in an AIDS patient. Med J Malaysia 2004; 59(1): 108-111.(130).
131. Subha ST, Raman R. Nocardia infection of the mastoid in an immunocompromised patient. Med J Malaysia 2004; 59(5): 688-689. (131).
132. Wong AR, Rasool AH, Abidin NZ, *et al.* Sildenafil as treatment for Human Immunodeficiency Virus-related pulmonary hypertension in a child. J Paediatr Child Health 2006; 42(3): 147-148.(132).
133. Othman N, Yip CW, Intan HI, *et al.* An abdominal mass owing to Penicillium marneffei in an HIV-infected 7-year-old boy: case report. Ann Trop Paediatr 2006; 26(3): 259-262.(133).
134. Chow YW, Leong CL, Chow HL, *et al.* Lactic acidosis in HIV patients receiving highly active antiretroviral therapy. Med J Malaysia 2007; 62(1): 78-80.(134).
135. Khairy-Shamel ST, Shatriah I, Adil H, *et al.* Orbital rhabdomyosarcoma in an HIV positive child. Orbit 2008; 27(5): 388-390.(135).
136. Ketan SH. Pancreatic tuberculosis in HIV positive patient: a case report. Borneo Journal of Medical Sciences 2010.(136).
137. Fong MY, Wong KT, Rohela M, *et al.* Unusual manifestation of cutaneous toxoplasmosis in a HIV-positive patient. Trop Biomed 2010; 27(3): 447-450.(137).
138. Isa WY, Daud KM. Distal renal tubular acidosis in HIV/AIDS patient. Intern Med 2011; 50(16): 1765-1768.(138).
139. Nimir AR, Osman E, Ibrahim IA, et al. Is it toxoplasma encephalitis, HIV encephalopathy or brain tuberculoma? BMJ Case Rep 2013; 2013: 10.1136/bcr-2013-008803.(139).
140. Nurfahzura MJ, Hanizasurana H, Zunaina E, *et al.* Successful treatment of syphilitic uveitis in HIV-positive patients. Clin Ophthalmol 2013; 7: 1651-1654.(140).
141. Saraswathy TS, Ng KP, Sinniah M. Human immunodeficiency virus type 1 subtypes among Malaysian intravenous drug users. Southeast Asian J Trop Med Public Health 2000; 31(2): 283-286.(141).

142. Tee KK, Saw TL, Pon CK, *et al.* The evolving molecular epidemiology of HIV type 1 among injecting drug users (IDUs) in Malaysia. AIDS Res Hum Retroviruses 2005; 21(12): 1046-1050.(142).

143. Tee KK, Pon CK, Kamarulzaman A, *et al.* Emergence of HIV-1 CRF01_AE/B unique recombinant forms in Kuala Lumpur, Malaysia. AIDS 2005; 19(2): 119-126(143).

144. Tee KK, Li XJ, Nohtomi K, *et al.* Identification of a novel circulating recombinant form (CRF33_01B) disseminating widely among various risk populations in Kuala Lumpur, Malaysia. J Acquir Immune Defic Syndr 2006; 43(5): 523-529.(144).

145. Tee KK, Takebe Y, Kamarulzaman A. Emerging and re-emerging viruses in Malaysia, 1997-2007. Int J Infect Dis 2009; 13(3): 307-318.(145).

146. Lau KA, Wang B, Miranda-Saksena M, *et al.* Evidence for possible biological advantages of the newly emerging HIV-1 circulating recombinant form from Malaysia - CRF33_01B in comparison to its progenitors - CRF01_AE and subtype B. Curr HIV Res 2010; 8(3): 259-271.(146).

147. Lau KA, Wang B, Kamarulzaman A, *et al.* Near full-length sequence analysis of a Unique CRF01_AE/B recombinant from Kuala Lumpur, Malaysia. AIDS Res Hum Retroviruses 2007; 23(9): 1139-1145.(147).

148. Lau KA, Wang B, Kamarulzaman A, *et al.* Continuous crossover(s) events of HIV-1 CRF01_AE and B subtype strains in Malaysia: evidence of rapid and extensive HIV-1 evolution in the region. Curr HIV Res 2008; 6(2): 108-116.(148).

149. Wang B, Lau KA, Ong LY, *et al.* Complex patterns of the HIV-1 epidemic in Kuala Lumpur, Malaysia: evidence for expansion of circulating recombinant form CRF33_01B and detection of multiple other recombinants. Virology 2007; 367(2): 288-297.(149).

150. Ng KT, Ong LY, Takebe Y, *et al.* Genome sequence of a novel HIV-1 circulating recombinant form 54_01B from Malaysia. J Virol 2012; 86(20): 11405-11406.(150).

151. Chow WZ, Al-Darraji H, Lee YM, *et al.* Genome sequences of a novel HIV-1 CRF53_01B identified in Malaysia. J Virol 2012; 86(20): 11398-11399. (151).

152. Mohamad S, Deris ZZ, Yusoff NK, et al. Assessing subtypes and drug resistance mutations among HIV-1 infected children who failed antiretroviral therapy in Kelantan, Malaysia. Braz J Infect Dis 2012;16(3):284-288. (152)

153. Ng KT, Ong LY, Lim SH, et al. Evolutionary history of HIV-1 subtype B and CRF01_AE transmission clusters among men who have sex with men (MSM) in Kuala Lumpur, Malaysia. PLoS One 2013;8(6):e67286. (153)

154. Chow WZ, Ong LY, Razak SH, et al. Molecular diversity of HIV-1 among people who inject drugs in Kuala Lumpur, Malaysia: massive expansion of circulating recombinant form (CRF) 33_01B and emergence of multiple unique recombinant clusters. PLoS One 2013;8(5):e62560. (154)

155. Oyomopito RA, Li PC, Sungkanuparph S, et al. Evaluating immunologic response and clinical deterioration in treatment-naive patients initiating first-line therapies infected with HIV-1 CRF01_AE and subtype B. J Acquir Immune Defic Syndr 2013;62(3):293-300. (155)

156. Tee KK, Saw TL, Pon CK, et al. The evolving molecular epidemiology of HIV type 1 among injecting drug users (IDUs) in Malaysia. AIDS Res Hum Retroviruses 2005;21(12):1046-1050. (156)

157. Ong LY, Razak SN, Lee YM, et al. Molecular diversity of HIV-1 and surveillance of transmitted drug resistance variants among treatment Naive patients, 5 years after active introduction of HAART in Kuala Lumpur, Malaysia. J Med Virol 2013 Wiley Periodicals, Inc. (157)

158. Tee KK, Kamarulzaman A, Ng KP. Short communication: low prevalence of genotypic drug resistance mutations among antiretroviral-naive HIV type 1 patients in Malaysia. AIDS Res Hum Retroviruses 2006;22(2):121-124. (158)

159. Tee KK, Kamarulzaman A, Ng KP. Prevalence and pattern of drug resistance mutations among antiretroviral-treated HIV-1 patients with suboptimal virological response in Malaysia. Med Microbiol Immunol 2006;195(2):107-112. (159)

160. Sungkanuparph S, Oyomopito R, Sirivichayakul S, et al. HIV-1 drug resistance mutations among antiretroviral-naive HIV-1-infected patients in Asia: results from the TREAT Asia Studies to Evaluate Resistance-Monitoring Study. Clin Infect Dis 2011;52(8):1053-1057. (160)

161. Chitra P, Bakthavatsalam B, Palvannan T. Beta-2 microglobulin as an immunological marker to assess the progression of human immunodeficiency virus infected patients on highly active antiretroviral therapy. Clin Chim Acta 2011;412(11-12):1151-1154. (161)

162. Tan DB, Yong YK, Tan HY, *et al.* Immunological profiles of immune restoration disease presenting as mycobacterial lymphadenitis and cryptococcal meningitis. HIV Med 2008; 9(5): 307-316.(162).

163. Sumatoh HR, Oliver BG, Kumar M, *et al.* Mycobacterial antibody levels and immune restoration disease in HIV patients treated in South East Asia. Biomark Med 2011; 5(6): 847-853.(163).

164. Lim YAL, Asma I, Surin J, *et al.* First genetic classification of Cryptosporidium and Giardia from HIV/AIDS patients in Malaysia. Infect Genet Evol 2011; 11(5): 968-974.(164).

165. Iqbal A, Lim YA, Surin J, *et al.* High diversity of Cryptosporidium subgenotypes identified in Malaysian HIV/AIDS individuals targeting gp60 gene. PLoS One 2012; 7(2): e31139.(165).

166. Jayaram G, Chew MT. Fine needle aspiration cytology of lymph nodes in HIV-infected individuals. Acta Cytol 2000; 44(6): 960-966.(166).

167. Zaidah AR, Chan YY, Asma HS, *et al.* Detection of Cryptosporidium parvum in HIV-infected patients in Malaysia using a molecular approach. Southeast Asian J Trop Med Public Health 2008; 39(3): 511-516.(167).

168. Al-Darraji HA, Razak HA, Ng KP, *et al.* The Diagnostic Performance of a Single GeneXpert MTB/RIF Assay in an Intensified Tuberculosis Case Finding Survey among HIV-Infected Prisoners in Malaysia. PLoS One 2013; 8(9): e73717.(168).

169. Lee CE, Sri Ponnampalavanar S, Syed Omar SF, *et al.* Evaluation of the dried blood spot (DBS) collection method as a tool for detection of HIV Ag/Ab, HBsAg, anti-HBs and anti-HCV in a Malaysian tertiary referral hospital. Ann Acad Med Singapore 2011; 40(10): 448-453.(169).

170. Chew CS, Cherry CL, Kamarulzaman A, *et al.* A longitudinal study of the effects of ART on plasma chemokine levels in Malaysian HIV patients. Dis Markers 2011; 31(5): 303-309.(170).

171. Centers for Disease Control and Prevention (CDC). Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. Morbidity and Mortality Weekly Report, December 18, 1992/41 (RR-17), 1993.

A Review of Malaria Research in Malaysia

Timothy William, FRCP* ** *, Jayaram Menon, FRCP** ***

*Infectious Disease Unit, Dept of Medicine, Queen Elizabeth Hospital, Kota Kinabalu, Sabah. **Department of Medicine, Queen Elizabeth Hospital, Kota Kinabalu, Sabah. ***Clinical Research Centre, Queen Elizabeth Hospital Kota Kinabalu, Sabah.

SUMMARY

One hundred and thirteen articles related to Malaria were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. Thirty eight articles were selected and reviewed on the basis of clinical relevance and future research implications. The epidemiology of malaria has undergone a significant change over the last decade with P. knowlesi, formerly a relatively unknown simian parasite rapidly becoming the most predominant malaria species to infect humans in Malaysia. The epidemiology, clinical features, diagnostic methods and treatment for P. knowlesi infection are described in these studies. In Malaysia, imported malaria from foreigners also poses a challenge. In view of these changes, new strategies on malaria control need to be devised and implemented, and treatment regimens need to be redefined to help Malaysia achieve the goal of malaria elimination by the year 2020.

KEY WORDS: *Malaria, Plasmodium knowlesi, Malaysia, Treatment, Epidemiology*

INTRODUCTION

Malaysia has shown considerable success in controlling malaria. Malaria elimination is now the goal of our country and we aim to be malaria-free by the year 2020. Artemesinin resistance is a challenge to malaria control internationally. However, *Plasmodium knowlesi* cases have increased over the past decade replacing other types of malaria species. It is now the most common cause of malaria in Malaysia, namely in Sabah and Sarawak, and poses a major challenge towards achieving the goal of malaria elimination in our country.

Malaria in humans is caused by five species of *Plasmodium; P. falciparum, P. vivax, P. malariae , P. ovale and P. knowlesi*. The long tailed and pig-tailed macaques (Macaca fascicularis and M. Nemestrina, respectively) are the natural hosts for *P. knowlesi*. These macaques are also the natural host for four other Plasmodium species (*P. cynomolgi, P. fieldi, P. coatneyi and P. inui*)

SECTION 1: REVIEW OF LITERATURE

THE DISCOVERY OF *P. KNOWLESI* MALARIA IN MALAYSIA

The first naturally-acquired case of human knowlesi malaria was acquired in Pahang, a state in the Peninsular Malaysia, in 1965. A second probable case was acquired in Johor a few years later. Knowlesi malaria was thought to be a rare disease until a large focus of human infection was described in Kapit, Sarawak in 2004[1]. Prof Balbir Singh and his team at the Malaria Research Centre at Universiti Malaysia Sarawak (UNIMAS) set out to investigate whether atypical *P. malariae* infections occurring predominantly in adults were attributable to a variant of *P. malariae* or some other Plasmodium species. They discovered using (polymerase chain reaction (PCR) assays, 120 (58%) of 208 patients at Kapit Hospital with malaria tested positive for *P. knowlesi*, whereas none was positive for *P. malariae*. *P. knowlesi* parasites in human erythrocytes were difficult to distinguish from *P malariae* by microscopy. Most of the *P knowlesi* infections were in adults. These infections were successfully treated with chloroquine and primaquine. This report was followed by another major finding by Dr Janet Cox-Singh and the group in UNIMAS, who found that *P. knowlesi* cases were widely distributed throughout Sarawak, Sabah and Pahang, They could also lead to fatal infections[2]. Fread Andreos *et al.* in 2008 and Daw Khin *et al.* in 2011 also described the widespread prevalance of *P. knowlesi* by PCR in Sabah[3,4].

These major scientific discoveries could have enormous implications on malaria control and treatment, mainly for Southeast Asia since every country in this region, except Laos, has described locally-acquired cases of *P. knowlesi*.

EPIDEMIOLOGY

Studies to understand the epidemiology of knowlesi malaria in Kapit by Lee *et al.* of UNIMAS have shown that the prevalence of malaria parasites in wild macaques is very high, with 94% (87/108) of macaques infected[5]. Furthermore, molecular studies on *P. knowlesi* derived from macaques and humans in Kapit, Sarawak have indicated that *P. knowlesi* is an ancient parasite and certain haplotypes are shared between human and macaque hosts. Taken together, these indicate that knowlesi malaria is an ancient zoonosis and humans have been acquiring *P. knowlesi* ever since they ventured into the forests where infected macaques were living. Definitive proof of how long *P. knowlesi* has been infecting humans in Sarawak is not available but a study on archival blood films showed that *P. knowlesi* had in fact already existed in significant numbers throughout Sarawak in 1996[6].

A retrospective review of malaria cases from the Sabah Health Department's malaria notification reports from 1992 to 2011 was conducted by Dr. Timothy William, *et al* to look at the trend of malaria cases in the state over a period of 20 years[7]. Notifications of *P. malariae* and *P. knowlesi* were grouped together. It was found that the total malaria notifications decreased significantly over 20 years. *P. falciparum* notifications peaked at 33,153 in 1994 and decreased 55-fold to 605 in 2011. P. vivax peaked at 15,857 in 1995 and decreased 25-fold to 628

Corresponding Author: tim7008@gmail.com

in 2011. The *P. malariae/P. knowlesi* notifications showed a peak of 614 in 1994 before reducing to less than 100 a year in the late 1990s/early 2000s. The *P. malariae/P. knowlesi* notifications, however, increased 10-fold from 2004 (n = 59) to 2011 (n = 703). In 1992, *P. falciparum, P. vivax and P. malariae/P. knowlesi* monoinfections accounted for 70%, 24% and 1% respectively of malaria notifications, compared to 30%, 31% and 35% in 2011. This showed that despite the decrease in the notification of human malaria, the number of *P. knowlesi* cases had increased significantly in recent years.

In Peninsular Malaysia, malaria is also prevalent but in much lower numbers. Indra *et al* in 2008 discovered that *P. knowlesi* infections also occurred in Peninsular Malaysia. *P. knowlesi* was detected in 77 (69.37%) of the 111 human samples, ten (6.90%) of the 145 monkey blood and in two (1.7%) Anopheles cracens. Sequence of the CSP gene were clustered with other *P. knowlesi* isolates[8].

Ruhani Yusof *et al* also confirmed that *P. knowlesi* was widespread in Peninsular Malaysia[9]. A total of 457 microscopically confirmed, malaria-positive blood samples were collected from 22 state and main district hospitals in Malaysia between September 2012 and December 2013. *P. knowlesi* was identified in 256 (56.5%) samples, followed by 133 (29.4%) cases of *P. vivax*, 49 (10.8%) cases of *P. falciparum*, two (0.4%) cases of *P. ovale* and one (0.2%) case of *P. malariae*. Twelve mixed infections were detected, including *P. knowlesi/P. vivax* (n = 10), *P. knowlesi/P. falciparum* (n = 1), and *P. falciparum/P. vivax* (n = 1). *P. knowlesi* (included mixed infections involving *P. knowlesi* (*P. knowlesi/P. vivax and P. knowlesi /P. falciparum*) showed the highest proportion in Sabah (84/115 cases, prevalence of 73.0%), Sarawak (83/120, 69.2%), Kelantan (42/56, 75.0%), Pahang (24/25, 96.0%), Johor (7/9, 77.8%), and Terengganu (4/5, 80.0%). However *P. knowlesi* infections in Selangor and Negeri Sembilan were found to be 16.2% (18/111 cases) and 50.0% (5/10 cases), respectively. They did not test samples from Kuala Lumpur, Melaka, Perak, Pulau Pinang, and Perlis during the study period and a microscopy positive sample for malaria in Kedah was negative by PCR.

A malaria survey was done in Selangor from 2006 to 201210. The patients were mainly from suburban areas unlike in East Malaysia. A total of 1623 laboratory confirmed malaria cases were reported from Selangor's nine districts; 72.6% of these cases (1178/1623) were attributed to imported malaria, 25.5% (414/1623) were local cases and 1.9% (31/1623) were considered as relapse and unclassified cases combined. In this study, the most prevalent infection was P. vivax (1239 cases, prevalence 76.3%) followed by *P. falciparum* (211, 13.0%), *P. knowlesi* (75, 4.6%), *P. malariae* (71, 4.4%) and *P. ovale* (1, 0.06%). Mixed infections comprising of *P. vivax* and *P. falciparum* were confirmed (26, 1.6%). A case of a patient with imported *P. ovale* infection which was initially misdiagnosed as *P. vivax* was reported.

Seven cases of naturally acquired human *P. knowlesi* infections were admitted to University Malaya Medical Centre in Kuala Lumpur from July 2007 till June 2008[11]. *P. knowlesi* reinfection was also reported in Sabah and in Peninsular Malaysia[12-13]. People may get repeated infections due to a lack of immunity for *P. knowlesi*. Other studies by Gurpreet Kaur *et al* and Norhayati, M *et al* have shown that malaria is common among the Orang Asli people[14-15].

Knowlesi malaria is not the only zoonotic malaria in Malaysia since this year; the first case of naturally acquired human infection of *Plasmodium cyanomolgi*, another malaria parasite of macaques, was reported in Malaysia[16].

THE TRANSMISSION OF *P. KNOWLESI*

Detailed studies on the transmission of knowlesi malaria have been undertaken in Sarawak where Dr Indra Vythilingam of IMR, working in collaboration with researchers at UNIMAS incriminated Anopheles latens as the vector for knowlesi malaria[17]. This vector is found in the forest and forest fringe, feeds predominantly after dusk and is attracted to both macaques and humans[18]. Two other species of mosquitoes (*An. cracens and An. hackeri*) have also been incriminated[8,19].

CLINICAL FEATURES OF *P. KNOWLESI* MALARIA IN ADULTS

A prospective study of the presentation and course of patients with acute *P. knowlesi* infection in Kapit Hospital which is a district hospital in Sarawak from July 2006 to February 2008 was done by Daneshvar C *et al*, from University Malaysia Sarawak (UNIMAS)20. One hundred and fifty two patients were enrolled in the study; 70% had *P. knowlesi*, 16% had *P. falciparum* and 14% had *P. vivax*. *P. knowlesi* infection presented with a non-specific febrile illness and clinical features could not distinguish between knowlesi and the human malarias, *P. vivax* and *P. falciparum*. The base line median parasitemia at admission was 1367 parasites/ml. The knowlesi malaria patients were all thrombocytopenic on admission or the next day. Most (93.5%) of the patients with *P. knowlesi* infection had uncomplicated malaria that responded to chloroquine and primaquine treatment. Seven patients with *P. knowlesi* infection (6.5%) had severe infections at hospital admission. Respiratory distress was the most common complication. Two patients with knowlesi malaria died, representing a case fatality rate of 1.8% (95% confidence interval, 0.2%–6.6%) but larger studies were recommended to determine the case fatality rate for knowlesi malaria.

Another important study was done in Queen Elizabeth Hospital (QEH), Kota Kinabalu, Sabah which is a tertiary hospital by Timothy William, Yeo Tsin Wen and researchers involving more ill patients21. They retrospectively studied patients with *P. knowlesi* malaria diagnosed by PCR from December 2007–November 2009. Fifty-six patients had PCR-confirmed *P. knowlesi* monoinfection and clinical records were available for review. Twenty-two (39%) had severe malaria; of these, six (27%) died. Thirteen (59%) had respiratory distress; 12 (55%), acute renal failure; and 12, shock. None experienced coma. Patients with uncomplicated disease received chloroquine, quinine, or artemether-lumefantrine, and those with severe disease received intravenous quinine or artesunate. Parasite clearance times were 1–2 days shorter with either artemether-lumefantrine or artesunate treatment. *P. knowlesi* was shown to be a major cause of severe and fatal malaria in Sabah.

P. knowlesi malaria in children

In Kudat, Sabah, Barber *et al* studied *P. knowlesi* infection in children[22]. The results showed that *P. knowlesi* in children usually resulted in uncomplicated malaria. They responded well to choloroquine and primaquine. Children commonly had anaemia and knowlesi infection was associated with moderately severe anaemia in addition to thrombocytopenia.

Malaria in dengue endemic areas

In areas that are endemic for dengue, patients presenting with fever and thrombocytopenia are often diagnosed as having dengue fever. Therefore clinicians need to be aware that malaria can also present with similar features. This was highlighted in a retrospective case series done in Peninsular Malaysia by Azira *et al*[23].

COMPARISON OF CLINICAL FEATURES BETWEEN THE DIFFERENT TYPES OF MALARIA SPECIES

A prospective study in QEH by Bridget Barber *et al* from the Queen Elizabeth Hospital (QEH) Infectious Disease Unit and the Menzies School of Health Research, Darwin Australia compared the risk, spectrum, and outcome of severe disease from *P. knowlesi, P. falciparum, and P. vivax* and outcomes following introduction of protocols for early referral and intravenous artesunate for all severe malaria[12]. From September 2010 to October 2011, the researchers prospectively assessed nonpregnant patients aged ≥12 years admitted to Queen Elizabeth Hospital (QEH), Sabah, with PCR–confirmed Plasmodium monoinfection. They found that severe malaria occurred in 38 of 130 (29%) patients with *P. knowlesi*, 13 of 122 (11%) with P. falciparum, and 7 of 43 (16%) with *P. vivax*.

RISK FACTORS FOR SEVERE *P.KNOWLESI* MALARIA

The commonest severity criteria in knowlesi malaria included parasitemia >100 000/μL (n = 18), jaundice (n = 20), respiratory distress (n = 14), hypotension (n = 13), and acute kidney injury (n = 9).

A very important finding was made in this study. On multivariate analysis, *P. knowlesi* was associated with a 2.96-fold (95% confidence interval, 1.19–7.38-fold) greater risk of severity than P. falciparum (P = .020). This clearly shows that P. knowlesi is potentially much more virulent than *P. falciparum*.

Only parasitemia and schizontemia >10% independently predicted knowlesi severity. The risk of severe knowlesi malaria increased 11-fold with parasitemia >20 000/μL, and 28-fold with parasitemia >100 000/μL. Nearly all (92%) knowlesi malaria patients received oral artemisinin therapy; 36 of 38 (95%) and 39 of 92 (42%) with severe and nonsevere disease, respectively, also received ≥1 dose of intravenous artesunate. No deaths occurred from any species.

Another study done earlier by Wilmann *et al* in Sarikei and Sibu, Sarawak showed that patients with high parasite density (≥ 35,000/μl) or with thrombocytopaenia (≤ 45,000/μl) were also more likely to develop complications (odds ratio(OR) = 9.93 and OR = 5.27, respectively)[24].

P. knowlesi is therefore the commonest cause of severe malaria in QEH Kota Kinabalu, with parasitemia the major risk factor for severity. It is recommended that IV artesunate be administered for patients with a parasitemia of >20000/μl for *P. knowlesi*. Early referral and treatment with artesunate was highly effective for severe malaria from all species and associated with zero mortality. This policy should therefore be strictly implemented in Malaysia.

LABORATORY DIAGNOSIS OF MALARIA

Challenges in the microscopic diagnosis of *P. knowlesi*

The only method of diagnosing malaria in hospital laboratories in Malaysia, is by microscopy which has its limitations. Molecular detection methods are more accurate and sensitive but are not rapid, cheap or qualitative so will not replace routine microscopy in rural hospitals where most malaria patients are admitted. Lee, Cox-Singh and Singh studied in detail the morphology of knowlesi malaria parasites They noted that the early trophozoites or ring forms of *P. knowlesi* resembled those of *P. falciparum* and the later erythrocytic stages of *P. knowlesi* were similar to those of *P. malariae*[25]. These findings confirm that it is virtually impossible in routine diagnostic laboratories to accurately differentiate the early ring forms of *P. knowlesi* from those of *P. falciparum*, and the later stages of *P. malariae* with those of *P. knowlesi* by microscopy. *P. knowlesi* trophozoites can also present with an atypical amoeboid morphology as described by a case report by Lee WC et al[26].

In view that Malaysia has five different Plasmodium species that infect humans, a study was done to see how accurate microscopy was to correctly diagnose them. The correct diagnosis is important for treatment and public health surveillance. A prospective study undertaken in QEH Kota Kinabalu Sabah to evaluate the accuracy of routine district and referral hospital-based microscopy by an experienced hospital microscopist, and microscopy performed by an experienced research microscopist, for the diagnosis of PCR-confirmed *P. falciparum*, *P. knowlesi*, and *P. vivax* malaria[27]. Among patients with *P. knowlesi* mono-infection, routine and cross-check microscopy, both identified 94 (72%) patients as "*P. malariae/P. knowlesi*". Routine microscopy identified 17 (13%) as P. falciparum and cross-check microscopy identified 28 (22%). Routine microscopy identified 13 (10%) as *P. vivax* and cross-check microscopy identified two (1.5%). Among patients with PCR-confirmed *P. falciparum*, routine and cross-check microscopy identified 110/122 (90%) and 112/118 (95%) patients respectively as *P. falciparum*, and 8/122 (6.6%) and 5/118 (4.2%) as "*P. malariae/P. knowlesi*". Among those with *P. vivax*, 23/43 (53%) and 34/40 (85%) were correctly diagnosed by routine and cross-check microscopy respectively, while 13/43 (30%) and 3/40 (7.5%) patients were diagnosed as "*P. malariae/P. knowlesi*". Four of 13 patients with PCR-confirmed *P. vivax* and misdiagnosed by routine microscopy as "*P. malariae/P. knowlesi*" were subsequently re-admitted with *P. vivax* malaria. The study concluded that microscopy does not reliably distinguish between *P. falciparum, P. vivax* and *P. knowlesi* in a region like Sabah where all three species occur.

Misdiagnosis of *P. knowlesi* as both *P. vivax* and *P. falciparum*, and vice versa, are common, potentially leading to inappropriate treatment, including chloroquine therapy for *P. falciparum* and a lack of anti-relapse therapy for *P. vivax*.

It is clear that relying solely on microscope diagnosis has its limitations in areas that are endemic for *P. knowlesi*. In this study, it was shown that only 1 out of 117 (0.85%) patients that was reported as *P. malariae / P. knowlesi* by microscopy was confirmed by PCR to actually have *P. malariae*. This is in sharp contrast to the finding that 94 out of these 117 (80.3%) patients was confirmed to have *P. knowlesi* by PCR. This confirms many other important earlier studies that the vast majority of microscopy results in Malaysia which are reported either as *P. malariae* or *P. malariae / P. knowlesi* are in actual fact *P. knowlesi*[1,3,6,11,20,28].

Rapid diagnostic tests (RDTs), while sensitive for the detection of falciparum malaria have not been assessed systematically for knowlesi malaria. A study was done in QEH, Kota Kinabalu, Sabah to prospectively evaluate the sensitivity of two combination RDTs for the diagnosis of uncomplicated and severe malaria from all three potentially fatal Plasmodium species using a pan-Plasmodium lactate dehydrogenase (pLDH)-P. falciparum histidine-rich protein 2 (PfHRP2) RDT (First Response) and a pan-Plasmodium aldolase-PfHRP2 RDT (ParaHIT)[29]. Among 293 hospitalised adults with PCR-confirmed Plasmodium monoinfection, the sensitivity of the pLDH component of the pLDHPfHRP2 RDT was 74% (95/129; 95% confidence interval [CI], 65 to 80%), 91% (110/121; 95% CI, 84 to 95%), and 95% (41/43; 95% CI, 85 to 99%) for PCR-

confirmed *P. knowlesi, P. falciparum*, and *P. vivax* infections, respectively, and 88% (30/34; 95% CI, 73 to 95%), 90% (38/42; 95% CI, 78 to 96%), and 100% (12/12; 95% CI, 76 to 100%) among patients tested before antimalarial treatment was begun. Sensitivity in severe malaria was 95% (36/38; 95% CI, 83 to 99), 100% (13/13; 95% CI, 77 to 100), and 100% (7/7; 95% CI, 65 to 100%), respectively. The aldolase component of the aldolase-PfHRP2 RDT performed poorly in all Plasmodium species. This study showed that the pLDH and the aldolase-based RDT did not demonstrate sufficiently high overall sensitivity for *P. knowlesi*. It was only sensitive for severe cases of malaria with high parasitaemia. Thus the tests may be falsely negative for patients who present with non-severe *P. knowlesi* malaria. Due to its 24-hour replication cycle, this could result in a fatal outcome.

Matthew Grigg *et al* also showed that combining two RDTS showed good specificity but poor sensitivity for the diagnosis of *P. knowlesi* malaria[30].

Foster D et al did a study comparing three RDTS. The RDTs had poor sensitivity and specificity for *P. knowlesi*. Patients with *P. knowlesi* could be misdiagnosed as *P. falciparum* with OptiMAL-IT, *P. vivax* with Paramax-3 and more correctly as non-*P. vivax*/non-*P. falciparum* with BinaxNOW® Malaria31. Therefore, more sensitive RDTs need to be developed for areas that are endemic for *P. knowlesi*.

Paul Divis *et al* reported the analytical and clinical validation of a new real-time PCR assay for *P. knowlesi* based on TagMan technology. The assay showed very good sensitivity, linearity and specificity with plasmid DNA and genomic DNA isolated that was isolated from patients that were infected with *P. knowlesi*. This can be a useful diagnostic tool for *P. knowlesi*[32].

Lau EL *et al* revealed that Loop-mediated isothermal amplification (LAMP) assays could be a potential alternative for molecular diagnosis and routine screening of *P. knowlesi* infection especially in malaria endemic countries, including Malaysia[33]. It could also be useful in monitoring malaria control and eradication programmes.

CLINICAL MANAGEMENT FOR MALARIA IN MALAYSIA

P. knowlesi

Chloroquine in the treatment of uncomplicated *P. knowlesi*

Dansehwar *et al* 's prospective observational study in Kapit, Sarawak showed that oral chloroquine and primaquine was excellent in the treatment of uncomplicated knowlesi malaria, The mean times to 50% (PCT50) and 90% (PCT90) parasite clearance were 3.1 (95% confidence intervals [CI] 2.8-3.4) hours and 10.3 (9.4-11.4) hours. These were more rapid than in a group of 23 patients with vivax malaria (6.3 (5.3-7.8) hours and 20.9 (17.6-25.9) hours; P = 0.02)[34].

Artemisinin Combination Therapy in the treatment of *P. knowlesi* malaria

The clinical studies done in QEH, Kota Kinabalu clearly showed that Artemesinin is effective in the treatment of uncomplicated and severe P.knowlesi. This antimalarial rapidly cleared parasitemia. Therefore policy changes were instituted in the management of malaria in Sabah . All patients with severe malaria were given intravenous artesunate immediately and referred to a Hospital with facilities for Intensive Care.

P. falciparum

The use of Fansidar (Sulphadoxine/Pyrimethamine) in the treatment of *P. falciparum* malaria

Despite the recommendation to use Artemesinin Combination Therapy as first line therapy for the treatment of *P. falciparum* malaria, Fansidar (Sulphadoxine/Pyrimethamine) is still sometimes used in Sabah and Sarawak. Many previous studies have shown that there is a significant resistance to this anti-malarial agent. Sophia Lau *et al* discovered that there was still a high prevalence of mutations in SDX/PYR-associated drug resistant genes in the interior districts of Sabah. This gives further evidence that Fansidar should never be used to treat malaria in Malaysia[35].

DEATHS DUE TO MALARIA

Despite these measures, 14 deaths from malaria were reported in other parts of Sabah during 2010-2011 and studied by Giri Shan *et al* [36].The deaths consisted of seven *P. falciparum*, six *P. knowlesi* and one *P. vivax* (all PCR-confirmed). Of the six *P. knowlesi* deaths, five were attributable to knowlesi malaria and one was attributable to *P. knowlesi*-associated enterobacter sepsis. Patients with directly attributable *P. knowlesi* deaths (N = 5) were older than those with P. falciparum (median age 51 [IQR 50-65] vs 22 [IQR 9-55] years, p = 0.06). Complications in fatal *P. knowlesi* included respiratory distress (N = 5, 100%), hypotension (N = 4, 80%), and renal failure (N = 4, 80%).

It was very notable that all patients with *P. knowlesi* were reported as P. malariae by microscopy. Only two of five patients with severe knowlesi malaria on presentation received immediate parenteral anti-malarial treatment. *P. knowlesi* is much more virulent than *P. malariae* and thus treatment with intravenous artesunate and close monitoring are of vital importance.

The patient with *P. vivax*-associated severe illness did not receive parenteral treatment. In contrast six of seven patients with severe falciparum malaria received immediate parenteral treatment. *P. knowlesi* was responsible, either directly or through gram-negative bacteraemia, for almost half of malaria deaths in Sabah. It was found that patients with severe non-falciparum malaria were less likely to receive immediate parenteral therapy.

The study emphasised the importance for microscopically diagnosed *P. malariae* to be reported as *P. knowlesi* to improve recognition and management of this potentially fatal species. All healthcare workers in the frontlines and clinicians should be informed that they need to treat all severe malaria regardless of the malaria species with immediate intravenous artesunate. Malaria infections including *P. knowlesi*, however, can also present atypically and thus resulting in a delay in diagnosis and management. This can lead to mortality[37].

POST-MORTEM FINDINGS OF P. KNOWLESI MALARIA

Post-mortem findings of a 40-year old male patient who died within two hours of presentation due to severe knowlesi malaria was reported by Cox-Singh *et al* 38. They found multiple petechial haemorrhages in the brain and endocardium. Lungs had features of Acute Respiratory Distress Syndrome (ARDS). Microscopically, there was sequestration of pigmented parasitised red blood cells in the vessels of the cerebrum, cerebellum, heart and kidneys. There was no evidence of any chronic inflammation in the brain or other organs. Brain sections were negative for intracellular adhesion molecule-1. The spleen and liver had abundant pigment containing macrophages and parasitised red blood cells. The

kidney had evidence of acute tubular necrosis and endothelial cells in heart sections were prominent. These findings are similar to fatal falciparum malaria.

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

In view that *P. malariae* and *P. knowlesi* are virtually indistinguishable microscopically and the overwhelming evidence that *P. malariae* is very rare compared to *P. knowlesi* in Malaysia, it is vital to report and notify them as *P. knowlesi* rather than *P. malariae* or *P. malariae / P. knowlesi* (except when the case is imported from a different country). In contrast to *P. knowlesi, P. malariae* which is much more benign rarely causes severe disease. Clinicians also need to be aware that *P. knowlesi* has a higher risk of causing severe malaria compared to the other species and also at lower parasite levels. Early diagnosis and treatment of malaria is very important to reduce mortality. Patients with severe malaria regardless of all species should be treated immediately with intravenous artesunate and closely monitored in a high dependency unit. Both chloroquine and Artemesinin Combination Therapy (ACT) has been shown to be effective for uncomplicated P. knowlesi. The use of an unified blood-stage treatment strategy using ACT for all Plasmodium species should also be considered as correctly diagnosing the malaria species may be challenging.

SECTION 3: FUTURE RESEARCH DIRECTION

There are still a number of gaps in our knowledge in regards to the dynamics of transmission for this infection, including risk factors for transmission, the mosquito vectors, and the occurrence of human-to-human transmission. We also should study the reasons for the changing trend of malaria species in Malaysia. There is also the need for sensitive RDTs capable of detecting knowlesi malaria. We must encourage interdisciplinary collaborative research on malaria among scientific groups from different fields such as entomology, social science, public health, clinical medicine, primatology and others in Malaysia. Research is currently underway in Sabah to define the biomedical, environmental and social risk factors for human infection with Plasmodium knowlesi. This large project named MONKEYBAR is conducted by the Malaysian Ministry of Health in collaboration with the London School of Hygiene and Tropical Medicine, Menzies School of Health Research, Darwin, Australia, University Malaysia Sabah, the Sabah Wildlife Department, University Malaya and other regional partner institutions from the Philippines. At the time of this writing, the Ministry of Health is also collaborating with the Menzies School of Health Research to conduct a randomised control trial comparing ACT with chloroquine in the treatment of *P. knowlesi* (ACTKNOW trial) and in the treatment of *P. Vivax*. These studies are funded by the Malaysian Ministry of Health and the Asia Pacific Malaria Elimination Network (APMEN). A study looking for artemesinin resistance in P.falciparum is also underway.

ACKNOWLEDGEMENT

We would like to acknowledge the valuable feedback of Prof. Balbir Singh from University Malaysia Sarawak and Dr. Indra Vythilingam from University Malaya during the preparation of this paper. We also would like to sincerely thank the Director-General of Health, Malaysia for his permission to publish this paper.

REFERENCES

1 Singh, B. *et al.* A large focus of naturally acquired Plasmodium knowlesi infections in human beings. The Lancet 363, 1017-1024, doi:10.1016/ s0140-6736(04)15836-4 (2004).

2 Cox-Singh, J. *et al.* Plasmodium knowlesi malaria in humans is widely distributed and potentially life threatening. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 46, 165-171, doi: 10.1086/ 524888 (2008).

3 Fread Anderios, Z. M., Ibrahim & Yusof, Ariffin Tajul. Detection of Malaria Parasites in Sabah by Nested Polymerase Chain Reaction- A Focus of Naturally Acquired Plasmodium knowlesi Infections,Sains Malaysiana 06, 137-141 (2008).

4 Daw Khin Saw Naing, F. A., Zaw Lin, & Geographic and Ethnic Distribution of P knowlesi infection in Sabah, Malaysia, International Journal of Collaborative Research on Internal Medicine & Public Health Vol. 3, 391-400.

5 Lee, K. S. *et al.* Plasmodium knowlesi: reservoir hosts and tracking the emergence in humans and macaques. PLoS pathogens 7, e1002015, doi:10.1371/ journal.ppat.1002015 (2011).

6 Lee, K. S., Cox-Singh, J., Brooke, G., Matusop, A. & Singh, B. Plasmodium knowlesi from archival blood films: further evidence that human infections are widely distributed and not newly emergent in Malaysian Borneo. International journal for parasitology 39, 1125-1128, doi:10.1016/ j.ijpara.2009.03.003 (2009).

7 William, T. et al. Increasing incidence of Plasmodium knowlesi malaria following control of P. falciparum and P. vivax Malaria in Sabah, Malaysia. PLoS neglected tropical diseases 7, e2026, doi:10.1371/ journal.pntd.0002026 (2013).

8 Vythilingam, I. *et al.* Plasmodium knowlesi in humans, macaques and mosquitoes in peninsular Malaysia. Parasites & vectors 1, 26, doi:10.1186/ 1756-3305-1-26 (2008).

9 Yusof, R. *et al.* High proportion of knowlesi malaria in recent malaria cases in Malaysia. Malaria journal 13, 168, doi:10.1186/ 1475-2875-13-168 (2014).

10 Braima, K. A. *et al.* Is there a risk of suburban transmission of malaria in Selangor, Malaysia? PloS one 8, e77924, doi:10.1371/ journal.pone.0077924 (2013).

11 Lee, C. E., Adeeba, K. & Freigang, G. Human Plasmodium knowlesi infections in Klang Valley, Peninsula Malaysia: a case series. The Medical journal of Malaysia 65, 63-65 (2010).

12 Barber, B. E. *et al.* A prospective comparative study of knowlesi, falciparum, and vivax malaria in Sabah, Malaysia: high proportion with severe disease from Plasmodium knowlesi and Plasmodium vivax but no mortality with early referral and artesunate therapy. Clinical infectious diseases 56, 383-397 (2013).

13 Lau, Y. L. *et al.* Plasmodium knowlesi reinfection in human. Emerging infectious diseases 17, 1314-1315, doi:10.3201/eid1707.101295 (2011).

14 Kaur, G. Prevalence of clinical malaria among an Orang Asli community in Malaysia. The Southeast Asian journal of tropical medicine and public health 40, 665-673 (2009).

15 Norhayati, M. *et al.* Clinical features of malaria in Orang Asli population in Pos Piah, Malaysia. The Medical journal of Malaysia 56, 271-274 (2001).

16 Ta, T. H. *et al.* First case of a naturally acquired human infection with Plasmodium cynomolgi. Malaria journal 13, 68, doi:10.1186/ 1475-2875-13-68 (2014).

17 Vythilingam, I. *et al.* Natural transmission of Plasmodium knowlesi to humans by Anopheles latens in Sarawak, Malaysia. Transactions of the Royal Society of Tropical Medicine and Hygiene 100, 1087-1088, doi:10.1016/ j.trstmh.2006.02.006 (2006).

18 Tan, C. H., Vythilingam, I., Matusop, A., Chan, S. T. & Singh, B. Bionomics of Anopheles latens in Kapit, Sarawak, Malaysian Borneo in relation to the transmission of zoonotic simian malaria parasite Plasmodium knowlesi. Malaria journal 7, 52, doi:10.1186/ 1475-2875-7-52 (2008).

19 Jiram, A. I. *et al.* Entomologic investigation of Plasmodium knowlesi vectors in Kuala Lipis, Pahang, Malaysia. Malaria journal 11, 213, doi:10.1186/ 1475-2875-11-213 (2012).

20 Daneshvar, C. *et al.* Clinical and laboratory features of human Plasmodium knowlesi infection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 49, 852-860, doi:10.1086/ 605439 (2009).

21 William, T. *et al.* Severe Plasmodium knowlesi malaria in a tertiary care hospital, Sabah, Malaysia. Emerging infectious diseases 17 (2011).

22 Barber, B. E. *et al.* Plasmodium knowlesi malaria in children. Emerging

infectious diseases 17, 814-820, doi:10.3201/eid1705.101489 (2011).

23 Azira, N. M., Zairi, N. Z., Amry, A. R. & Zeehaida, M. Case series of naturally acquired Plasmodium knowlesi infection in a tertiary teaching hospital. Tropical biomedicine 29, 398-404 (2012).

24 Willmann, M. *et al.* Laboratory markers of disease severity in Plasmodium knowlesi infection: a case control study. Malaria journal 11, 363, doi:10.1186/ 1475-2875-11-363 (2012).

25 Lee, K. S., Cox-Singh, J. & Singh, B. Morphological features and differential counts of Plasmodium knowlesi parasites in naturally acquired human infections. Malaria journal 8, 73, doi: 10.1186/ 1475-2875-8-73 (2009).

26 Lee, W. C. *et al.* Hyperparasitaemic human Plasmodium knowlesi infection with atypical morphology in peninsular Malaysia. Malaria journal 12, 88, doi: 10.1186/ 1475-2875-12-88 (2013).

27 Barber, B. E., William, T., Grigg, M. J., Yeo, T. W. & Anstey, N. M. Limitations of microscopy to differentiate Plasmodium species in a region co-endemic for Plasmodium falciparum, Plasmodium vivax and Plasmodium knowlesi. Malaria journal 12, 8, doi:10.1186/ 1475-2875-12-8 (2013).

28 William, T. *et al.* Severe Plasmodium knowlesi malaria in a tertiary care hospital, Sabah, Malaysia. Emerging infectious diseases 17, 1248-1255, doi:10.3201/ eid1707.101017 (2011).

29 Barber, B. E. *et al.* Evaluation of the sensitivity of a pLDH-based and an aldolase-based rapid diagnostic test for diagnosis of uncomplicated and severe malaria caused by PCR-confirmed Plasmodium knowlesi, Plasmodium falciparum, and Plasmodium vivax. Journal of clinical microbiology 51, 1118-1123, doi: 10.1128/ JCM.03285-12 (2013).

30 Grigg, M. J. *et al.* Combining Parasite Lactate Dehydrogenase-Based and Histidine-Rich Protein 2-Based Rapid Tests To Improve Specificity for Diagnosis of Malaria Due to Plasmodium knowlesi and Other Plasmodium Species in Sabah, Malaysia. Journal of clinical microbiology 52, 2053-2060, doi:10.1128/ JCM.00181-14 (2014).

31 Foster, D. *et al.* Evaluation of three rapid diagnostic tests for the detection of human infections with Plasmodium knowlesi. Malaria journal 13, 60, doi:10.1186/ 1475-2875-13-60 (2014).

32 Divis, P. C., Shokoples, S. E., Singh, B. & Yanow, S. K. A TaqMan real-time PCR assay for the detection and quantitation of Plasmodium knowlesi. Malaria journal 9, 344, doi:10.1186/ 1475-2875-9-344 (2010).

33 Lau, Y. L. *et al.* Specific, sensitive and rapid detection of human plasmodium knowlesi infection by loop-mediated isothermal amplification (LAMP) in blood samples. Malaria journal 10, 197, doi:10.1186/ 1475-2875-10-197 (2011).

34 Daneshvar, C. *et al.* Clinical and parasitological response to oral chloroquine and primaquine in uncomplicated human Plasmodium knowlesi infections. Malaria journal 9, 238, doi: 10.1186/ 1475-2875-9-238 (2010).

35 Lau, T. Y., Sylvi, M. & William, T. Mutational analysis of Plasmodium falciparum dihydrofolate reductase and dihydropteroate synthase genes in the interior division of Sabah, Malaysia. Malaria journal 12, 445, doi: 10.1186/ 1475-2875-12-445 (2013).

36 Rajahram, G. S. *et al.* Deaths due to Plasmodium knowlesi malaria in Sabah, Malaysia: association with reporting as Plasmodium malariae and delayed parenteral artesunate. Malaria journal 11, 1-7 (2012).

37 Rajahram, G. S., Barber, B. E., Yeo, T. W., Tan, W. W. & William, T. Case Report: Fatal Plasmodium Knowlesi Malaria Following an Atypical Clinical Presentation and Delayed Diagnosis. The Medical journal of Malaysia 68, 71-72 (2013).

38 Cox-Singh, J. *et al.* Severe malaria - a case of fatal Plasmodium knowlesi infection with post-mortem findings: a case report. Malaria journal 9, 10, doi: 10.1186/ 1475-2875-9-10 (2010).

A Review of Tuberculosis Research in Malaysia

Swarna Nantha Y, MRCGP

Outpatient Department, Klinik Kesihatan Seremban, Jalan Rasah 70300, Seremban.

SUMMARY

One hundred seventy four articles related to tuberculosis were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. One hundred fifty three articles were selected and reviewed on the basis of clinical relevance and future research implications. Topics related to epidemiology, clinical presentation, detection methods and treatment were well researched. However, limited information was available on screening and behavioural interventions. The younger population were more vulnerable to tuberculosis infection and had higher prevalence of risk factors that reactivate tuberculosis infection. Screening of tuberculosis was conducted primarily on healthcare workers, tuberculosis contacts, prisoners and foreign workers. Data on the clinical presentation of pulmonary and extrapulmonary tuberculosis was comprehensive. There was a general focus on related risk factors such as HIV and diabetes mellitus. A great degree of information was available on the treatment and various detection methods to identify tuberculosis. The efficacy and the practicality of investigative methods was analysed in this review. In conclusion, the direction of research should be aimed at novel preventive and control measures of tuberculosis. There should be emphasis on the screening of high risk groups (other than HIV) within the population namely diabetic patients, smokers and immunosuppressed individuals. The design of health policies should be guided by information gathered from research evaluation of community-based behavioural interventions.

KEY WORDS: *Pulmonary tuberculosis, extra pulmonary tuberculosis, latent tuberculosis, risk factors, HIV, diabetes mellitus*

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY

Pulmonary tuberculosis

There is a rise in the incidence of tuberculosis cases in the country between the year 2011 and 2012[1]. Within that same time frame, there was also a concurrent rise in rate of relapse[1]. In 2001, tuberculosis was the second most commonly notified communicable disease in Malaysia[2]. A third of the national tuberculosis cases were from the state of Sabah[2]. In a survey, 83% (172/ 207) of patients were diagnosed to have pulmonary tuberculosis[3].

The incidence of tuberculosis in Manjung was 49.5/100000 population[4]. Smear positive tuberculosis rate amongst the population in Manjung was at 64% of the total tuberculosis cases in Perak[4]. Close to 98% (102/104) with pulmonary tuberculosis were detected in the moderate to advance stages of the disease[5].

Extra pulmonary tuberculosis

Ten percent (20/195) to 11% (22/207) of tuberculosis cases at a tertiary level chest clinic were classified as extra pulmonary tuberculosis[3,6]. About 14% (8/57) of pulmonary tuberculosis patients also had extra pulmonary involvement[7].

Twenty percent (30/149) of HIV-infected tuberculosis cases have been diagnosed with extra pulmonary tuberculosis[8]. In populations with risk factors for the reactivation of tuberculosis (HIV or diabetes mellitus, 7% (109/1548) of patients were confirmed cases of tuberculous lymphadenitis[9].

Population with risk factors related to tuberculosis

The population with diabetes mellitus is a major factor in the reactivation of tuberculosis, followed by smoking, chronic kidney disease/end stage renal failure and age related factors[10].

Diabetes mellitus

The prevalence of diabetes among tuberculosis patients at tertiary centres range between 14-33% [14% (25/173), 15% (53/352), 27% (338/1267), 30% (60/200) and 33% (68/207)][3,11-14] Patients with diabetes mellitus (DM) were more likely to have pulmonary tuberculosis (OR=2.079, $p<0.001$)[13]. The evidence for this was seen in large scale studies[15]. A greater percentage of pulmonary tuberculosis patients (91%, 1509/1651) were in the TB-DM group[15]. Four smaller scale studies had conflicting evidence on this matter. A study supporting this view discovered 82% (107/131) of patients diagnosed with pulmonary tuberculosis suffering from either diabetes mellitus, hypertension, ischaemic heart disease or all three conditions[16]. Three other studies revealed the prevalence of tuberculosis among diabetics between the range of 18 and 30%[7,17,18].

Little data was available on the prevalence of a specific extra pulmonary tuberculosis among diabetic population. One study found 16% (17/109) of patients with tuberculous lymphadenitis had diabetes mellitus[9].

Smokers

The prevalence of tuberculosis was higher in a smoking population[10]. In Malaysia, smoking prevalence rate is high amongst tuberculosis patients[19]. It was estimated that 40% (70/176) to 50% (102/207) of tuberculosis patients were smokers[3,11]. Smoking was prevalent in 57% (135/237) of pulmonary tuberculosis patients[18] while only 21% (41/195) of extra pulmonary tuberculosis patients had either smoking and/or drinking habits[6].

Most TB-HIV patients were smokers[20]. In a study assessing resurgence of tuberculosis in immunosuppressed patients, a

Corresponding Author: yogarabin@gmail.com

large number of HIV/AIDS patients with tuberculosis were smokers (61%, 177/290)[21]. A similar trend was seen in diabetic patients with tuberculosis where 46% (91/200) of this population were smokers[14].

Prevalence rates in tuberculosis patients who have been continuously smoking was higher than current and ex-smokers [(54%, 54220/100 000) vs (40% (329/817) and (14% (114/817)][19].

HIV
In an assessment designed to identify the frequency of opportunistic infections, tuberculosis was the most common cause of AIDS-defining illnesses (48%)[22].

In a two-year multi-centred study, the prevalence of HIV amongst tuberculosis patients was estimated at 7.7% (15/200)[14]. Higher prevalence rate was seen (15.9%) in a three-month survey[23]. A lower prevalence rate was recorded (2.4%) in a one-year study at an urban centre (5/207)[3]. A two-year study at a rural setting revealed a prevalence rate of 14% (25/176), comparable to findings at urban centres[11]. Hence, the combination of population density and duration of the study seem to yield different prevalence rates.

The prevalence of inpatients being diagnosed with concomitant HIV and tuberculosis was at 1.5% (2/131) in a seven-year survey[16]. Twelve percent (57/1857) of HIV positive patients at drug rehabilitation centres and prisons had tuberculosis co-infection[24]. Prisoners comprise 50% (13/25) of all HIV-infected tuberculosis patients receiving treatment at a tertiary centre chest clinic[23].

HIV patients had greater rates of pulmonary tuberculosis (68-79%) and lesser rates of extra pulmonary tuberculosis (20-22%)[25,26]. In large scale studies, prevalence rates ranged between 79% (117/149) and 86% (249/290)[8,27]. However, in a smaller study, only 11% (6/57) of pulmonary tuberculosis cases were detected to have HIV co-infection[7].

In patients with AIDS, pulmonary tuberculosis was the most common infection (29%, 37/128), followed by Pneumocystis carinii pneumonia (PCP) (28%, 36/128) and extra pulmonary tuberculosis (12%, 15/128)[28].

In one study, tuberculous lymphadenitis was the most common form of extra pulmonary tuberculosis[26]. About 10% (11/109) of tuberculous lymphadenitis patients had HIV infection[9].

Fifty two percent (16/176) of the mortality of tuberculosis cases were related to HIV infection[11]. Fifty one percent of notified TB deaths were associated with HIV co-infection amongst prisoners[24].

Other factors related to immunosuppression
Age and chronic kidney disease/end-stage renal failure (CKD/ESRF) were found to be related to the reactivation of tuberculosis[10]. Long term utilisation of steroids contributed to 2% (1/57) of pulmonary tuberculosis cases[7].

Healthcare workers (HCW)
The average notification of tuberculosis amongst healthcare workers in the five years studied was twice as high than that of the general population (280.4/100 000 vs 153.9/100 000)[29].

The incidence of TB amongst healthcare workers was 280.4 per 100 000 population from the year 1999 to 2004[29]. Incidence of latent tuberculosis infection in healthcare workers was 9.9 per 100 workers per year[30].

Intravenous drug users (IVDU)
The common mode of transmission of HIV in patients with tuberculosis was via intravenous drug injection (74%, 110/149)[25]. There was a significant association between HIV infection via intravenous drug abuse and the incidence of tuberculosis infection ($p<0.05$)[22]. Thus, it was not uncommon that almost 74% (19/25) of the HIV-infected tuberculosis patients were indeed IVDUs[23].

There was a predominance of pulmonary tuberculosis when compared to extra pulmonary tuberculosis amongst IVDUs. Seventy seven percent (191/290) of HIV-infected pulmonary tuberculosis patients were IVDUs27 while only 5% (10/195) of extra pulmonary tuberculosis patients were seen in this population[6].

Smaller numbers of IVDUs [1.5% (2/131)] were inpatients with tuberculosis[16]. A larger number of IVDUS (15%) received outpatient pulmonary tuberculosis treatment[31].

Hepatitis C virus (HCV) infection
HIV-infected patients with pulmonary tuberculosis were strongly associated with HCV infection[20].

Latent tuberculosis infection
Studies involving the prevalence of latent tuberculosis infection (LTBI) were limited to only specific groups in the community (prisoners, healthcare workers and tuberculosis contacts).

Prisoners
There was a high prevalence of LTBI [88% (234/266)] amongst prisoners consisting of both HIV and non HIV population[32]. Screening of LTBI in prisoners with HIV using interferon-ϒ-release assay (IGRA) detected a 12% (15/125) of previously undiagnosed active pulmonary TB[33].

Healthcare worker (HCW)
One study conducted at four hospitals revealed an 11% prevalence rate of LTBI among HCWs[34].

Contacts
Thirty percent (12/40) of the contacts of HIV positive pulmonary tuberculosis patients had positive tuberculin skin test (TST) compared to 53% (47/94) of the contacts of HIV negative patients [OR= 0.41, 95% CI 0.07-0.87; p=0.016][35].

Drug resistance rates
No multidrug-resistant tuberculosis (MDR-TB) cases were found amongst 252 HIV patients with tuberculosis in a study conducted at the National Tuberculosis Center[36]. At one tertiary setting, 1.9% (4/207) of patients had drug resistant tuberculosis[3].

Adverse events
The majority of patients (85%, 111/131) did not complain of side effects from anti-TB treatment16 while in a separate study, only 8.3% (9/109) of patients had adverse effects from anti TB treatment[37]. One study analysing the adverse effects of anti-TB treatment found the prevalence of drug-induced hepatitis to be at 9.7%[38].

Treatment regimens seem to influence the incidence of adverse drug reactions. Eleven percent (19/176) developed adverse drug reaction; 11 were from the 2SHRZ/4SHR2 category[11].

Demographics

Gender, Age and Ethnicity
Tuberculosis was predominant in a male population[11,16,24,39]. The majority of pulmonary tuberculosis cases were also males[3,7,17,39]. Males also had a higher preponderance of TB-related deaths[40].

Taking into account risk factors related to tuberculosis, there were higher rates of male HIV-infected tuberculosis patients when compared to females[8,20,21,25,26,36,41]. Males formed a large proportion of HIV patients with pulmonary tuberculosis (97%, 241/290)[27]. In contrast, one study had a significant female distribution in the TB-DM group ($p<0.05$)[20]. However in four other prevalence studies, there were more males than females with tuberculosis and diabetes[12,14,15].

Majority of non HIV-infected extra pulmonary tuberculosis patients were females (50%, 96/195)[6]. Miliary (5%, 13/263) and tuberculosis of the lymph nodes (11%, 29/263), were commonly found in foreign-born female patients[39]. Spinal tuberculosis (70%, 37/52)[42] and pleural effusion due to tuberculosis was significantly higher in males ($p=0.048$)[43].

Table I shows different types of TB and their association with age. Table II shows different types of TB and their association with ethnicity.

Education level
Fifty two percent (108/207) of tuberculosis cases had secondary education3. Seventy eight percent (76/97) of TB/HIV patients had completed secondary or tertiary education[7,23,41].

Socioeconomic status
The increase in the incidence of tuberculosis was more predominant amongst the socioeconomically deprived[44]. Foreign-born single males (48%, 125/263) and married females (71%, 187/263) had a greater percentage of tuberculosis infection[39].

In a survey involving pulmonary tuberculosis patients, married patients constitute about 67% (37/57) of detected cases while 65% (37/57) were unemployed(35%,18/57)[7]. Fifty percent (96/195) of non HIV-infected patients with extra pulmonary tuberculosis were unemployed[6].

In the HIV-infected tuberculosis category, being single and unemployed was a recurring theme[8,16,20,21,23,25,27,41]. When employed, HIV-infected tuberculosis patients often held non-professional occupations[41]. In HIV-infected tuberculosis patients, there were significant associations with age, family member to room ratio, sex and marital status[41].

SCREENING

Pulmonary tuberculosis
Only specific groups of the population were involved in studies pertaining to pulmonary tuberculosis screening. These groups were contacts of HIV patients, foreign workers and prisoners with HIV[33,35,49].

Contacts of HIV positive patients were less likely to contract pulmonary tuberculosis[35]. Only 30% (12/40) of contacts of HIV positive PTB patients had a positive TST when compared to 53% (47/94) of the contacts of HIV negative patients [OR= 0.41, 95% CI 0.07-0.87; $p=0.016$][35].

Pulmonary tuberculosis was the second most commonly detected disease during pre-employment medical examination of Indonesian domestic helpers at a private clinic[49].

Using a new nucleic acid amplification technology (through polymerase chain reaction), the screening of HIV-infected male and female prisoners detected 12% (15/125) of previously undiagnosed active pulmonary tuberculosis[33].

Latent tuberculosis
The focus of screening of LTBI was directed towards healthcare workers (HCWs), contacts of tuberculosis patients and drug abusers[30,34,50,51].

Screening of HCW revealed that the prevalence of latent tuberculosis infection in Malaysia was relatively low for an intermediate TB burden country[34]. There was a high incidence of TB exposure at the emergency department amongst HCWs screened with IGRA[30]. Working at the emergency department was significantly associated with TB infection[30].

At a tertiary centre, a positive TST (≥ 10mm) was seen in 4% (38/1024) of patients who were screened based on contact tracing records[50]. The yield (active tuberculosis cases) of contact tracing was low at 0.5% possibly due to the utilisation of a less accurate test and poor prioritisation of patients[50]. There is a need for a more accurate test such as IGRA[50].

A positive TST was seen in 87% of drug abusers who were screened for LTBI at a voluntary drug treatment centre[51].

RISK FACTORS

Diabetes mellitus
A greater number of tuberculosis patients (91%, 1509/1651) are diabetics[15]. The reactivation of tuberculosis seem to occur at least four years after the initial diagnosis of diabetes[14]. Age was a significant predictor of tuberculosis infection in patients with diabetes when compared to non-diabetic patients($p<0.05$)[15]. Tuberculosis patients with diabetes or HIV infection usually present with cough with or without sputum, fever and loss of appetite and/or weight[20]. The duration of symptoms was longer in non-diabetic tuberculosis patients[14]. Diabetes increased the mortality rate (7.5%) of diabetic patients compared to patients with only TB or diabetes[14].

Diabetes increased the likelihood of contracting pulmonary tuberculosis[14,16,18]. Diabetes is a strong risk factor for the development of pulmonary tuberculosis (30%, 71/237)[18]. When comparisons were made, diabetic patients were more likely to develop pulmonary tuberculosis (89%, 178/200) than non-diabetic tuberculosis patients (59%, 118/200)[14,16].

Smoking
Risk of activation of latent tuberculosis infection in smokers is two-fold than that of a non smoking population[10]. Smokers were found to be significantly associated with advanced tuberculosis disease on diagnosis[5].

HIV
Tuberculosis is a common cause of AIDS defining diseases[52,53]. It is also the leading cause of morbidity and mortality in AIDS patients[52]. HIV was the most common co-infection and was implicated in 15% of tuberculosis deaths[40]. Patients with TB/HIV with three or more opportunistic infections are closely associated with death[48].

Bacillus Calmette–Guérin (BCG) vaccination was ineffective in this group[20]. This was evidenced by the significant presence of BCG vaccination amongst HIV-infected group who had tuberculosis ($p<0.05$)[20].

The presentation of tuberculosis in HIV infected patients might be influenced by reduced CD4 counts[53]. This could also explain why HIV-infected patients with tuberculosis are less infectious to their contacts than HIV-negative patients[35]. However, in an isolated finding amongst prisoners, tuberculosis symptoms were similar between HIV infected and non HIV infected individuals[32].

In general, HIV-infected tuberculosis patients commonly present with cough, fever, with or without sputum production, lymphadenopathy, chest infiltrations, loss of appetite and/or loss of weight[8,20,21,25].

Cough and hemoptysis are the most common presenting symptoms in HIV patients[36]. HIV co-infection in tuberculosis patients was also significantly associated with fever and lymphadenopathy ($p<0.05$)[20]. AIDS patients with tuberculosis had a significant association with fever, cough, sputum or hemoptysis ($p<0.05$)[54]. The CD4 cell level played a significant role in tuberculosis ($p<0.05$)[54]. HIV patients with unsuccessful treatment outcome were associated with intravenous drug use, lymphadenopathy (OR 2.01; 95% CI 1.09-3.72) and low serum albumin (OR 4.61; 95% CI 1.73-12.27)[55].

A history of IVDU in HIV patients was directly linked to the incidence of tuberculosis infection ($p<0.05$)[22]. HIV-related tuberculosis with IVDU was associated with unemployment ($p<0.05$)[22]. There was a significant association between occupation or mode of HIV transmission and tuberculosis infection ($p<0.05$)[54].

Pulmonary tuberculosis was the most common form of tuberculosis found in both HIV and diabetic groups (90%, 62/67)[20,36]. It was also the most common pulmonary opportunistic infection amongst AIDS patients at a hospital setting[56]. Close to 86% (249/290) of HIV-infected patients had pulmonary tuberculosis 21. There was significant association between patients with HIV infection from IVDU and pulmonary tuberculosis ($p<0.05$)[27]. Cough and hemoptysis were significantly related to pulmonary tuberculosis amongst HIV patients[26,36]. TB-HIV group with pulmonary tuberculosis was significantly associated with HCV infection ($p<0.05$)[20].

Extra pulmonary tuberculosis in HIV patients was associated with CD4 counts less than 100[57]. There is significant association between HIV and extrapulmonary tuberculosis (summary OR: 1.3; 95% CI 1.05-1.6)[57]. Close to 14% (41/290) to 56% (140/252) of HIV patients had extra pulmonary, miliary or disseminated tuberculosis[20,21,36]. In one study, lymph nodes were commonly involved[53]. There were also higher rates of TB meningitis, pleural TB and TB pericarditis[53].

As part of routine monitoring of anti-tuberculosis treatment, HIV infection was a significant risk factor in the development of TB drug-induced hepatitis ($p<0.005$)[38].

Healthcare workers (HCWs)

From a demographic perspective, factors such as age, gender, history of tuberculosis contact outside the work place, duration of service and failure to use respiratory protection were considered risk factors for the development of tuberculosis among healthcare workers[29]. Ethnicity, designation, family contact and TB related knowledge did not significantly contribute to risk of contracting tuberculosis[29]. Working at the emergency department was significantly associated with the risk of TB infection[30].

Risk of LTBI was higher in HCWs who were aged 35 years and older [9.46 (CI: 2.22; 40.50)], and who had a history of living in the same house with close family members or friends with active tuberculosis [8.60 (CI: 1.36; 10.02])[34].

Immunosuppression

The development of prostatic tuberculosis was linked to an immunocompromised state[58]. Extensive steroid therapy led to the development of pulmonary tuberculosis which was identified through tracheal aspirate sample[59].

Prisoners

Factors correlated with tuberculosis symptoms amongst prisoners were increasing age (aOR 1.07, 95%CI 1.01-1.13), lower body mass index (aOR 0.82, 95%CI 0.7-0.96) and TST-reactive status (aOR 3.46, 95%CI 1.20-9.97)[32]. Undiagnosed active pulmonary tuberculosis among HIV infected prisoners was associated with longer duration of drug use[33].

CLINICAL FEATURES

Out of the 90% (209/232) of patients who had previous medical consultations for suspected tuberculosis, chest radiographs or sputum examination were not performed in 40% (93/232) of these patients[17]. Hence, appropriate care should be given to suspected tuberculosis patients as delay by healthcare providers was associated with advanced disease on diagnosis[5].

Most Malaysian inpatients with tuberculosis had a cluster of prolonged productive cough, night sweats, fever, anorexia, and weight loss (57%, 75/131)[16]. The rest had hemoptysis (34%, 45/131) and few had diarrhoea and dysphagia (9%, 12/131)[16]. The presentation was different amongst foreigners. Male foreign-born workers with tuberculosis were associated with fever (70%, 184/263), cough (91%, 239/263) and positive BCG vaccination status whereas females had higher predilection to lymphadenopathy (22%, 58/263)[$p<0.05$][39].

Patients with advanced features of tuberculosis had higher chances of death[40] and were usually malnourished or had loss of appetite[5].

Socioeconomic status did not affect the severity of disease[5]. Most patients had no history of contact with tuberculosis patients (72%, 41/57)[7].

Gender

The female gender was significantly associated with delay in the diagnosis of pulmonary tuberculosis[60].

Duration

Majority of newly diagnosed pulmonary tuberculosis patients had clinical symptoms for many years[61]. In one study, nearly half (45%, 104/232) of tuberculosis patients had symptoms for more than one year[17]. Patients with pulmonary tuberculosis had symptoms more than two weeks before hospital admission (OR 25.10; 95 CI 4.63-136.05; $p<0.001$)[62].

Common symptoms

Cough was the most common symptom in pulmonary tuberculosis (92%, 218/237)[18]. Only 8% (19/237) to 22% (51/232) had typical symptoms of cough, fever, loss of appetite and loss of weight[17,18]. However, pulmonary tuberculosis patients were more malnourished than normal people[63] and had significant history of night sweats (OR 5.43; 95% CI 1.10-

26.79; p=0.038)[62]. Hemoptysis was only seen in 4% (6/160) of patients with tuberculosis[64]. Risk factors for pulmonary tuberculosis include diabetes mellitus (18%, 42/232), positive family history of tuberculosis (17%, 39/232) and previous tuberculosis infection (5%, 12/232)[17]. The most common location for AIDS with tuberculosis was the pulmonary region (85%, 104/123)[54].

Tuberculous effusion
The most common cause of exudative pleural effusion was tuberculosis (44%, 82/186), followed by malignancy (30%, 56/186)[65]. Conversely, in a smaller study the most common cause for pleural effusion was malignancy (34%, 38/111), followed by tuberculosis (23%, 26/111) and parapneumonic effusions (19%, 21/111)[66].

Tuberculous effusions were frequent in the first five decades (73%, 60/82) of life and were the most common type of pleural effusion in this age group (70%, 60/86)[65]. However, a statistical significant association was found between a younger median age and tuberculous effusion (34.5 years) (mean age 34.5 years; p<0.001)[65,67]. Tuberculous and malignant lung effusions had more predominance on the right side of lung[67] and were smaller than malignant pleural effusions (p<0.001)[67].

Atypical presentations
Clinical and radiological manifestations of pulmonary tuberculosis may be atypical[17]. Five percent (17/163) of non immunocompromised inpatients were initially suspected to have community-acquired pneumonia and were later diagnosed to have pulmonary tuberculosis[62]. In one case report, a patient with upper lung collapse was given the provisional diagnosis of submucosal tumour but was discovered to have tuberculosis after a second attempt at bronchocopy[68]. Pulmonary cryptococcosis in a non-HIV infected person could present in a similar manner as tuberculosis or lung cancer[69]. There was a rare case report of a pneumatocoele which was due to TB pneumonia at two weeks of age[70].

A HIV-infected patient had no systemic symptoms of pulmonary tuberculosis but was confirmed through bronchoalveolar lavage, an elevated ESR level and a strongly positive IGRA test[71].

Pulmonary tuberculosis with concomitant extra pulmonary presentation
Fifteen percent (35/232) of pulmonary tuberculosis patients presented with extrapulmonary diagnosis[17]. Concurrent pulmonary and spine tuberculosis were seen in 67% of patients (22/33)[46].

Empirical treatment to identify pulmonary tuberculosis
Out of 107 patients who were empirically treated as smear negative pulmonary tuberculosis, only 11% (11/107) of patients were eventually diagnosed as 'non-TB' based on absence of both clinical and diagnostic findings or discovery of another cause of the pulmonary condition[37].

Extrapulmonary tuberculosis
The most common sign amongst extra pulmonary tuberculosis patients was lymphadenopathy (46%, 90/195)[6]. Patients also had previous history of tuberculosis (4%, 8/195) and contact with tuberculosis patients (9%, 18/195)[6]. Patients with extrapulmonary tuberculosis were also at significant risk of developing anti-TB drug-induced hepatitis (p<0.008)[38].

Spine
More than half [52% (17/33)] of patients with tuberculosis of the spine had neurological manifestations[46]. Other common presentations were backache (94%, 50/52), abscess (45%, 25/53) neurological deficit (44%, 23/53) and gibbus deformity (22%, 12/52)[42]. A high percentage of spinal tuberculosis did not have BCG scar (82%, 43/52) and 18% (10/52) had evidence of concurrent pulmonary tuberculosis[42]. In some cases, there is difficulty in differentiating spinal tuberculosis from a metastasis[72].

Vertebral involvement and complications
The most common vertebra involved was the 9th vertebra and the least common was the 3rd vertebra[42]. The average number of vertebra affected was 342. Most lesions involved the thoracic level (48%, 14/31) with 65% involving the pedicle region[73]. Disc collapse, prevertebral abscess and kyphosis were more severe in the pedicle group[73].

A case of Pott's disease of the spine with psoas abscess had been reported[74].

Tuberculous lymphadenitis
Cough and fever were the common symptoms found amongst patients with tuberculous lymphadenitis[9]. Lymph node involvement was seen in 46% (90/195) of extra pulmonary tuberculosis patients6. Lymphadenopathy (34%, 84/252) was the most common sign in HIV patients with extra pulmonary tuberculosis[36].

Genitourinary
Genitourinary tuberculosis in developing countries comprises approximately 15-20% of extrapulmonary cases of tuberculosis[58]. Seventy eight percent (7/9) of patients with tuberculosis of the genital tract had ascites, vague abdominal distension, weight loss[75]. These cases were misdiagnosed as ovarian carcinoma[75].

Atypical presentation
An atypical genitourinary tuberculosis could mimic a cervical carcinoma[76]. High degree of suspicion should be practised in HIV patients with symptoms similar to acute prostatitis. A case report diagnosed a case of prostatic tuberculosis through biopsy[58].

Complication
A spontaneous perforation of the bladder was due to tuberculosis[77].

Gastrointestinal tuberculosis (GITB)
In general, GITB presents with right iliac fossa pain (26%, 9/34), bowel obstruction (26%, 9/34), diarrhoea (18%, 6/34) and ascites (12%, 4/34) 47. Sites of TB involvement includes caecum (38%, 13/34), ileum (29%, 10/34), mesenteric lymph nodes (26%, 9/34), small intestines (21%, 7/34) and ascending colon (18%, 6/34)[47].

Abdominal tuberculosis
Ileocaecal regions, peritoneum and hepatobiliary system were the most commonly affected sites[78]. Clinical presentation include abdominal pain (62%, 21/34), anorexia (44%, 15/34), weight loss (56%, 19/34), fever (41%, 14/34) and abdominal distention (29%, 10/34)[78].

Tongue tuberculosis
Tuberculosis of the tongue presented with the symptoms of sore throat and dysphagia for three months[79].

Intestinal tuberculosis
Patients with intestinal tuberculosis often present with perianal fistula, appendicitis, ascites, rectal, intestinal or gastric 'growth', 'ulcerative colitis' or recurrent anaemia[80]. Patients could also present with sub-acute intestinal obstruction resembling Crohn's disease[81].

Tuberculous peritonitis
In a patient with abdominal pain and fever for two weeks and poor response to broad spectrum antibiotics, CT scan was the best modality in detecting tuberculous peritonitis[82].

Gallbladder tuberculosis
Symptoms of jaundice and right hypochondrial led to the use of CT scan to confirm gallbladder empyema. The diagnosis of gallbladder tuberculosis was confirmed by biopsy results[83].

Oesophageal tuberculosis
Oesophageal tuberculosis were first suspected as malignancies but was eventually diagnosed as tuberculosis[84].

Knee joint
Clinical presentation includes diffuse swelling of the knee, involvement of small joints of hand, fever, loss of appetite and weight[85-87]. In all three cases, the diagnosis was obtained through biopsy[85-87]. Magnetic resonance imaging (MRI) of the knee was helpful in two of the cases and was inconclusive in the other[85-87].

Bone

Tuberculosis of the talus
A swelling over antero-medial aspect of foot with irregular lytic lesion on x-ray was subjected to aspiration of fluid and curretage[88]. Histopathological examination of the bone grafting confirmed the diagnosis of tuberculosis[88].

Tuberculosis of the distal radius
A lesion with the features of suspected giant cell tumour was resected from distal radius. The histopathological report confirmed the lesion was tuberculosis[89].

Cervical tuberculosis
An elderly patient presented with one month of worsening neck pain and progressive upper and lower limb weakness was confirmed as cervical tuberculosis[90].

Atypical presentation
Ewing's sarcoma had similar presentation as tuberculosis in a young patient[91].

Hepatic system

Tuberculous liver abscess
Tuberculous liver abscess was seen in a young male patient who was diagnosed with Burkholderia pseudomallei and acid fast bacilli abscess of liver[92].

Bile duct tuberculosis
A HIV patient presented with biliary peritonitis due to spontaneous common bile duct perforation was later confirmed to be tuberculosis[93].

Abdominal tuberculosis
Most commonly affected sites were the ileocaecal regions, peritoneum and hepatobiliary system[78].

Vascular
The treatment of tuberculous vasculitis had good results from endovascular stenting of a stenotic subclavian artery[94].

A patient with persistent backache after the completion of treatment for spinal tuberculosis was diagnosed as pseudoaneurysm of infrarenal aorta[95].

Ocular

Clinical features in adults
Central retinal vein occlusion like signs and symptoms were seen in two case reports[96,97]. There were cases with redness and mucopurullent discharge of the eye[98] or headache and blurring of vision[99].

Out of the six case reports in adults, four case reports of ocular tuberculosis had a positive Mantoux and/or IGRA test[97-100]. Majority of these cases had no positive finding on chest x-ray, systemic blood screening, or sputum analysis[96,97,99,100]. In two case reports, anti-tuberculosis treatment was commenced based on Mantoux and IGRA test results[97,99]. The decision to commence anti-tuberculosis treatment in the remaining two cases of ocular tuberculosis depended on the analysis of vitreous fluid and conjunctival biopsy[97,99].

Clinical features in children
An immunocompetent child had bilateral optic neuritis[101]. Ocular tuberculosis was diagnosed based on a positive Mantoux test and a raised ESR[101]. All other blood tests and imaging were normal[101].

The other case report involves an immunocompetent patient with a reactivation of ocular tuberculosis after anti-tuberculosis treatment[102].

Splenic tuberculosis
A case of splenic tuberculosis was seen in a patient with prolonged fever and hepatosplenomegaly[103].

Endocrine
An adrenal tuberculosis infection presented as an egg-shell calcification of the adrenals[104]. Pancreatic tuberculosis was diagnosed in a HIV patient with nonspecific symptoms of pancreatic disease[105].

Others
Miliary and pleural involvement in extra pulmonary tuberculosis patients were at 20% (39/195) and 13% (25/195) respectively[6].

Clinical presentation in latent tuberculosis infection (LTBI)
Working at a tertiary centre had an increased risk for tuberculosis infection and was significantly associated with the level of occupational tuberculosis exposure[106]. This was seen in a study where medical ward HCWs were at significantly higher risk of positive TST reaction/LTBI (odds ratio, 2.18; 05% CI, 1.44 to 3.57; p= 0.002)[106]. Employment of more than one year and working as a nurse were significantly associated with positive TST reaction at a cut-off point of 15mm or greater[106].

Clinical presentation in non tuberculous mycobacterium infection (NTMI)
A case report documents an NTMI in a smoker with shortness of breath and loss of weight. Patient was diagnosed based on a positive Mantoux test and responded well to anti-tuberculosis treatment[107].

Complications

Majority of patients with tuberculosis had no complications due to the disease (65%, 85/131)[16]. However, few very common complications were detected namely pleural effusion, pneumothorax and pulmonary fibrosis[16].

DIAGNOSIS

Pulmonary and extrapulmonary tuberculosis

Tuberculin sensitivity test (TST)

Tuberculin sensitivity test reactions amongst the Malaysian population seem to range between 10-15mm[108]. Seventy two percent (74/103) and 57% (59/103) of tuberculosis patients had TST cut-off points of 10mm and 15mm respectively[108]. Tuberculin sensitivity test reading of 10mm had a higher sensitivity than a 15mm result[108].

Tuberculin sensitivity test results were significantly linked to the severity of a co-morbidity in a patient[108]. Tuberculin sensitivity test results were frequently negative in patients with higher levels of comorbidities (10mm cut-off, p=0.003; 15mm cut-off, p=0.012)[108].

In the assessment of the influence of post exposure infection of tuberculosis amongst contacts, only 30% (12/40) of contacts of HIV-PTB patients had positive TST compared to 53% (47/94) of the contacts of HIV negative patients [OR= 0.41, 95% CI 0.07-0.87; p=0.016][35].

Sputum/blood culture

Both culture methods (BACTEC MGIT 960 and BACTEC 460 TB) managed to detect Mycobacterium tuberculosis in 15% (42/279) specimens (respiratory and non respiratory) 109. Eighty percent (37/42) was detected by BACTEC MGIT 960 method while 83% (35/42) was detected by radiometric BACTEC 460 TB[109]. The BACTEC MGIT 960 technique was found to be more rapid, as sensitive and less labour intensive than the 'gold standard' BACTEC 460[109].

CD4 counts

In most HIV-infected tuberculosis cases, CD4 counts were less than 200 cells/mm^3 [21,36]. The TB-HIV deaths were associated with CD4 counts <200 cells/mm^3 and increase for every 10^3 cells per microliter unit increase in total white blood cell[48].

Pulmonary tuberculosis

Chest x-ray

Sixty nine percent (90/131) of inpatients with tuberculosis at a tertiary centre had positive chest x-ray finding[16]. At initial presentation, 46% to 73% (173/237) of pulmonary tuberculosis patients had advanced chest x-ray findings[7,18]. Larger proportions of patients without co-morbidities had typical presentation on chest x-ray[17]. Sixty two percent (144/232) of pulmonary tuberculosis patients had typical changes on chest x-rays while 39% (88/232) were not typical[17].

Tuberculous and malignant lung effusions had more predominance on the right side of the lung[67]. Tuberculous effusions (12%) were smaller than malignant pleural effusions (44%)(p<0.001)[67].

Tuberculosis among community acquired pneumonia (CAP) inpatients were significantly associated with chest radiograph showing upper lobe involvement (OR 8.23; 95% CI 1.59-42.53; p=0.012) or cavitary infiltrates (OR 19.41; 95% CI 2.94-128.19; p=0002)[62].

1. HIV patients

Only half of HIV-infected tuberculosis patients had pulmonary lesions on chest x-ray (55%, 82/149)[25]. Eighty four percent (67/80) of HIV patients had atypical clinical and investigative findings[110]; 5.4% (8/149) had pleural lesions while another 5.4% (8/149) had either hilar or perihilar lymph node lesions25. Sixteen percent (13/80) of HIV/TB cases had post primary pattern with opacities distributed at the upper zones with or without cavitation[110].

When comparisons were made in relation to CD4 counts, only one (out of 80) patient with CD4 counts less than 200 had typical pattern on chest x-ray[110]. Patients with CD4 counts more than 200 had typical pattern on chest x-ray[110].

Severity of tuberculosis chest x-ray was moderate to severe in sputum negative HIV patients[26].

2. Diabetic patients

A comparison between TB-DM and a non-diabetic group showed no difference in radiological findings[15]. However, opacity or cavity of the upper lobe involvement was lower in the TB-DM group than the non-diabetic group (89% and 91% respectively)[15].

Tuberculin sensitivity test

Seventy four percent (42/57) pulmonary tuberculosis cases had a positive Mantoux test[7]. Patients with concurrent HIV and tuberculosis infection had a lesser chance of a reactive TST[26]. These patients also had a stronger positive tuberculin skin test results (p<0.05)[20]. No correlation was found between TST results and sputum culture or chest x-ray severity in this group of patients[26]. On the other hand, post TST indurations of 52% and 26% amongst HCWs were of ≥ 10mm and 15mm greater respectively[106].

Sputum AFB

Almost 58% (37/57) - 89% (117/131) of pulmonary tuberculosis cases had a positive sputum AFB smear[5,7,16,18]. Only one study contradicted the findings described above by showing that only 23% (58/232) of pulmonary tuberculosis patients were tested positive for AFB sputum smear[17]. In the same study, another 11% of tuberculosis cases (26/232) were diagnosed via a positive sputum culture result[17]. Sputum results may even be negative in patients with typical clinical symptoms and chest radiograph changes[17]. Only 17% (33/237) of the pulmonary tuberculosis patients tested smear negative while 44% (104/237) were weakly positive for AFB and 25% (59/237) heavily positive sputum for AFB[18].

Although chest x-rays had typical findings, 40% (21/52) of newly diagnosed pulmonary tuberculosis patients did undergo previous investigations for tuberculosis[61]. In others, the diagnosis was excluded solely due to a negative sputum smear result[61].

1. HIV patients

Tuberculosis patients with HIV positivity often present with negative sputum smear for AFB (p<0.05)[23,26]. In line with these findings, only 51% (76/149) of HIV-infected tuberculosis patients had positive sputum smears[8,25].

2. Diabetic patients

The only study was carried out to analyse this issue found 74% (148/200) of diabetic patients having positive AFB smears compared to non-diabetic patients (51%, 102/200)[14].

Sputum culture

Culture results of pulmonary samples helped identify

tuberculosis in 11% (12/109) of patients who were treated empirically as smear negative PTB[37]. This is important in the treatment of HIV-infected tuberculosis where there were greater rates of smear negative sputum and sputum positive cultures[26].

Newer techniques of sputum culture has been assessed with Lowenstein-Jensen (LJ) culture as the gold standard[111]. The BBL MGIT had higher sensitivity and specificity than AFB smear microscopy[111]. A total of 20% (101/510) specimens were positively detected by BBL MGIT, 12% (60/510) by primary LJ medium culture and 6% (31/510) through direct smear examination[111]. The mean time to detection was significantly shorter for BBL MGIT than for LJ culture ($p<0.0001$)[111].

Blood
Immunocompromised CAP inpatients with concomitant tuberculosis infection were significantly associated with total white blood cell count on admission of 12 x 109/L or less (OR 6.28; CI 1.21-32.52; p=0.029) and lymphopenia (OR 4.73; 95% CI 1.08-20.85; p=0.040)[62].

The mean CD4 counts in HIV-infected tuberculosis patients were significantly lower[110]. Fifty three percent of all patients with AIDS-defining illness (mainly tuberculosis) had CD4 counts less than 200 cells/mm^3 at the time of diagnosis[22]. AIDS patients with CD4 counts less than 200 were more likely to produce normal chest x-rays, middle and lower zone parenchymal changes and mediastinal lymphadenopathy[110]. Lower levels of serum albumin ($p<0.023$) and higher levels serum globulin ($p<0.025$) were associated with drug-induced hepatitis on anti-TB treatment[38].

Interferon-Ɣ-release assay (IGRA)
Reversion and conversion occurred frequently amongst healthcare workers[30].

Polymerase chain reaction (PCR)
Single Xpert assay accurately detected only eight previously undiagnosed TB cases out of 15 culture positive TB cases[33]. This resulted in a sensitivity, specificity, positive predictive value and negative predictive value of 53%, 100%, 100% and 94%[33]. However, the assay managed to only detect 7% (1/15) of active TB cases among HIV patients[33].

In the analysis of pleural fluid for tuberculosis, PCR outperformed AFB staining and LJ medium methods112. It had a 19%, 96%, 67% and 72% in sensitivity, specificity, positive predictive value and negative predictive value respectively[112].

Bronchocopy and pleuroscopy
Between 40-49% of pulmonary tuberculosis cases were diagnosed from specimens obtained from bronchoscopy[17,66]. The value of bronchocopic evaluation was seen in a case study involving HIV-infected patient[71]. Effusion fluid analysis did not reveal Mycobacterium tuberculosis on staining but IG-Ɣ levels were elevated[71]. A bronchoalveolar lavage revealed AFB on smear and culture[71].

In a region of high prevalence of tuberculosis, pleuroscopy aided in about 52% (32/62) of the cases of unexplained pleural effusion[43].

Effusion analysis
Microscopic analysis of tuberculous effusion showed a lymphocyte predominance, with higher lymphocyte percentage but lower red cell count and higher protein content[67]. The PCR analysis of pleural effusion identified 9% (6/67) of cases while AFB staining identified none and LJ medium identified 1.5% (1/67) 112. Pleural biopsy had a better yield (69%) in terms of identifying tuberculosis than Mycobacterium culture of effusion (24%) while pleural fluid staining was negative[71].

A combination of investigations (staining, sputum, pleural biopsy, lavage) yielded the diagnosis in 92% of patients with tuberculous effusion[66]. This was evidenced in a case study involving a HIV-infected patient where effusion fluid did not reveal Mycobacterium tuberculosis but a bronchoalveolar lavage revealed AFB on smear and culture[71].

Extrapulmonary tuberculosis
Histopathological studies seem to be the most useful diagnostic tool in diagnosing patients with extra pulmonary tuberculosis (52%, 101/195)[6]. X-rays were able to isolate findings attributable to tuberculosis in 42% (82/195) of patients with extra pulmonary tuberculosis[6].

Spine tuberculosis

1. Imaging
Tuberculosis of the spine occurred mostly at the thoracic vertebrae (30%, 10/33), followed by the lumbar vertebrae (27%, 9/33)[46]. The most common radiological lesion seen in spinal tuberculosis was of the paradiscal type (47%, 25/53)[42]. Close to 12% (4/33) of the spine tuberculosis cases had characteristic skip lesions[46].

2. Blood
In a study that analysed various modalities that could be used in diagnosing spinal tuberculosis, PCR had high specificity and sensitivity (94% and 100%)[113].

3. Erythrocyte sedimentation rate played a role in screening as well as assessing the neurological severity in patients with tuberculosis of the spine[46,114]. Erythrocyte sedimentation rate was normal only in 9% (3/33) of tuberculosis patients46. Erythrocyte sedimentation rate helped differentiate patients who had neural deficit from those who were neurologically normal[114].

4. Sputum smear and bacterial growth
Sputum smear results and bacterial culture growth for Mycobacterium are of limited value in the management of tuberculosis of the spine[114].

5. Histology
The percentage of patients with spinal tuberculosis diagnosed through histological examination was 44% (23/53)[42]. In diagnosing spinal tuberculosis, histopathogical examinations yielded 82% in sensitivity and 100% in specificity[113].

6. Culture
Lowenstein-Jensen culture had a sensitivity of 6% and a sensitivity of 100% in detecting spinal tuberculosis[113].

Tuberculous lymphadenitis
The most frequent specimen used in the diagnosis of extra pulmonary tuberculosis was lymph nodes (35%, 68/195)[6]. A high degree of positive results (83%, 90/109) were obtained in cases of tuberculous lymphadenitis through fine needle aspiration[9].

Gastrointestinal tuberculosis (GITB)
Patients with abdominal tuberculosis had significantly lower serum haemoglobin (p=0.036) than pulmonary tuberculosis cases[78]. Sixty eight percent (24/34) of GITB cases were confirmed through histopathological tissue studies[47]. Chest radiographs suggested TB in 47% of these cases (16/34)[47].

Table I: Age of population in various tuberculosis categories

Category	Age range or associated factors/Studies
Tuberculosis in general	• Mean age 33.3 years +/- 9.95, predominant in younger population (up to 34 years of age)[39] • Majority of patients in 20-60 years[11] • Highest frequency in 34-45 years[26] • Higher among >60 years24 • Increased incidence in elderly[44]
Tuberculosis death in general	• 24-44 years[40]
Tuberculosis in foreign-born	• Mean age of 14-72 years[39]
Tuberculosis amongst inpatients	• 21-60 years[16]
Delay and extreme delay in management of tuberculosis	• 30-39 years[45]
HIV-infected tuberculosis patients	• Mean age 34 years[8,25] • Mean age 36 years[41] • 18-75 years, mean age of 36.1 years[21] • 21-62 years[20] • Younger patients and unmarried patients[20] • 30-39 years[23] • Mean age for HIV/TB co-infection
Tuberculosis with diabetes	• More likely in 46-60 years[13] • 21-78 years[20] • Mean age of these patients was significantly higher than that of non-diabetic patients ($p<0.05$)[15] Married patients with diabetes had greater chances of contracting the disease ($p<0.05$)[20]
Tuberculosis+HIV+DM	• 29-73 years[12]
Pulmonary tuberculosis	• Majority in 45-64 years[7] • Predominant age group amongst HIV patients 35-44 years[27] • 35% (90/237) in the productive age group[18] • 46% (109/237) were more than 50 years of age[18]
Extra pulmonary tuberculosis in general	• Mean age 39 years, with the largest number of patients in the ages between 25-34 years[6] • 79% of patients were less than 50 years of age[6]
Tuberculous lymphadenitis	• Mean age 36.4 years[9]
Tuberculosis of the spine	• Mean age 40.2 years[42] • Mean age of 36.5 years (n=33) with a peak incidence in the second decade of life (27%, 9/33)[46] • 72% (24/33) of cases were males[46]
Gastrointestinal tuberculosis	• 30-40 years (58%, 20/34)[47].

In a case study, CT scan proved the best modality in detecting a case of tuberculous peritonitis[82].

Ocular tuberculosis
Most imaging, blood and sputum investigations had negative results. The detection and treatment of ocular tuberculosis relied on positive results of Mantoux and IGRA tests[96,97,99,100].

Splenic tuberculosis
Splenic tuberculosis was confirmed by a percutaneous splenic biopsy that revealed granuloma formation and Langhan's giant cells[103].

Endocrine
Endoscopic ultrasound, CT scan and ultrasound guided tissue biopsy was an essential tool in the diagnosis of pancreatic tuberculosis[105].

Non tuberculous mycobacterium infection (NTMI)
Patient with NTMI was diagnosed based on a positive Mantoux test and a positive response to anti-tuberculosis treatment[107].

Detection of latent tuberculosis infection

Tuberculin skin test
Tuberculin skin test had poor detection rate of tuberculosis amongst HIV infected prisoners[32]. The utilisation of TST and IGRA could be a viable option in the screening of diabetic patients with comorbidities for latent tuberculosis infection[10].

MANAGEMENT

Pulmonary tuberculosis

The commonly used treatment regime between the year 1998 and 2004 was the 2SHRZ/4SHR regime[3,7,11].

Only 17% of pulmonary tuberculosis patients were successfully treated with empirical anti-tuberculosis therapy that were based on clinical and radiological features[36]. However, empirical treatment of suspected tuberculous effusions led to clinical improvements in 65% (40/62) - 84% (81/109) of patients[37,115]. There were isolated clinical improvements in 13% (12/109) and radiological improvements alone in 3%

Table II: Influence of ethnicity and geography in various tuberculosis categories

Category	Ethnicity and related factors/Studies
Tuberculosis in general	• Majority were Chinese in ethnicity (56%, 116/207), followed by Malays (34%, 70/207)[3] • Predominantly of Malay ethnicity (96%, 169/176) and another 2.8% (5/173) were Chinese[11] • Highest tuberculosis incidence rates involved patients of Indian descent[24] • 43% (56/131) of patients admitted to UMMC with the diagnosis of tuberculosis were Malays followed by patients with Chinese ethnicity (22%, 29/131)[16] • High incidence of tuberculosis amongst the indigenous people but patients with Chinese descent comprise a larger number of infected cases[44]
Tuberculosis in foreigners	• Foreign nationalities contribute to 15% of all notified cases[24] • 87% of foreign-born patients with tuberculosis were from Southeast Asian countries (87%, 71/263)[39]
HIV-infected tuberculosis patients	• Majority were of Malay descent (94%, 140/149)[8] • Majority were of Malay descent (17%, 4/25)[23] • Majority were Malays at 47% (136/290)[21] • Majority were of Malay descent[25] • Majority were Malays (74%, 72/97)[41] • The majority were Malays[20]
Tuberculosis with diabetes	• The majority were Malays[20] • Chinese were more likely to be associated with diabetes mellitus (odds ratios [OR] = 1.401, P= 0.011)[13]
Pulmonary tuberculosis	• High percentage amongst the Malay population (95%, 54/57)[7] • Majority of HIV patients with pulmonary tuberculosis were Malays (48%, 118/290)[27]
Extrapulmonary tuberculosis in general	• Malay patients represented the majority of patients (49%, 96/195)
Tuberculous lymphadenitis	• Higher amongst Malays (41%, 45/1548) followed by patients who were of Chinese descent (34%, 37/1548)[9]
Spinal tuberculosis	• More common among Iban patients (50%, 26/52)[42]
Gastrointestinal tuberculosis	• Most cases involved Malays (74%, 25/34), followed by Chinese (12%, 4/34) and Indians (9%, 3/34)[47]
Tuberculosis mortality	• Indians showed the highest case fatality rate amongst patients treated for tuberculosis[40] • Death in TB-HIV co-infection was associated with being Malay (ahR 4.48; 95%CI 1.73-11.64)[48]

(3/109)[37,115]. Effusions with the size smaller than 1/10 were three times more likely to have complete resolution than larger effusions after commencing anti-tuberculosis treatment (p=0.04)[115].

Higher percentage of HIV patients with pulmonary tuberculosis (42%) were treated successfully with a short-course (six months) of anti-TB therapy[36].

Extra pulmonary tuberculosis

In contrast to the treatment of pulmonary tuberculosis, successful treatment of extra pulmonary infection in HIV patients (43%) required a longer duration of anti-tuberculosis therapy[36].

Spine tuberculosis

1. Surgery

Based on the findings of a study, the preferred surgical procedure was radical anterior debridement and fusion supplemented by anterior or posterior instrumentation of the spine if needed[46]. The radical surgical debridement and grafting rate was at 39%[46]. In 30 patients who received surgical treatment, there was a 4 degree correction in the kyphosis angle of the spine; after six months of treatment, 24 of them had excellent and good outcomes while six had a fair outcome [42].

Endoscopic, endonasal approach was the best approach in the surgical management of cranio-vertebral junction stenosis[116].

2. Chemotherapy

Anti-tuberculosis chemotherapy was still preferred as the cornerstone of treatment as opposed to surgical intervention[46]. However, it was discovered that in 23 patients treated conservatively with anti-TB, there was an increment of 8 degrees of kyphosis angle[42]. Twenty two others had a fair result and only one had poor outcome after six months of treatment[42].

Gastrointestinal tuberculosis (GITB)

Although most patients with GITB (34/34) responded well to anti-tuberculous treatment[47], abdominal tuberculosis had a higher rate of adverse events related to anti-tuberculous treatment (p<0.001)[78].

In one study, CT scan findings were a major predictor for the early initiation of anti-TB regime in tuberculous peritonitis[82]. The eventual diagnosis was confirmed later through histopathological studies obtained from a laparotomy[82].

Ocular tuberculosis

The effective treatment of ocular tuberculosis will require a combination of anti-tuberculous therapy and oral corticosteroids[100]. This was contradictory to another finding

seen in a case report where the resolution of symptoms in ocular tuberculosis was achieved after a six months therapy consisting of only anti-TB treatment[96]. Topical and systemic steroids were ineffective[96].

Genitourinary tuberculosis
Although anti-TB is the mainstay of treatment, surgical intervention might be needed in selected cases[76].

Vasculitis
There has been reports on the benefits and good outcomes of endovascular stenting of a stenotic subclavian artery in cases of tuberculous vasculitis[94]. The repair of a tuberculous aortic pseudoaneurysm with in situ silver-impregnated vascular in lay graft led to an uneventful post operative recovery[95].

Joint
After anti-tuberculosis treatment was commenced, a patient with tuberculous synovitis of the knee joint experienced improvements in symptoms and overall health[86].

Latent tuberculosis infection

Bacillus Calmette–Guérin vaccination prevents the risk of conversion of latent tuberculosis infection to clinical tuberculosis[117]. However, the evidence for mass BCG vaccination of healthcare workers remains controversial and inconclusive[117].

PROGNOSIS AND TREATMENT OUTCOME

A treatment success rate of 82% was seen amongst patients who were diagnosed at an outpatient and hospital setting[2]. Fifty two percent (95% CI 45.7-57.9) of patients sought treatment 30 days from the onset of symptoms[45]. Another 24% (95 CI 18.6-29.0) of patients received consultation after 90 days of developing the illness[45].

Pulmonary tuberculosis

Among the significant factors for the unsuccessful treatment outcome of pulmonary tuberculosis were age, gender, educational level, employment status, family incomes, co-existence of extra pulmonary TB, smoking, diabetes mellitus, HIV status, sputum cultures, chest x-ray findings and duration of delay for diagnosis[118].

Fifty four percent (31/57) of patients with pulmonary tuberculosis had completed treatment[7]. Twenty six percent (15/57) had died and 18% (10/57) had defaulted treatment7. Male foreign-born patients with pulmonary tuberculosis had higher percentages of treatment completion at ≥ 6 (38%, 100/263) and ≥ 9 (13%, 34/263) months when compared to their female counterpart[39].

Extrapulmonary tuberculosis

Gender differences
Treatment success rate was higher amongst females with extrapulmonary tuberculosis (9%, 24/263)[39].

Tuberculous lymphadenitis
In the treatment of tuberculous lymphadenitis, 57% (62/109) patients were treated successfully while 5% (5/109) had died during treatment[9].

Spinal tuberculosis
Treatment of spinal tuberculosis resulted in an excellent outcome in 40% (24/53) of patients[42]. Fifty three percent (28/53) of patients had fair results and 2% (1/53) had poor result[42].

Abdominal tuberculosis
Abdominal tuberculosis (ATB) had a higher rate of adverse events of anti-tuberculosis treatment ($p<0.001$)[78].

Pancreatic tuberculosis
A patient with pancreatic tuberculosis experienced symptomatic improvement following commencement of anti-tuberculosis drugs[119].

Tuberculosis in HIV infected patients

Failure rate and loss to follow up
A higher percentage of failure rate was seen in HIV-infected tuberculosis patients (28%, 19/67)[20]. HIV-infected patients with tuberculosis had a 55% (160/290) to 57% (165/290) frequency of loss to follow up[21,27].

Survival rates
Upon commencement of treatment, the median survival weeks of HIV infected tuberculosis patients was at 13.5 weeks[25]. Survival at 2, 6, and 12 months after initiating tuberculosis treatment were 91%, 83% and 79% respectively[48].

In the treatment amongst immunosuppressed patients, the commonly used regimen for HIV-infected TB patients was EHRZ+B6[20]. The highest percentage of treatment success was at six months of anti-tuberculosis treatment[20]. Amongst HIV/AIDS + TB infected patients who survived, 11% (32/290) of patients who completed treatment fell in the six or more months treatment category while 21% (61/290) fell in the nine or more months treatment category[21].

Mortality rates
Death was seen in 0.8% (2/290) of HIV patients with pulmonary tuberculosis[27]. Twenty three percent (53/227) of patients with HIV/TB co-infection had died at the end of the study with 40% of deaths within two months of TB diagnosis48. Another study found 39% (58/149) of HIV infected tuberculosis patients have died after three years[8]. Also, not receiving HAART treatment was associated with death among TB/HIV co-infected patients[48]. Seventy four percent (110/149) of these patients had died without completing the six months anti-TB regime[8,25]. Out of those who survived, only 32% (93/290) were successfully treated for their illness[27].

Predictors of unsuccessful treatment
Unsuccessful treatment outcome among HIV-infected TB patients were associated with intravenous drug use (OR 2.72; 95% CI 1.44-5.16), not receiving antiretroviral treatment (OR 5.10; 95% CI 2.69-9.69), lymphadenopathy (OR 2.01; 95% CI 1.09-3.72) and low serum albumin (OR 4.61; 95% CI 1.73-12.27) 55. Males (OR=0.721, p=0.049) and patients with relapse of tuberculosis (OR=0.494, p=002) were less likely to have successful treatment outcomes[13].

Tuberculosis in diabetic patients

The treatment outcome was similar in tuberculosis cases with or without diabetes mellitus[13]. Better treatment results were seen in patients between the age 46-60 years (OR=1.567, p=0.001)[13]. However, one study showed TB/DM patients, primarily of the pulmonary type, had more treatment success with a longer duration of treatment of nine months (33%)[15]. Lower proportion of patients in the TB/DM group defaulted treatment (19.8%)[15].

The highest percentage of treatment success were in both groups at six months of anti- tuberculosis treatment[20]. Significantly higher percentage of success rate in treatment

(<0.05) was found in tuberculosis patients with diabetes (35%, 24/69) than TB/HIV patients (19, 13/67)[20]. A success rate of 22% (n=15) was seen in TB/DM patients with nine months of anti-tuberculosis, similar to patients with a 12 month regimen[20].

Smoking cessation

Patients receiving integrated treatment of smoking cessation and TB regime had significantly higher rate of success in quitting smoking when compared with those who received the conventional TB treatment alone (p=0.019)[120]. There were also higher rates of treatment default and failure in the conventional TB treatment group[120].

Prisoners

There was poor success rate in the implementation of preventive isoniazid treatment at correctional facilities[121]. Adverse consequences and treatment interruption ranged from 1 to 55%[121].

Adverse effects

Eleven percent (19/176) of patients developed adverse drug reaction at a tertiary centre, and 58% (11/19) were from the 2SHRZ/4SHR2 regime[11]. The most common adverse effects include nausea and vomiting (41%, 54/131), drug induced hepatitis[16,20], blurring of vision[16,20] and skin rashes[16,20]. There was a case report of ethambutol ocular toxicity in a patient with pulmonary tuberculosis treatment which resolved within two months after cessation[122].

Adverse drug reactions seem to be more common in patients with extra pulmonary tuberculosis[38,78]. The prevalence of drug-induced hepatitis was 9.7% and the significant risk factors were the presence of HIV infection and extra pulmonary tuberculosis[38].

Drug resistance

A study on the cases of tuberculosis at a tertiary centre reported no drug resistant cases within the study year[11].

The TB-DM group experience lower resistance to anti-tubercular (1.4%) therapy when compared to non-diabetics[15]. No cases of drug resistance or deaths were notified amongst the TB-HIV and TBDM patients[20].

PREVENTION AND CONTROL MEASURES

Based on the results of one study, the efficacy of BCG in preventing tuberculosis was low. About 64% (113/176) of the tuberculosis patients had BCG scars[11]. This brings to question the efficacy of the vaccine[11].

A Geographic Information System (GIS) application helps identify the geographical distribution and the trend of tuberculosis in a particular region[123]. This helps in tuberculosis surveillance activities[123].

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

EPIDEMIOLOGY

In general, there was a lack of prevalence data amongst population who were susceptible to LTBI and eventually primary progressive tuberculosis. There was also very little prevalence data from a primary care perspective. It is valid to call for mandatory health examination for all foreign workers arriving in Malaysia within one month of arrival regardless of whether or not they are certified fit in their countries of origin[49].

SCREENING

Healthcare workers are at high risk of contracting tuberculosis. Hence, it is recommended that they should also undergo TB screening at least once every two years[29]. The HCWs need to have an up-to-date knowledge of the pattern of health and disease and their determinants in each district[2]. They should emphasise the use of Directly Observed Therapy, Short-course (DOTS) in high risk populations[118]. Screening by age, chest x-rays and HIV status helps categorise patients who are vulnerable to unsuccessful treatment[118]. Implementation of TB screening for HIV patients is important to reduce TB mortality[40].

Tuberculin skin test may be replaced with a more accurate and specific method, interferon gamma release assay (IGRA) in highly prioritised group[10,50]. Tuberculin skin test and IGRA used in combination is an economical method to screen tuberculosis in high risk populations[10]. A TST cut-off of 15mm or greater may correlate better with Mycobacterium tuberculosis infection than a cut-off of 10mm or greater in a setting with high prevalence of BCG vaccination[106]. Polymerase chain reaction (single Xpert assay) improved TB case detection and outperformed AFB smear but yielded low sensitivity in screening prison HIV patients[33]. The PCR is a rapid method for the detection of Mycobacterium tuberculosis in pleural fluid but is a weak test in terms of sensitivity[112]. Hypertonic saline should be used to induce sputum and sputum culture should be done prior to commencing an anti-tuberculosis regime[124]. Pleuroscopy was a safe diagnostic procedure and sampling nodules was satisfactory[43].

DETECTION

The BBL MGIT system will be a suitable alternative to LJ culture for the routine diagnosis of pulmonary tuberculosis[111]. Fine needle aspiration is the most reliable diagnostic test for tuberculous lymphadenitis[9]. The PCR is a reliable method to identify spinal tuberculosis even after two weeks of anti-TB treatment[113]. The ESR could be used in the prediction of the evolution of paraplegia in spinal tuberculosis[114], and MRI could be used to detect early pedicle involvement in spinal tuberculosis[73]. A high index of suspicion is required to diagnose ocular tuberculosis when all other systemic investigations are negative, especially where TB is endemic[97].

TREATMENT AND PREVENTION

Educating and providing patients with more information about tuberculosis could lead to compliance to DOTS[125]. Healthcare workers are recommended to take extra precautions (wearing protective equipment) in the first ten years of service when performing procedures that are considered high risk in the development of tuberculosis infection[29]. Tuberculosis infection control need to be strengthened, especially at the Emergency Department where there was a large incidence of TB as evidenced by the study[30]. Specific guidelines on preventive measures for ambulatory care setting, including radiology clinics, should be developed to enable HCWs working in those areas to reduce the risk of infection[126].

Smoking has a negative impact on tuberculosis treatment outcomes[19]. The integrated approach of smoking cessation and tuberculosis treatment has shown benefits and might influence the future lung health of tuberculosis patients who quit smoking[120].

Empirical treatment of anti TB treatment is an acceptable practice if clinical suspicion is high in patients coming to our region[17,37,64]. Once confirmed, smaller effusions related to pleural tuberculosis can be given anti-tuberculosis treatment alone while larger effusions could benefit from thoracentesis[115].

In patients with drug-induced hepatitis with liver enzymes five times above normal, an alternative regimen of streptomycin, oxfloxacin and ethambutol should be commenced[127].

There was a higher percentage of HIV patients with pulmonary tuberculosis (42%) who were treated successfully with a short-course (six months) of anti-TB therapy[36] while extra pulmonary infection required a longer duration of treatment in order to be successful[36].

In cases of tuberculosis of the spine, surgery provides faster pain relief46. However, the decision to pursue surgical intervention should only be after careful patient selection in order to prevent morbidity and mortality[46]. The effective treatment of ocular tuberculosis will require a combination of anti-tuberculous therapy and oral corticosteroids[100,102]. A trial of anti-tuberculous drugs should be considered for patients with a high clinical suspicion of gastrointestinal tuberculosis[80]. In the assessment of a regional tuberculosis programme, healthcare workers were encouraged to examine each child for BCG scars and if it is not present by the age of three months, the child should be re-vaccinated[24].

SECTION 3: FUTURE RESEARCH DIRECTION

Future studies should focus on the analysis of LTBI in high-risk population such as diabetes mellitus, smokers, the elderly and CRF/ESRF patients[10]. Research at a primary care setting could uncover a 'hidden' reservoir of LTBI in diabetics, CRF/ESRF and elderly patients.The role of future research in the detection of LTBI in a Malaysian setting might be necessary to gauge the disease reservoir before implementing prophylactic measures for risk groups involved[10].

Multicentered and multidisciplinary initiatives are important to gauge research on the risk of LTBI amongst HCWs. There is a role for GIS in studying the top spots for diseases, mapping the spread of the disease with a focus on population or areas with higher density. There is the need to study treatment of latent TB infection such as who should be treated. Another area to study is the outcome of MDR TB.

There has been a call to not only focus on secondary prevention, but also primary prevention of tuberculosis[10]. With the rise of tuberculosis in the nation, the pressing issue of prophylactic treatment of high risk groups in the Malaysian society requires further evaluation[10].

ACKNOWLEDGEMENT

I would like to sincerely thank the Director-General of Health, Malaysia for his permission to publish this paper. I wish to thank Clinical Research Centre team for its contribution and support. I would also like to especially thank Dr. Lim Ai Wei (CRC) for her diligence in editing this article and rendering it to its current form.

REFERENCES

1. World Health Organization (WHO). Global health observatory data repository: Tuberculosis, incidence and case detection. [Internet]. WHO. 2014 [cited 2014 Apr 27]. Available from: http://apps.who.int/gho/data/node.main.1315?lang=en.
2. Dony JF, Ahmad J, Khen Tiong Y. Epidemiology of tuberculosis and leprosy, Sabah, Malaysia. Tuberc. 2004 ;84(1-2): 8–18.
3. Elfatih IE, Abdul Razak M, Mohamed Izham MI *et al.* A survey of tuberculosis cases in Penang Hospital: preliminary findings. Malaysian J. Pharm. Sci. 2004; 2(2): 1–8.
4. Muzaffar Z, Ling H, Sujinder S, *et al.* Improving the rate of acid fast bacilli sputumm screening: Sitiawan Health Clinic experience. J. Health Manag. 2012; 10(2): 20.
5. Hamimah S. The severity of pulmonary tuberculosis disease and the contributing factors, places visited and place of diagnosis for cases from Pendang District 2000. 2000;
6. Nissapatorn V, Kuppusamy I, Rohela M, *et al.* Extrapulmonary tuberculosis in Peninsular Malaysia: retrospective study of 195 cases. Southeast Asian J Trop Med Public Heal. 2004; 35(Suppl 2): 39–46.
7. Jamalludin AR. Review of pulmonary tuberculosis cases in Kuala Terenggany from 1998-2001. Int. Med. J. 2003;2(2).
8. Mohammad Z, Naing NN. Characteristics of HIV-infected tuberculosis patients in Kota Bharu Hospital, Kelantan from 1998-2001. Southeast Asian J Trop Med Public Heal. 2004; 35(1): 140–143.
9. Khan AH, Sulaiman SA, Muttalif AR *et al.* Tuberculous lymphadenitis at Penang General Hospital, Malaysia. Med Princ Pr. 2011; 20(1): 80–84.
10. Swarna Nantha Y. Influence of diabetes mellitus and risk factors in activating latent tuberculosis infection : a case for targeted screening in Malaysia. Med J Malaysia. 2012; 67(5): 465–470.
11. Siti Fatimah A, Syed Azhar SS, Mohamed Izham MI. Evaluation of the tuberculosis management at Dungun Hospital. Malaysian J. Pharm. Sci. 2004; 2(2): 35–36.
12. Gnanasan S, Ting KN, Wong KT, *et al.* Convergence of tuberculosis and diabetes mellitus: time to individualise pharmaceutical care. Int J Clin Pharm. 2011; 33(1): 44–52.
13. Sulaiman SA, Khan AH, Muttalif AR, *et al.* Impact of diabetes mellitus on treatment outcomes of tuberculosis patients in tertiary care setup. Am J Med Sci. 2013; 345(4): 321–325.
14. Syed Suleiman SA, Ishaq Aweis DM, Mohamed AJ, *et al.* Role of diabetes in the prognosis and therapeutic outcome of tuberculosis. Int J Endocrinol. 2012; 2012(645362): 1–6.
15. Nissapatorn V, Kuppusamy I, Jamaiah I, *et al.* Tuberculosis in diabetic patients: a clinical perspective. Southeast Asian J Trop Med Public Heal. 2005; 36(Suppl 4): 213–220.
16. Jetan CA, Jamaiah I, Rohela M, *et al.* Tuberculosis: an eight year (2000-2007) retrospective study at the University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. Southeast Asian J Trop Med Public Heal. 2010; 41(2): 378–385.
17. Ismail Y. Pulmonary tuberculosis - a review of clinical features and diagnosis in 232 cases. Med J Malaysia. 2004; 59(1): 56–64.
18. Abdul Razak M. Significance of symptoms and investigations in tuberculosis case finding. J. Pharm. Sci. 2004; 2(2): 29–30.
19. Awaisu A, Nik Mohamed, Abd Aziz N, *et al.* Tobacco use prevalence, knowledge, and attitudes among newly diagnosed tuberculosis patients in Penang State and Wilayah Persekutuan Kuala Lumpur, Malaysia. Tob Induc Dis. 2010; 8(1): 2–9625–8–3.
20. Nissapatorn V, Kuppusamy I, Josephine FP, *et al.* Tuberculosis: a resurgent disease in immunosuppresed patients. Southeast Asian J Trop Med Public Heal. 2006; 37(Suppl 3): 153–160.
21. Nissapatorn V, Kuppusamy I, Anuar AK, *et al.* Tuberculosis: clinical manifestations and outcomes. Southeast Asian J Trop Med Public Heal. 2003; 34(Suppl 2): 147–152.
22. Nissapatorn V, Lee C FQ *et al.* AIDS-related opportunistic infections in Hospital Kuala Lumpur from 1994 to 2001. Jpn J Infect Dis. 2003; 56(5-6): 187–192.
23. Mazlinah M. Sociodemographic characteristics and clinical manifestations of tuberculosis patients with and without human immunodeficiency virus at Chest Cclinic, Hospital Terengganu. Undocumented.
24. Venugopalan B. An evaluation of the tuberculosis control programme of Selangor state, Malaysia for the year 2001. Med J Malaysia. 2004; 59(1): 20–25.
25. Wan MZ, Syed Hatim N, Naing NN. Characteristics of HIV-Infected Tuberculosis Patietns In Kota Bharu Hospital, Kelantan From 1998 To 2001. Malaysian J. Pharm. Sci. 2004; 2(2): 20–20.
26. Velaiutham S, Abdul Razak M, Khatijah B. Characteristics of pulmonary tuberculosis in HIV seropositive patients in Chest Clinic, Penang Hospital. Malaysian J. Pharm. Sci. 2004; 2(2): 31.
27. Nissapatorn V, Kuppusamy I, Init I, *et al.* Pulmonary tuberculosis in HIV/AIDS patients. Trop Biomed. 2002; 19(1): 49–53.
28. Lian YL, Heng BS, Nissapatorn V, *et al.* AIDS-defining illnesses: a comparison between before and after commencement of highly active antiretroviral therapy (HAART). Curr HIV Res. 2007; 5(5): 484–489.
29. Jelip J, Mathew GG, Yusin T, *et al.* Risk factors of tuberculosis among health care workers in Sabah, Malaysia. Tuberc. 2004; 84(1-2): 19–23.

30. Rafiza S Rampal KG. Serial testing of Malaysian health care workers with QuantiFERON(R)-TB Gold-In-Tube. Int J Tuberc Lung Dis. 2012; 16(2): 163–168.
31. Mahmud M. Infectious disease among heroin addicts receiving outpatient treatment in Muar. Malaysian Anti-Drugs J. 2007; 1: 73–80.
32. Margolis B, Al-Darraji HA, Wickersham JA, *et al.* Prevalence of tuberculosis symptoms and latent tuberculous infection among prisoners in northeastern Malaysia. Int J Tuberc Lung Dis. 2013; 17(12): 1538–1544.
33. Al-Darraji HA, Razak HA, Ng KP, *et al.* The diagnostic performance of a single GeneXpert MTB/RIF assay in an intensified tuberculosis case finding survey among HIV-infected prisoners in Malaysia. PLoS One. 2013; 8(9): e73717.
34. Rafiza S, Rampal KG. Prevalence and risk factors of latent tuberculosis infection among health care workers in Malaysia. BMC Infect Dis. 2011; 11(19-2334): 11–19.
35. Mohammad Z, Naing NN, Salleh R, *et al.* A preliminary study of the influence of HIV infection in the transmission of tuberculosis. Southeast Asian J Trop Med Public Heal. 2002; 33(1): 92–98.
36. Nissapatorn V, Kuppusamy I, Sim BL, *et al.* Tuberculosis in HIV/AIDS patients: a Malaysian experience. Southeast Asian J Trop Med Public Heal. 2005; 36(4): 946–953.
37. Loh LC, Abdul Samah SZ, Zainudin A, *et al.* Pulmonary disease empirically treated as tuberculosis - a retrospective study of 107 cases. Med J Malaysia. 2005; 60(1): 62–70.
38. Marzuki OA, Fauzi AR, Ayoub S, *et al.* Prevalence and risk factors of anti-tuberculous drug induced hepatitis in Malaysia. Singapore Med J. 2008; 49(9): 688–693.
39. Nissapatorn V, Kuppusamy I, Wan-Yusoff WS et al. Clinical analysis of foreign-born patients with tuberculosis found in Malaysia. Southeast Asian J Trop Med Public Heal. 2005;36(3):713–721.
40. Venugopalan B, Rajendra P. A retrospective study of death among patients treated for tuberculosis in Klang Chest Clinic for the year 1999. Med J Malaysia. 2001; 56(1): 39–43.
41. Narwani H, Naing NN. Comparison of socio-economic and demographic characteristics of HIV and HIV-infected tuberculosis patients in Kota Bharu Hospital, Kelantan. J. Kesihat. Masy. 2004; 10: 38–40.
42. Ahmad hata R, Razak M, Ting FS. The pattern of spinal tuberculosis in Sarawak General Hospital. Med J Malaysia. 2001; 56(143-150).
43. Kannan SK, Lin WJ, Teck TS, *et al.* Pleuroscopy: early experience in an East Malaysian state with high tuberculosis prevalence. J Bronchol. Interv Pulmonol. 2009; 16(4): 250–253.
44. Noridah O, Hairul Izwan Ar, Hazlee AH. A review of tuberculosis in Kinta District. IMR Q. Bull. 2003; (54):2 4–28.
45. Christina R, Fielding K, Godfrey-Faussett P, *et al.* Delays in seeking treatment for symptomatic tuberculosis in Sabah, East Malaysia: factors for patient delay. Int J Tuberc Lung Dis. 2011; 15(9): 1231–1238.
46. Dharmalingam M. Tuberculosis of the spine-the Sabah experience. Epidemiology, treatment and results. Tuberc. 2004; 84(1-2): 24–28.
47. Radzi M, Rihan N, Vijayalakshmi N, *et al.* Diagnostic challenge of gastrointestinal tuberculosis: a report of 34 cases and an overview of the literature. Southeast Asian J Trop Med Public Heal. 2009; 40(3): 505–510.
48. Ismail I, Bulgiba A. Predictors of death during tuberculosis treatment in TB/HIV co-infected patients in Malaysia. PLoS One. 2013; 8(8): e73250.
49. Leong CC. Pre-employment medical examination of indonesian domestic helpers in a private clinic in Johor Bahru - an eight year review. Med J Malaysia. 2006; 61(5): 592–598.
50. Atif M, Sulaiman SA, Shafie AA, *et al.* Tracing contacts of TB patients in Malaysia: costs and praticality. Springerplus. 2012; 1: 40–1801–1–40.
51. Al-Darraji HA, Wong KC, Yeow DG, *et al.* Tuberculosis screening in a novel substance abuse treament center in Malaysia: Implications ofr a comprehensive approach for integrated care. J Subst Abus. Treat. 2013;
52. Nissapatorn V. Lessons learned about opportunistic infections in Southeast Asia. Southeast Asian J Trop Med Public Heal. 2008; 39(4): 625–641.
53. Tengku Saifudin TI, Lee C. HIV associated opportunistic pneumonias. Med J Malaysia. 2011; 66(1): 76–82.
54. Nissapatorn V, Lee C, Ithoi I, *et al.* Tuberculosis in AIDS patients. Malays J Med Sci. 2003; 10(1): 60–64.
55. Ismail I, Bulgiba A. Determinants of unsuccessful tuberculosis treatment outcomes in Malaysian HIV-infected patients. Prev Med. 2013; 57(Suppl): S27–S30.
56. Nissapatorn V, Lee CKC KA. Impact of pulmonary opportunistic infections among AIDS patients in General Hospital Kuala Lumpur, Kuala Lumpur, 2001. Trop Biomed. 2001; 18(2): 117–121.
57. Naing C, Mak JW, Maung M, *et al.* Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. Lung. 2013; 191(1): 27–34.
58. Lee PY, Ong TA, Dayangku Norlida AO. Tuberculous prostatic abscess in an immunocompromised patient. Malaysian Fam. Physician. 2010; 5(3): 145–147.
59. Saraswathi S, Noorizan AA, Yahaya H, *et al.* Tuberculosis development in a patient with chronic history of steroid abuse: a case report. Malaysian J. Pharm. Sci. 2004; 2(2): 34.
60. Chang CT, Esterman A. Diagnostic delay among pulmonary tuberculosis patients in sarawak, Malaysia: cross-sectional study. Rural Remore Heal. 2007; 7(2): 667.
61. Ismail Y. Tuberculosis - are we missing the diagnosis? Singapore Med J. 2002; 43(4): 172–176.
62. Liam CK, Pang YK, Poosparajah S. Pulmonary tuberculosis presenting as community-acquired pneumonia. Respirology. 2006; 11(6): 786–792.
63. Sharma G, Koley S, Sandhu JS *et al.* A study of changes in the body composition components in the patients with pulmonary tuberculosis. Med J Malaysia. 2008; 63(2): 118–121.
64. Wong CM, Lim KH, Liam CK. The causes of haemoptysis in Malaysian patients aged over 60 and the diagnostic yield of different investigations. Respirology. 2003; 8(1): 65–68.
65. Liam CK, Lim KH, Wong CM. Causes of pleural exudates in a region with a high incidence of pulmonary tuberculosis. Respirology. 2000; 5(1): 33–38.
66. How SH, Chin SP, Zal AR, *et al.* Pleural effusions: role of commonly available investigations. Singapore Med J. 2006; 47(7): 609–613.
67. Liam CK, Lim KH, Wong CM. Differences in pleural fluid characteristics, white cell count and biochemistry of tuberculous and malignant pleural effusions. Med J Malaysia. 2000; 55(1): 21–28.
68. Abdul Rani MF, Cheung HS, Sunita A. Endobronchial tuberculosis mimicking pulmonary neoplasm. Int. Med. J. 2002; 1(1).
69. How SH, Kuan YC, Ng TH, *et al.* An unusual cause of haemoptysis and headache: cryptococcosis. J Pathol. 2008; 30(2): 129–132.
70. Rohana J, Lau DS, Hasniah AL, *et al.* Pneumatocoele in a neonate with perinatal tuberculosis. Arch Dis Child Fetal Ed. 2013; 98(2): F121.
71. Khajotia R, Manthari K. An apparently healthy young man with a peculiar-looking chest radiograph. Can Fam Physician. 2011; 57(3): 311–313.
72. Zamzuri Z, Adham S, Shukrimi A, et al. Metastatic adenocarcinoma of the lung mimicking spinal tuberculosis. Int. Med. J. 2011; 10(2): 43–46.
73. Yusof MI, Hassan E, Rahmat N, *et al.* Spinal tuberculosis: the association between pedicle involvement and anterior column damage and kyphotic deformity. Spine (Phila Pa 1976). 2009; 34(7): 713–717.
74. Elnaim AL. Bilateral psoas abscess and extensive soft tissue involvement due to late presentation of Pott's disease of the spine. Indian J Surg. 2011; 73(2): 161–162.
75. Chow TW, Lim BK, Vallipuram S. The masquerades of female pelvic tuberculosis: case reports and review of literature on clinical presentation and diagnosis. J Obs. Gynaecol Res. 2002; 28(4): 203–210.
76. Lim PS, Atan IK, Naidu A. Genitourinary tuberculosis: an atypical clinical presentation. Case Rep Obs. Gynaecol. 2012; 2012: 727146.
77. Ho CCK, Siti Aishah MA, Praveen S, *et al.* Spontaneous bladder perforation: a rare complication of tuberculosis. Int J Infect Dis. 2010; 14(Suppl 3): e250–2.
78. Chong VH. Differences in patient profiles of abdominal and pulmonary tuberculosis: a comparative study. Med J Malaysia. 2011; 66(4): 318–321.
79. Hussaini J, Mutusamy S, Omar R, *et al.* Base of tongue tuberculosis: a case report. Acta Med Iran. 2012; 50(2): 151–152.
80. Ismail Y, Muhamad A. Protean manifestations of gastrointestinal tuberculosis. Med J Malaysia. 2003; 58(3): 345–349.
81. Praveen S, Razman J. The TB-Crohn's affair- a never ending dilemma. Med J Malaysia. 2008; 63(3): 259–260.
82. Karuppannan M, Noorizan AA, Abdul Razak M. Is computed tomography (CT) scan a rational indicator to initiate tuberculosis treatment in patient with tuberculous peritonitis? A case report. Malaysian J. Pharm. Sci. 2004; 2(2): 23.
83. Leong DK, Chan KW, Ramu P, *et al.* Tuberculosis of gallbladder with candidiasis, a rare entity. Med J Malaysia. 2011; 66(2): 146–147.
84. Momin RN CV. Oesophageal tuberculosis: rare but not to be forgotten. Singapore Med J. 2012; 53(9): e192–4.
85. Aminuddin CA, Samsudin OC, Shukur MH. Tuberculous bursitis around the knee mimicking benign tissue tumour. Int. Med. J. 2004; 3(1).

86. Mah ESL, Bux SI. Tuberculous synovitis of the knee with unusually thick synovial granulation tissue: a case report. Internet J. Orthop. Surg. 2007; 6(2).
87. Ong PS, Wahinuddin S. Osteoarticular tuberculosis mimicking rheumatoid arthritis. Mod Rheumatol. 2012; 22(6): 931–933.
88. Anand A, Sood LK. Isolated tuberculosis of talus without ankle and subtalar joint involvement. Med J Malaysia. 2002; 57(3): 371–373.
89. Pan KL, Ibrahim S. Tuberculosis of the distal end of the radius mimicking a giant-cell tumour. Med J Malaysia. 2000; 55(Suppl C): 105–106.
90. Rohana AG, Norasyikin AW, Suehazlyn Z, *et al.* A case of persistent hyponatremia due to reset thermostat. Med J Malaysia. 2006; 61(5): 638–640.
91. Shalini B, Wahinuddin S, Monniaty M, *et al.* Ewing's sarcoma mimicking tuberculosis - a case report. Malays J Med Sci. 2002; 9(1): 52–54.
92. Azali HY, Norly S, Wong LM, *et al.* Liver abscess caused by tuberculosis and meliodosis. Asian J Surg. 2007; 30(2): 138–140.
93. Jarmin R, Alwi RI, Shaharudin S, *et al.* Common bile duct perforation due to tuberculosis: a case report. Asian J Surg. 2004; 27(4): 342–344.
94. Guru K, Yahya M. It's aneurysmal, it's stenotic, its tuberculosis. Med J Malaysia. 2011; 66(5): 515–516.
95. Hussein H, Azizi ZA. Tuberculous aortic pseudoaneurysm treated with in situ silver-impregnated vascular inlay graft. Asian J Surg. 2008; 31(2): 87–89.
96. Mahyudin M, Choo MM, Ramli NM, *et al.* Ocular tuberculosis intially presenting as central retinal vein occlusion. Case rep Ophthalmol. 2010; 1(1): 30–35.
97. Ooi YL, Tai LY, Subrayan V, *et al.* Combined optic neuropathy and central retinal artery occlusion in presumed ocular tuberculosis without detectable systemic infection. Ocul Immunol Inflamm. 2011; 19(5): 370–372.
98. Hah YK, Ang EL, Zunaina E, *et al.* An uncommon presentation of ocular tuberculosis. Int. Med. J. 2006; 13(3): 199–201.
99. Nor-Masniwati S, Zunaina E, Azhany Y. Ocular tuberculosis with multiple cerebral abscesses. Case Rep Ophthalmol Med. 2012; 606741.
100. Kok HS, George TM, Bastion CM, *et al.* Two cases of retinal vasculitis in ocular tuberculosis involving different parts of the vascular system. Med. Health. 2006; 1(1): 91–93.
101. Norazizah MA, Wan Hazabbah, Rohaizan Y *et al.* Isolated optic neuritis secondary to presumed tuberculosis in an immunocompetent child. Med J Malaysia. 2012; 67(1): 102–104.
102. Norliza W, Muda W, Hashim SE, *et al.* Reactivation of ocular tuberculosis in a young immunocompetent patient. Int. Med. J. 2007; 14(1): 45–47.
103. Hamizah R, Rohana AG, Anwar SA, *et al.* Splenic tuberculosis presenting as pyrexia of unknown origin. Med J Malaysia. 2007; 62(1): 70–71.
104. Imisairi AH, Hisham AN. Adrenal tuberculosis: the atypical presentations of eggshell-like calcifications. ANZ J Surg. 2009; 79(6): 488–489.
105. Ketan SH. Pancreatic tuberculosis in HIV positive patient: a case report. Borneo J. Med. Sci. 2010; 4.
106. Tan LH, Kamarulzaman A, Liam CK *et al.* Tuberculin skin testing among healthcare workers in the University of Malaya Medical Centre, Kuala Lumpur, Malaysia. Infect Control Hosp Epidemiol. 2002; 10: 584–590.
107. Kasthoori JJ, Liam CK, Wastie ML. Lady Windermere Syndrome: an inappropriate eponym for an increasingly important condition. Singapore Med J. 2008; 49(e47-9).
108. Loh LC, Chan SK, Ch'ng KI, Tan LZ, Vijayasingham P, Thayaparan T. Influence of co-morbidity in the interpretation of tuberculin skin reactivity in multi-ethnic adult patients with tuberculosis. Med J Malaysia [Internet]. 2005 Oct;60(4):426–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16570703
109. Ganeswrie R, Chui CS, Balan S, *et al.* Comparison of BACTEC MGIT 960 syste and BACTEC 460 TB system for growth and detection of Mycobacteria from clinical specimens. Malays J Pathol. 2004; 26(2): 99–103.
110. Kooi ES, Mahayidin M. Pulmonary tuberculosis in HIV infection: the relationship of the radiographic appearance to CD4 T-lymphocytes count. Malays J Med Sci. 2001; 8(1): 34–40.
111. Fadzilah MN, Ng KP, Ngeow YF. The manual MGIT system for the detection of M. tuberculosis in respiratory specimens: an experience in the University Malaya Medical Centre. Malays J Pathol. 2009; 31(2): 93–97.
112. Salleh SA, Hussin S, Rahman MM. Nested PCR for the rapid detection of TB from pleural fluid at HUKM Malaysia. Pak J Biol Sci. 2008; 11(13): 1728–1732.
113. Ahmad Hata R, Ibrahim SF, Wong CC. The role of polymerase chain reaction (PCR) in diagnosis of spinal tuberculosis afer pre-operative anti-tuberculosis treament. Malaysian Orthop. J. 2011; 5(1): 8–12.
114. Tan SC, Harwant S, Selvakumar K, *et al.* Predictive factors in the evolution of neural deficit in tuberculosis of the spine. Med J Malaysia. 2001; 56(Suppl C): 46–51.
115. Selvarajah VS, Samudram S, Chua LT, *et al.* Efficacy of anti-tuberculosis treatment alone on reslution of tuberculosis pleural effusions. IeJSME. 2007; 2: 30–33.
116. Puraviappan P, Tang IP, Yong DJ, *et al.* Endoscopic, endonasal decompression of spinal stenosis with myelopathy secondary to cranio-vertebral tuberculosis: two cases. J Laryngol Otol. 2010; 124(7): 816–819.
117. Liam CK. Risk of tuberculosis to healthcare workers. Med J Malaysia. 2001; 56(1): 107–111.
118. Nik MR, Mohd NS, Wan Mohammad Z, *et al.* Factors associated with unsuccessful treatment outcome of pulmonary tuberculosis in Kota Bharu, Kelantan. Malaysian J. Pharm. Sci. 2011; 11(1): 6–15.
119. Redha S, Suresh RL, Subramaniam J, *et al.* Pancreatic tuberculosis presenting with recurrent acute pancreatitis. Med J Malaysia. 2001;56(1):95–97.
120. Awaisu N, Nik Mohamed MH, Mohamad Noordin N, *et al.* The SCIDOTS Project: evidence of benefits of an integrated tobacco cessation intervention in tuberculosis care on treatment outcomes. Subst Abus. Treat Prev Policy. 2011; 6: 26–597X–6–26.
121. Al-Darraji HA, Kamarulzaman A, Altice FL. Isoniziazid preventive therapy in correctional facilities: a systematic review. Int J Tuberc Lung Dis. 2012; 16(7): 871–879.
122. Tan AK, Mallika PS, Aziz S, *et al.* Ethambutol ocular toxicity in a patient with pulmonary tuberculosis - a case report. Malaysian Fam. Physician. 2008; 3(2): 87–90.
123. Azhar Shah S, Md Idris MN, Abdul Hadi HS *et al.* Usage of GIS application for tuberculosis control in Cheras, Kuala Lumpur, malaysia. Malaysian J. Public Heal. Med. 2002; 2(2): 15–26.
124. Vitus S, Dhanaraj P, Zaitun Y, *et al.* Is pulmonary tuberculosis case properly identified in Lahad Datu? A clinical audit in 2003. Malaysian J. Pharm. Sci. 2004; 2(2): 43.
125. O'Boyle SJ, Power JJ, Ibrahim MY, *et al.* Factors affecting patient compliance with anti-tuberculosis chemotherapy using the directly observed treatment, short-course strategy (DOTS). Int J Tuberc Lung Dis. 2002; 6(4): 307–312.
126. Tan L KA. Preventing tuberculosis in healthcare workers of the radiology deparment: a Malaysian perspective. Biomed Imaging Interv J. 2006; 2(1): e3.
127. Adyani MR, Noorizan AA, Yahaya H, *et al.* Sudden onset of anti-tubeculosis drug-induced hepatotoxicity in a critically ill patient. Malaysian J. Pharm. Sci. 2004; 2(2): 22.

Nipah Encephalitis – An Update

Sherrini Bazir Ahmad, MRCP, Chong Tin Tan, FRCP

Neurology, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

SUMMARY

Between September 1998 to May 1999, Malaysia and Singapore were hit by an outbreak of fatal encephalitis caused by a novel virus from the paramyxovirus family. This virus was subsequently named as Nipah virus, after the Sungei Nipah village in Negeri Sembilan, where the virus was first isolated. The means of transmission was thought to be from bats-to-pigs and subsequently pigs-to-human. Since 2001, almost yearly outbreak of Nipah encephalitis has been reported from Bangladesh and West Bengal, India. These outbreaks were characterized by direct bats-to-human, and human-to-human spread of infection. Nipah virus shares many similar characteristics to Hendra virus, first isolated in an outbreak of respiratory illness involving horses in Australia in 1994. Because of their homology, a new genus called Henipavirus (Hendra + Nipah) was introduced. Henipavirus infection is a human disease manifesting most often as acute encephalitis (which may be relapsing or late-onset) or pneumonia, with a high mortality rate. Pteropus bats act as reservoir for the virus, which subsequently lead to human spread. Transmission may be from consumption of food contaminated by bats secretion, contact with infected animals, or human-to-human spread. With wide geographical distribution of Pteropus bats, Henipavirus infection has become an important emerging human infection with worldwide implication.

Key words: *Nipah Encephalitis, Nipah Virus, Hendra Virus, Japanese Encephalitis*

INTRODUCTION

It has been nearly fourteen years since the severe outbreak of *Nipah* encephalitis, the fatal viral encephalitis that initially affected a substantial number of people from several pig-farming villages in Malaysia and abattoir workers in Singapore. In Malaysia, 265 cases of *Nipah* encephalitis and 105 deaths were estimated from September 1998 to May 1999[1], with highest death rate reported from Bukit Pelanduk district of *Negeri Sembilan* state[2]. The initial outbreak was first thought to be another endemic of *Japanese encephalitis* (JE), a flavivirus transmitted to human via *Culex* mosquitoes and is known to have caused major porcine-associated outbreaks in Malaysia in 1974 (*Langkawi*), 1988 (*Penang*) and 1992 (*Serian* district of *Sarawak*). However, epidemiological features were unlike JE[3]. Electron microscopy, immunohistochemistry and immunofluorescence study of the cerebrospinal fluid (CSF) from several affected patients later identified a newly isolated strain of syncytium-forming virus that has features of the *Paramyxoviridae* family and shares close similarities to the *Hendra virus* (HeV)[3]. Viral genomic sequencing subsequently identified that this novel virus is distinct from Hendra and was named *Nipah virus* (NiV), after the *Sungei Nipah* village, where the virus was first isolated[1,4].

EPIDEMIOLOGY

The outbreak initially involved pig-farming villages in *Ipoh*, a town in *Perak*, which subsequently spread to the southern part of Peninsular Malaysia in *Selangor* and *Negeri Sembilan* states, including the *Sikamat* and *Bukit Pelanduk* villages[5]. JE was initially suspected to be the causative agent for this fatal outbreak in 1998 because of the apparent detection of JE antibodies in some patients and temporal history of exposure to infected pigs. However, certain clinical and epidemiologic features of this outbreak seem to be atypical to JE i.e. most patients were adult males rather than children, clustering of cases within members in the same household, which suggests an infection of high attack rate (as opposed to the JE virus which caused symptomatic encephalitis in 1 in 300 of those infected); and the fact that many patients have been previously immunized against JE[2]. Furthermore, the effort of clearing the affected areas from JE virus-bearing mosquitoes failed to cease the rising numbers of infected patients.

Figure 1 demonstrated the geographical distribution of pig farming villages affected by the outbreak in *Negeri Sembilan*. No cases were reported from the Malay villages in *Bukit Pelanduk* despite the close proximity with the adjacent Chinese farms with clustering of the encephalitis infection. There was also no reported case of NiV in *Sungai Pelek*, which is a village north of *Bukit Pelanduk,* across the *Sepang River*, which also has pig farms, within the reach of mosquito flight. This suggested that close contact with infected pigs is required to develop the infection. The Muslims from the Malay villages are prohibited from having any close contacts with pigs due to their religious belief. Pig-to-pig and pig-to-human transmissions were thought to be from direct contact with the pigs' excretions including urine, saliva, pharyngeal and tracheal secretions, except for two cases of transmission from infected dogs[5-8]. Two affected patients were involved in repairing pig cage and supervising the pig culling operation[5].

All these epidemiological features make mosquito-borne JE unlikely and this was confirmed when Chua and his colleagues from the University of Malaya discovered the new virus and named it as *Nipah virus*[1].

HUMAN-TO-HUMAN TRANSMISSION

The isolation of virus from urine and tracheal secretions from affected patients in Malaysia suggested that human-to-human transmission is possible[9-10]. Serum IgG antibodies to NiV were isolated from 3 health-care workers. One of the cases was a staff nurse who also had MRI changes similar to those seen in acute NiV. She cared for the infected patients, but had no previous contact with pigs. She remained asymptomatic despite the positive serology and MRI changes. These show that human-to-human transmission of infection did occur during the Malaysian outbreak. However, because of the early practice of barrier nursing, it was not common[9,11,12].

Corresponding Author: sherrini@ummc.edu.my

FROM MALAYSIA TO SINGAPORE

The spread of the epidemic was thought to be due to the massive 'fire sales' and movements of infected pigs from Perak to other neighbouring states in the country [Figure 2], including *Selangor* and *Negeri Sembilan*. The outbreak subsequently spread to involve the abattoir workers in *Singapore* due to the international export of pigs from the affected areas[7,13]. The outbreak was successfully contained in Peninsular Malaysia after a nation-wide surveillance of pig farms and the mass culling of sick pigs[5]. Pigs from Malaysia were banned from being imported into Singapore and all abattoirs in the country were closed temporarily[14].

NIPAH VIRUS

Nipah virus is a member of *Paramyxoviridae* and is now classified as genus *Henipavirus* (Hendra + Nipah), due to very high genomic resemblance between these two viruses. In cell culture, the viral nucleocapsids have the typical 'herringbone' appearance with negative staining, characteristic for paramyxovirus[15]. It is the largest paramyxoviral genome described so far with a total length of 18, 246 nucleotides, only 12 nucleotides longer than *Hendra*[4]. There is a high degree of nucleotide homology in the various genes of HeV and NiV that exceeds 70%, and a high amino acid identity of more than 80% in most genes[16].

CLINICAL FEATURES

All symptomatic patients from Malaysia had neurological features at presentation and none had primary respiratory disease. However, 2 of the 11 cases in Singapore presented with pneumonia without encephalitis[7]. Like any other viral encephalitis, prodromal symptoms of sore throat, myalgia, fever, headache, vomiting and altered mental status are common. Three main medical centres in Malaysia have published reviews on their clinical experience in managing this potentially fatal illness[17-19]. They were the *University Malaya Medical Centre, Kuala Lumpur General Hospital* and *Seremban Hospital*. A number of severely infected patients were also transferred from *Seremban Hospital to Kuala Lumpur General Hospital*, with the later skewed towards more severe patients [Table 1]. Febrile encephalitis seems to be the main clinical feature in infected NiV patients. Prodromal symptoms include fever, headache, nausea, vomiting, dizziness, lethargy, non-productive cough and myalgia. In a review by Goh KJ *et al*, 97% (91of 94 patients) had fever and more than half presented with headache. Close to half of (55%) patients had reduced level of consciousness with majority showing signs of brainstem dysfunction such as abnormal vestibule-ocular reflex, pinpoint pupils with variable reactivity and vasomotor dysautonomia i.e. hypertension, and tachycardia. All the seizures occurred in patients with reduced level of consciousness with almost all having generalized tonic-clonic attacks. Interestingly, about one third of their patients had segmental myoclonus, usually associated with more severe infection. The myoclonus characteristically involved the diaphragm and anterior neck muscles; but was also seen in other parts including arms, legs, and facial muscles[17]. The focal myoclonus is not time-locked to any focal discharges on the EEG findings, suggesting that the myoclonus is most likely to be brainstem or spinal cord in origin[20]. Absent/reduced tendon reflexes and hypotonia, tachycardia and hypertension were the other common signs particularly in those with more severe disease. Other reported signs include cerebellar dysfunction and bilateral postural tremors of arms[17].

Tan *et al* reported high infection rate in the household of infected farms in which 33% of them were affected by the disease[5], with 8-11% of the household members had subclinical disease[5,6]. It is thought that exposure to infected pigs correlates to the development of symptomatic disease[5]. About one sixth (16%) of patients with asymptomatic NiV infection may have abnormal cerebral MR imaging[11]. The MRI abnormalities were similar to that of acute Nipah encephalitis but less numerous. These patients developed antibody to *Nipah* virus (IgG) without any symptoms. It is an important aspect of the disease as some of these patients went on to develop late-onset encephalitis[21].

Table II summarises the mortality rate of patients with *Nipah encephalitis*, based on data from three different hospitals in Malaysia[17-19]. As shown, the overall mortality was close to 39%. The mortality in patients from the Kuala Lumpur General Hospital was higher probably because the Centre had patients with more severe disease. All patients, except one, were in a comatose state requiring ventilator support[18]. Evidence of severe brain-stem involvement, segmental myoclonus, seizures, and areflexia was associated with high mortality[17]. Chong *et al* also found that diabetic patients had increased mortality by 123% ($p<0.001$) and it is speculated that immunoparesis might be the reason to this observation[22].

LABORATORY TESTING

Table II summarises the laboratory findings of patients with Nipah encephalitis, based on data from three different hospitals in Malaysia1[7-19]. Thrombocytopenia has been frequently reported[7,17-19] and present in 30-60% of patients, whilst leukopenia in 11-60% [23]. Abnormal liver functions with raised alanine and aspartate aminotransferase were present in 33-61% and 42-60% of patients respectively[23]. Lower platelet count and higher liver enzyme were associated with higher mortality. They were thought to be nonspecific changes in very ill patients[17]. Cerebrospinal fluid analysis from patients in Malaysia mostly showed normal glucose with raised white cell counts and protein[24]. These changes are non-specific and can be seen in any other CNS viral infections. Nevertheless, 25% of symptomatic patients had normal CSF findings[17-19].

Anti-*Nipah virus* IgM and IgG antibody can be detected in both serum and CSF of infected patients. Antibodies can be tested using IgM-capture enzyme-linked immunosorbent assay (ELISA) technique. This technique initially utilizes Hendra virus antigen to detect antibodies against Nipah virus, as both of these viruses share very close structural similarities. The IgM antibodies were obtained using *Hendra virus*-infected γ-irradiated Vero E6 cells and anti-*Hendra* hyperimmune mouse ascitic fluid antibody. The IgG antibodies were detected using indirect IgG ELISA assay[23].

The rate of detecting *anti-Nipah* IgM is the highest on day 12 of illness with a sensitivity of 100%[25]. In a study of 176 patients from *Seremban Hospital* and *University Malaya Medical Centre*, the antibody was positive in 44-50% of patients at day one of illness and increased to 60-71% by day 4. The sensitivity for detecting anti-Nipah IgG is 100% by day 25-26 of illness[25]. The rate of IgG detection is relatively low in the first week of illness (7-29%). The assay was subsequently switched to *Nipah virus*-infected Vero E6 cells and there was no significant difference in the sensitivity and specificity of the assay between the two antigens used. Other methods used to support viral detection include plaque reduction neutralisation and RT-PCR assay to detect viral RNA[26]. NiV grow well in Vero cells, but require BSL4 laboratory. Positive viral isolation from CSF is associated with high mortality, similar to the cases seen in JE[27]. Interestingly, the presence of CSF IgM does not have protective effect in disease severity and mortality[28].

Close to all (97.%) of electroencephalograph (EEG) carried out in the acute phase of encephalitis were abnormal. The most common abnormality was continuous diffuse slow slowing with or without focal discharges (87.5%). The degree of slowing correlated with severity of disease. Independent bitemporal periodic complexes were associated with 100% mortality[24].

RADIOLOGICAL AND HISTOPATHOLOGICAL FINDINGS

Abnormal chest radiographs were reported in 6-24% cases in Malaysia[17,19]. In contrary, 3 out of 11 patients in Singapore presented with primary lung disease and abnormal chest radiographs[7].

Magnetic resonance imaging (MRI) of the brain was a very useful diagnostic tool for diagnosing Nipah encephalitis with 100% sensitivity among the Malaysian patients 29. Patients with acute encephalitis showed small, disseminated discrete hyperintense lesions in the subcortical and deep white matter, to a lesser extent, the gray matter, best seen on fluid attenuated inversion recovery (FLAIR) images. These changes are thought to be due to small vessels vasculitis and thrombosis, which resulted in focal disseminated areas of ischaemia and microinfarctions. However, there is poor correlation between disease severity and outcome with changes on MRI brain. These MRI changes also differ from the typical MRI brain seen in JE and *Herpes Simplex Virus (HSV) encephalitis*. In JE, the usual MRI changes are high signal intensity areas on T2-weighted and low signal intensity on T1-weighted sequences seen classically in bilateral thalami with or without haemorrhagic changes. These lesions can also be seen in the white matter, brainstem and basal ganglia[30]. MRI changes in HSV encephalitis classically involve oedematous changes and confluent high signal areas on T2-weighted sequence in the temporal lobe and limbic system[31].

Pathologically, the lung, heart and kidney were affected but the brain is the most severely affected organ[2]. Histopathological findings from post-mortem examination of the brain tissues include syncytial giant cell formation, vasculitis, and viral inclusions. There were also perivascular cuffing, parenchymal inflammation and neuronophagia[32]. Neuronal damage occurred via two possible mechanisms. Firstly, the formation of multinucleated syncytium in the endothelium of the blood vessels caused inflammation and vasculitis, which subsequently resulted in vascular thrombosis and occlusion leading to cerebral micro-infarction/ischaemia. Secondly, the findings of viral inclusions support possible direct viral cytolysis of parenchymal cells[24]. These findings are not specific for NiV encephalitis per se and can be seen with other encephalitides. However, the presence of syncytial multinucleated endothelial cells is exclusive for *Nipah* and *Hendra* virus encephalitis[32]. The vasculitic changes on autopsy correspond to the discrete small hyperintense lesions found on MRI brain of these patients. Vasculitis changes are also seen in other organs, the heart, lung and spleen, indicating widespread systemic involvement 32.

LONG-TERM NEUROLOGICAL AND FUNCTIONAL OUTCOME

Neurological and neuropsychiatric sequelae may persist years after the initial presentation and[33]. Of the survivors of the acute infection, 21% (14/64) of those from UMMC and 19% of those from *Seremban* Hospital had persistent cognitive impairment and residual neurological deficits including cerebellar signs, tetraparesis, cranial nerve palsies and peripheral nerve lesions[17,19]. The survivors of the patients from Kuala Lumpur Hospital did poorly, with 6 out of 7 patients having significant neurological deficits. However, the patients in Hospital Kuala Lumpur had more severe illness 18. Long-term neurological assessment and serological pattern done on 39 NiV infection survivors, 10 years after the Malaysian outbreak, showed that fatigue (31%) and daytime somnolence (26%) were the common persistent clinical features. About a fifth (21%) had focal neurological deficits. Of those with previous encephalitis, 38% of had a significant disability on the Modified Rankin scale. All patients were tested negative for IgM antibodies and positive for IgG[34].

TREATMENT

To date, the most important mode of treatment of acute *Nipah* encephalitis remains supportive, using mechanical ventilation for patients with respiratory failure, anticonvulsants for seizures, and management of secondary infection and rehabilitation[17]. Empirical treatment with ribavirin, a broad-spectrum antiviral against both DNA and RNA that can cross blood-brain barrier, was tried during the outbreak in Malaysia. In an open label trial of 140 patients treated with the drug, there was a 36% reduction in mortality with more survivors without residual neurological deficits. The latter however was not statistically significant[35]. The number was too small to allow comparison between the efficacies of oral vs. intravenous preparation of Ribavirin. Ribavirin has been shown to inhibit NiV replication in vitro[35]. However, more studies are needed to understand the pathogenesis of *Nipah* encephalitis, both at the biological and molecular level so that a more targeted therapy can be developed. The current animal models have shown that Ribavirin may delay *Nipah* virus disease and death but has no therapeutic effect against *Hendra* virus infection in hamsters[36].

Chloroquine, an antimalarial drug, also has been tried on animal studies with no therapeutic benefit. Similarly, the potential development of vaccine using NiV glycoproteins as the immunological target is still at an experimental level. At present, research are being done to look at therapeutic options of using human monoclonal antibody that may potentially inhibit glycoprotein-mediated entry of these viruses into cells[39] and applying RNA interference to inhibit *Henipavirus* replication in vitro[37].

RELAPSED AND LATE-ONSET NIPAH ENCEPHALITIS

One of the unique and interesting feature of NiV infection is the development of relapsed and late-onset encephalitis, which may occur months or years after the acute illness[21,33,38].The longest delay in the onset of late-onset encephalitis is 11 years[39]. Relapsed encephalitis occurs after the recovery from acute encephalitis and late-onset encephalitis occurs after asymptomatic or mild non-encephalitic infection. It is believed that the relapsed and late-onset encephalitis represent the same disease process, the only difference being that in the later, the initial infection is not severe enough to cause neurological manifestation[21]. Tan *et al* reported a prevalence rate of relapsed encephalitis of 9%, and late-onset encephalitis of 5%[21,38].

The relapsed and late-onset encephalitis are usually of acute onset. The common clinical features are fever, headache, seizures and focal neurological signs with CSF pleocytosis[21]. As compared to the acute encephalitis, more of the patients with relapsed and late-onset had seizures. Their MRI brain showed areas of confluent cortical involvement, rather than the small, disseminated discrete hyper intense lesions seen in acute cases[29]. The EEG shows more focal slowing and sharp waves discharges, corresponding to the predominance of focal MRI and clinical lesions[21,29,38]. Relapsed and late-onset *Nipah* encephalitis has lower mortality rate than patients with acute encephalitis (18% vs. 40%)[1,17,19]. This could be explained by the minimal brainstem involvement in the relapsed and late-onset encephalitis patients[21].

Immunohistochemistry of the autopsy tissue suggests that the relapsed and late-onset cases are due to recurrent attacks from the persistent virus that remained dormant in the brain, and became reactivated by some unknown triggering factors[21]. Even though small vessels vasculitis associated with thrombosis and vascular occlusion were found in brain autopsy of patients with acute Nipah encephalitis, this was not demonstrated in relapsed cases[32,38]. However, viral inclusions and larger parenchymal lesions were more abundantly found in relapsed cases with focal encephalitis but no evidence of peri-venous demyelination[38]. These lesions would correlate with the confluent lesions seen on MRI brain of the patients[32,38]. Interestingly, though the viral antigen can be demonstrated by the positive immunolocalization, the CSF culture failed to isolate the virus. This suggests that the Nipah virus, like the measles virus in subacute sclerosing pan encephalitis, could have undergone mutations, resulting in the failure of viral morphogenesis at the cell membrane[17,21].

BATS AS RESERVOIR

Malaysia is a home for at least 13 species of fruit bats (2 species of flying foxes) and more than 60 species of insectivorous bats. Fruit bats or flying foxes of the family *Pteropodidae (Pteropus vampyrus and Pteropus hypomelanus)* had been identified as the natural reservoir for NiV in Malaysia[40]. *Pteropus hypomelanus* was thought to have infected the pigs in Malaysia from their saliva through half-eaten fruits[6,40]. NiV has also been isolated from the half-eaten fruits and the urine of these roosting bats from *Tioman Island*[41]. These partially eaten fruits may have been dropped or thrown into pigsties and subsequently infected the pigs that consumed the contaminated fruits.

The infected pigs act as amplifying hosts and contributed to pig-to-pig and pig-to-human transmission of the virus[40]. The reason for virus spill-over from bats to pigs and subsequently to human were attributed to multiple factors including encroachment of bats into cultivated fruit orchards in West Coast of Peninsular Malaysia following deforestation and reduction in wildlife habitat; severe haze, prolonged El Nino-related drought resulting in reduction in availability of flowering and fruiting forest trees for foraging by the bats, and poor pig farming practice[42].

OUTBREAKS IN BANGLADESH AND INDIA

No further outbreak was reported in Malaysia and Singapore after the mass culling of pigs[43]. However, the global public health community was again alerted when cases of Nipah encephalitis were reported in Bangladesh. There was recurrent *Nipah* encephalitis in Bangladesh almost annually since 2001 affecting close to 200 patients with 70% mortality. The latest outbreak was reported between January and March this year, resulting in 17 total deaths[44-46]. Two Indian outbreaks were reported in the neighbouring Siliguri in 2001 and Nadia District in West Bengal in 2007[46-49].

In contrast to the viral strains found in Malaysia, Cambodia and Thailand, the NiV isolated from the outbreak in Bangladesh showed some differences in their nucleotide sequences, suggestive of a different strain that might have co-evolved within the local natural reservoirs[50]. Studies from the outbreaks between 2001-2010 showed that the bat-to-human transmission in Bangladesh was associated with different pathways. Firstly, transmission occurred via drinking raw date palm sap contaminated with the virus from urine or saliva of these fruit bats[51,52] and subsequently led to human-to-human spread via respiratory droplets or bodily fluids. Close to half (62/ 122) of the cases identified in Bangladesh between 2001 and 2007 involved human-to-human transmission[53]. The other possible pathway is through animal-to-human transmission from contacts with secretions from infected pigs, cows and goats[16,48].

Nipah encephalitis was first reported in Siliguri, West Bengal, India, in 2001. It involved 66 patients, 75% had hospital exposure; i.e. they were hospital staffs, those who attended or visited patients in the hospital. The mortality rate was 74%. No cause was initially identified. Retrospective analysis of patients' samples (serum and urine) for *Nipah virus* was subsequently carried out and 9 out of 18 patients tested positive for IgM and IgG antibodies for NiV[46]. Studies to detect intermediate host was not carried out but human-to-human transmission on the ward was thought to be due to nasocomial infections, inadequate barrier-nursing and spreading of the virus via respiratory secretions and urine from infected patients. Sequencing analysis of this virus reveal close similarities to the strains in Bangladesh, as opposed to the ones in Malaysia[46]. This finding supports the environmental and geographical influence on the genetic evolution of this virus.

EPIDEMIOLOGY AND CLINICAL FEATURES IN INDIA AND BANGLADESH COMPARED TO MALAYSIA AND SINGAPORE

Table III illustrates the difference in epidemiologic and clinical features of NiV encephalitis outbreaks between Malaysia and Singapore, versus Bangladesh and India[54,55]. As shown, the Malaysian and Singapore outbreak did not recur since 1999, but there was almost yearly outbreak in Bangladesh since 2001. The outbreak involved mainly adults in Malaysia and Singapore, but all ages in Bangladesh and India. The mode of spread was from bats-to-pigs, and pigs-to-human in Malaysia and Singapore; whereas in Bangladesh and India, transmission mainly occurs via bats-to-human through consumption of contaminated date palm juice, and human-to-human spread.

As for the clinical features, respiratory illness was not a prominent feature in the Malaysian patients. However, 3 of 11 affected patients in Singapore presented with atypical pneumonia with abnormal chest radiographs. One of them later developed encephalitis[7]. On the other hand, half to two thirds of the patients from the Bangladesh and Indian outbreak had respiratory symptoms, with chest radiographs of some patients showing changes consistent with acute respiratory distress syndrome. The prominent respiratory involvement and the relative lack of implementation of the infectious control practices probably underlie the human-to-human transmission in the Bangladesh and Indian outbreak.

Segmental myoclonus was a prominent feature in acute Nipah encephalitis patients in Malaysia. However, this was not seen in cases from Bangladesh and India. The typical changes in the MRI brain of the Malaysian patients were disseminated high-signal intensity lesions. Despite lack of MRI brain facilities in Bangladesh, the neuroimaging findings of 4 patients from Rajbari district differ from that of Malaysian patients, in which confluent high signal lesions involving both gray and white matter was the prominent features[56].

In Bangladesh, Sejvar *et al* conducted a study on 22 patients who survived NiV illness between 2005 and 2006, to assess their neurological and functional outcome based on questionnaire, neurological examinations and MRI brain imaging. Close to a third of patients (32%) had persistent neurologic and cognitive dysfunction. Almost all had disabling chronic fatigue syndrome and more than half had behavioural and neuropsychiatric changes, similar to the long-term findings on survivors in Malaysia and Singapore[33,34]. The behavioural and neuropsychiatric disturbances manifested as violent outbursts,

Table I: Summary of clinical presentations in Nipah encephalitis patients treated in three major hospitals in Malaysia[17-19].

Clinical symptoms	Nipah Virus*	UMMC Goh *et al.*[17]	HKL Sim *et al.*[18]	Seremban Hospital Chong *et al.*[19]
	N=215	N=94	N=18	N=103
Age (mean)/ range in years	37 (4-75)	37 (13-68)	37 (14-64)	38 (4-75)
Sex (M/F)	M>F	4.5:1	11:7	7.5:1
Mean Incubation period** (days)	14 days or less	N=94 Several days to 8 weeks (92% =<14 days)	N=6 13 (2-30)	N=49 10+/- 8.7 (1-32)
Fever	95.4% (205)	91	17	97
Headache	74.9% (161)	61	12	88
Dizziness	37.7% (81)	34	8	39
Reduced level of consciousness/ altered mental status	71.6% (154)	52	17	85
Vomiting	31.6% (68)	25	7	36
Myalgia	28.8% (62)	11	4	47
Chills and Rigors	47.1% (57)	N/A	6	51
Diarrhoea	18.2% (22)	N/A	1	21
Sore throat	20.4% (21)	N/A	N/A	21
Cough	20.9% (45)	13	3	29
Arthralgia	6.6% (8)	N/A	1	7
Hyporeflexia	60.5% (130)	53	18	59
Segmental Myoclonus	49.3% (106)	30	17	59
Brainstem Dysfunction				
-hypertension	43.3% (93)	36	5	52
-tachycardia	42.3% (91)	37	1	53
-abnormal pupils	52.1% (49)	49	N/A	N/A
*-abnormal VOR****	38.3% (36)	36	N/A	N/A
-profused/ segmental sweating	26.2% (27)	N/A	N/A	27
-Nystagmus	20% (43)	15	3	25
Ptosis	17.7% (38)	4	4	30
Meningism	19.1% (41)	26	3	12
Seizures	23.2% (26)	22	4	N/A
Limb weakness	15.3% (33)	10	8	15
Hypotonia	39.6% (78)	53	N/A	25

** Cumulative data collected from case series of patients treated at University Malaya Medical Centre (UMMC), Kuala Lumpur Hospital (HKL), and Seremban Hospital (SH)*

** Incubation period = interval between last contact with pig and the first onset of clinical symptoms

All patients had direct contact or were in close proximity to pigs

*** VOR: Vestibulo-ocular reflex (Doll's eyes reflex)

Table II: Summary of laboratory findings, treatment and mortality in Nipah encephalitis patients treated in Malaysia[17-19].

	Nipah Virus*	UMMC Goh *et al.*[17]	HKL Sim *et al.*[18]	Seremban Hospital Chong *et al.*[19]
	N=215	N=94	N=18	N=103
Positive sera Hendra IgM serology (N)	79% (191)	71% (83)	100% (17)	81% (91)
Positive CSF Hendra IgM serology (N)	38% (124)	31% (83)	30% (10)	58% (31)
Abnormal CSF (N) *– raised protein, raised white cell count*	78% (161)	75% (92)	78% (15)	83% (54)
Number of patients treated with Ribavirin	71.6% (154)	73	14	67
Death	39% (83)	32% (30)	61% (11)	41% (42)

Table III: Differences in epidemiologic and clinical features of Nipah virus encephalitis outbreaks in Malaysia, Singapore, India and Bangladesh. (Modified from: Chang LY, Tan CT. *Nipah Virus Infection*. Jackson AC ed: Viral Infections of the Nervous System. Springer Basel, 2013, 317-336.)[54].

	Malaysia-Singapore	Bangladesh-India
Age and occupation	Mainly adult pig farm workers	Adults, children and healthcare workers
Spread	Bats-to-pigs, pigs-to-human Human-to-human occasional	Direct bats-to-human infection by consumption of date palm juice and fruits contaminated by bats. Also reported possibility of bats-to-cows, bats-to-pigs Human-to-human spread important
Respiratory involvement	14-29%; 2 out of 11 patients in Singapore present with pneumonia without encephalitis	Cough (62%), respiratory difficulty (69%); chest radiographs with acute respiratory distress syndrome in some patients
Encephalitis	Segmental myoclonus seen in 32-54%	Segmental myoclonus not reported
MR Imaging	Disseminated small high-signal intensity lesion hallmark of MR imaging	Confluent high-signal brain lesion in limited MR imaging
Relapsed and late-onset encephalitis	About 10%	Delayed onset neurological abnormalities in 4 out of 22 patients in a follow-up study
Mortality	32-41%	73%

Table IV: The detection of Nipah virus in various species of bats around the world. (Reproduced with permission from Chong *et al. Nipah virus and bats*. Neurology Asia 2009, 14;73-76.)[63].

Location	Bat Species	Evidence of Infection
East coast, Australia	*Pteropus conspicillatus, P. alecto, P. scapulatus, P. poliocephalus*	Serology
Papua New Guinea	*Dobsonia moluccense, P. neohibernicus, D. andersoni, P. capistratus, P. hypomelanus, P. admiralitatum*	Serology
West coast, Peninsular Malaysia	*Cynopterus brachyotis, Eonycteris spelaea, P. hypomelanus, P. vampyrus, Scotophilus kuhlii*	Serology (ELISA) and serum neutralizing test
Tioman Island, East coast, Peninsular Malaysia	*Pteropus hypomelanus*	Virus culture, gene sequencing
Bangladesh	*P. giganteus*	Serology
Thailand	*Pteropus hypomelanus, P. lylei, P. vampyrus, Hipposideros larvatus*	Serology (ELISA) and RT-PCR
Cambodia	*Pteropus lylei*	Serology (ELISA), seroneutralising test and PCR
Sumatra, Java, Indonesia	*Pteropus vampyrus*	Serology (ELISA), virus neutralizing test
Yunan and Hainan Island, China	*Myotis sp., Rousettus leschenaultia,*	Serology (ELISA) and serum neutralizing, PCR
India	*Pteropus giganteus*	Serology (ELISA) and serum neutralizing test
Ghana	*Eidolon helvum, Epomophorus gambianus, Hypsingathus monstrosus*	Serology (Luminex multiplexed binding assay)
Madagascar	*Eidolon dupreanum, Pteropus rufus*	Serology (ELISA), serum neutralizing test

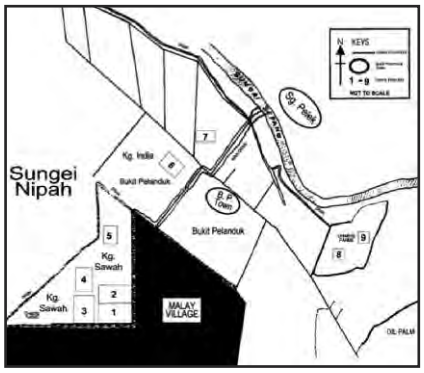


Fig. 1: Map showing geographical distribution of affected pig farming villages (numbered 1-9) in Bukit Pelanduk. (Reproduced with permission from: Tan *et al. Epidemiological aspects of Nipah Virus infection*. Neurol J Southeast Asia 1999, 4:77-81)[5]

Fig. 2: Map of peninsular Malaysia showing spread of Nipah encephalitis outbreak among neighbouring states. (Reproduced with permission from Sim *et al. Nipah Encephalitis: A report of 18 patients from Kuala Lumpur Hospital*. Neurol J Southeast Asia 2002, 7: 13-18)[18].

irritability, frequent nightmares, personality change and depression[57].

Relapsed and late-onset encephalitis is another unique feature of the NiV infection among the Malaysian patients. The long-term outcome study by Sejvar *et al.* from Bangladesh also showed that 4 out of 22 patients had delayed neurological symptoms manifesting as oculomotor palsy and cervical dystonia.

There were therefore significant differences in the epidemiologic and clinical features of NiV infection in the Malaysian and Singapore outbreaks, as compared to the subsequent Bangladesh and Indian outbreaks. These differences are likely to be due to local socio-cultural and economic factors, such as the consumption of date palm juice in Bangladesh, as well as genetic variation of NiV.

HENDRA VIRUS

As previously stated earlier in this review, Nipah and Hendra viruses are two new zoonotic viruses that have emerged in recent years. Both are from the paramyxoviridae family and shares many similar characteristics. Because of their homology, a new genus called *Henipavirus* (Hendra + Nipah) was created for these two viruses.

Hendra virus was first isolated in an outbreak of acute respiratory illness involving horses in Australia in 1994. A horse trainer and stable handler were also infected, manifesting with respiratory illness from which the horse trainer died. A second human death occurred in 1995, where a farmer who had contact with ill horses about a year earlier died from encephalitis. Another two deaths involving veterinary workers occurred in the Hendra virus outbreaks in July 2008 and July 2009, also in Australia. Up until 2011, there have been 14 outbreaks of Hendra virus infection, all involving horses, 5 of these involving subsequent horse-to-human transmission, with 4 deaths among a total of 7 human cases[58].

Thus, *Hendra virus* is able to cause respiratory and encephalitic illness in humans who have close contact with infected horses. The predisposition to affect brain and lung is comparable to NiV infection. Similarly, there is also acute encephalitis and delayed neurological manifestation, with high mortality rate. The reservoir of *Hendra virus* is also the *Pteropus* genus of fruit bats, but the infection is transmitted through sick horses[59-61].

Brain necropsy of the 2 fatal cases of acute and relapsing *Hendra virus* encephalitis suggest that the pathology and pathogenesis are similar to *Nipah virus* with neuronal infection and micro-infarction/vasculitis in the brain. There is also widespread vasculitis involving lung, kidney and other major organs[62].

THE WORK ON BATS WORLD WIDE AND ITS IMPLICATION

To date, the outbreak of NiV and Hendra virus infections in Malaysia, Bangladesh, and Australia have been attributed to Pteropus bats as the reservoir. Human becomes infected directly from the bats by consuming contaminated food such as date palm juice in Bangladesh, or indirectly via contact with sick animals such as pigs or horses. The distribution and evidence of Henipavirus or related virus is therefore crucial in predicting future outbreak. In Malaysia, other than *Pteropus* vampyrus and *Pteropus hypomelanus*, Yob *et al* also found serum-neutralizing antibodies to NiV from 5 out of 14 different species of bats sampled from other states in Peninsular Malaysia[40]. However, these neutralizing antibodies titres were much lower when compared to the anti-*Hendra* virus titres isolated from the flying foxes in Australia.

Pteropus bats live in the tropics and subtropics of Asia, Australia, islands off East Africa and some oceanic islands in both the Indian and Pacific Oceans. Other than Malaysia, neutralizing antibodies to NiV has also been identified in *Pteropus* bats in Cambodia, Thailand, India, Bangladesh and Madagascar, with *Pteropus Giganteus* being abundantly found in Bangladesh[63]. The isolation of *Nipah virus* from different species of bats around the world (Table 4) raised the question of whether these bats posses further threat to human and whether the same virus can potentially infect other species of bats in different parts of the world[63,64]. More work needs to be done in trying to determine factors that could potentially influence the transmission and pathogenic potentials of this virus, especially in humans living in close proximity to these bat colonies.

WHAT HAVE WE LEARNT?

The emergence of this new paramyxovirus has cost us not only many lives, but also a great socio-economic burden. The initial positive serology testing for JE had possibly delayed the identification and treatment of NiV. In fact, a proportion of patient's sera that were tested positive were subsequently found to be of false positive[65]. Pig farmers treated with JE vaccines returned to the hospitals, being infected by this fatal virus, which had cost them not only their lives, but also the lives of their family members. This experience has thought us the importance of recognizing new outbreaks and searching for

novel diseases, especially in this globalized world with ease of travelling, and also when there are atypical features to the clinical presentation. In his recounting of the discovery of Nipah virus, Chua concluded *"epidemiology and clinical knowledge opened the mind to the possibility of other virus than JE during the 1998/99 Malaysian viral encephalitis outbreak. Viral culture led to the discovery of the novel infective agent which was not possible with serology and RT-PCR"*[65].

ACKNOWLEDGEMENT

We would like to sincerely thank the Director-General of Health, Malaysia for his permission to publish this paper.

REFERENCES

1. Chua KB, Bellini WJ, Rota PA, Harcourt BH, Tamin A, Lam SK, Ksiazek TG, Rollin PE, Zaki SR, Shieh W, Goldsmith CS, Gubler DJ, Roehrig JT, Eaton B, Gould AR, Olson J, Field H, Daniels P, Ling AE, Peters CJ, Anderson LJ, Mahy BW, Nipah virus: a recently emergent deadly paramyxovirus. Science, 2000. 288: p. 1432-1435.
2. Chua KB, Goh KJ, Wong KT, Kamarulzaman A, Tan PS, Ksiazek TG, Zaki SR, Paul G, Lam SK, Tan CT, Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia. Lancet, 1999. 354: p. 1257-1259.
3. Solomon T, Nguyen MD, Rachel Kneen, Mary Gainsborough, David W Vaughn, Vo Thi Khanh, Japanese Encephalitis. J Neurol Neurosurg Psychiatry, 2000. 68: p. 405-415.
4. Harcourt B, Tamin A, Ksiazek TG, Rollin PE, Anderson LJ, Bellini WJ, Rota PA, Molecular characterisation of Nipah virus, a new emergent paramyxovirus. Virology, 2000. 271: p. 334-339.
5. Tan KS, Tan CT, Goh KJ, Epidemiological aspects of Nipah virus infection. Neurol J Southeast Asia, 1999. 4: p. 77-81.
6. Parashar UD, Sun LM, Ong F, Mounts AW, *et al*, Case-control study of risk factors for human infection with a new zoonotic paramyxovirus, Nipah virus, during 1998-1999 outbreak of severe encephalitis in Malaysia. J Infect Dis, 2000. 181: p. 1755-1759.
7. Paton NI, Leo YS, Zaki SR, *et al*, Outbreak of Nipah-virus infection among abattoir workers in Singapore. Lancet, 1999. 354(9186): p. 1253-1256.
8. Mohd Nor MN, Gan CH Ong BL, Nipah virus infection in pigs in peninsular Malaysia. Rev Sci Tech Off Int Epiz, 2000. 19(1): p. 160-165.
9. Tan CT, Tan KS, Nasocomial transmissibility of Nipah virus. J Infect Dis, 2001. 184(10): p. 1367.
10. Chua KB, Lam SK, Goh KJ, Hooi PS, *et al*, The presence of Nipah virus in respiratory secretions and urine of patients during an outbreak of Nipah virus encephalitis in Malaysia. J Infect Dis 2001. 42: p. 40-43.
11. Tan KS, Ahmad S, Tan CT, *et al*, Patients with asymptomatic Nipah virus infection may have abnormal cerebral MR imaging. Neurol J Southeast Asia, 2000. 5(69-73).
12. Mounts AW, Kaur H, Parashar UD, *et al*, A cohort study of health care workers to assess nasocomial transmissibility of Nipah virus, Malaysia. J Infect Dis, 1999. 183: p. 810-813.
13. Lee KE, Umapathi T, Tan CB, *et al*, Neurological manifestatios of Nipah virus encephalitis, a novel paramyxovirus. Ann Neurol 1999. 46(428-432).
14. Chew MH, Arguin PM, Shay DK, Goh KT, *et al*, Risk factors for Nipah virus infection among abattoir workers in Singapore J Infect Dis, 2000. 181(1760-1763).
15. Hyatt A, Zaki SR, Goldsmith CS, Wise TG, Hengstberger SG, Ultrastructure of Hendra virus and Nipah virus within cultured cells and host animals Microbes Infect, 2001. 3: p. 297-306.
16. ICDDRB outbreaks of encephalitis due to Nipah/Hendra-like viruses, Western Bagladesh. Health and Science Bulletin, 2003. 1(5): p. 1-6.
17. Goh KJ, Tan CT, Chew NK, Tan PSK, *et al*, Clinical features of Nipah Encephalitis among pig farmers in Malaysia. N Engl J Med 2000. 342: p. 1229-1235.
18. Sim BF, Jusoh R, Chang CC, Khalid R, Nipah encephalitis: A report of 18 patients from Kuala Lumpur Hospital. Neurol J Southeast Asia, 2002. 7(13-18).
19. Chong HT, Kunjapan SR, Thayaparan T, *et al*, Nipah encephalitis outbreak in Malaysia, clinical features in patients from Seremban. Neurol J Southeast Asia, 2000. 5(61-67).
20. Chew NK, Goh KJ, Tan CT, Ahmad Sarji S, Wong KT, Electroencephalography in acute Nipah encephalitis. Neurol J Southeast Asia, 1999. 4(45-51).
21. Tan CT, Goh KJ, Wong KT, *et al*, Relapsed and late-onset Nipah encephalitis. Ann Neurol, 2002. 51(703-708).
22. Chong HT, Tan CT, Goh KJ, *et al*, Occupational exposure, age, diabetes mellitus and outcome of acute Nipah encephalitis Neurol J Southeast Asia, 2001. 6(7-11).
23. Wong KT, Shieh WJ, Zaki SR, Tan CT, Nipah virus infection, an emerging paramyxoviral zoonosis Springer Semin Immunopathol, 2002. 24: p. 215-228.
24. Tan CT, Chua KB, Wong KT, Nipah virus - A review ASM Science Journal 2000. 3(1): p. 91-96.
25. Ramasundram V, Tan CT, Chua KB, Chong HT, Goh KJ, *et al*, Kinetics of IgM and IgG seroconversion in Nipah virus infection. Neurol J Southeast Asia, 2000. 5: p. 23-28.
26. Daniels P, Ksiazek T, Eaton B, Laboratory diagnosis of Nipah and Hendra virus infections Microbes Infect, 2001. 3: p. 289-295.
27. Chua KB, Lam SK, Tan CT, *et al*, High mortality in Nipah Encephalitis is associated with the presence of virus in cerebrospinal fluid Ann Neurol, 2000. 48(5): p. 802-805.
28. Ramasundram V, Tan CT, Chong HT, Goh KJ, *et al,* Presence of CSF IgM do not have protective efefct in Nipah Encephalitis Neurol J Southeast Asia, 1999. 4: p. 73-76.
29. Ahmad S, Abdullah BJ, Goh KJ, Tan CT, Wong KT, MR imaging features of Nipah encephalitis. AJR, 2000. 175: p. 437-442.
30. Shoji H, Kida H, Hino H, 1994. J Neuroimaging Magnetic resonance imaging findings in Japanese encephalitis: white matter lesions. 4: p. 206-211.
31. Hansman Whiteman ML, Bowen BC, Donovan Post MJ, Bell MD, Intracranial infection, in Magnetic resonance imaging of the brain and spine, A. SW, Editor. 1996, Lippincott-Raven Philadelphia. p. 707-772.
32. Wong KT, Shieh WJ, *et al,* Pathology and pathogenesis of an emerging paramyxoviral zoonosis. Am J Pathol, 2002. 161(6): p. 2153-2167.
33. Ng BY, Lim CC, Yeoh A, Lee WL, Neuropsychiatric sequelae of Nipah virus encephalitis J Neuropsychiatry Clin Neurosci, 2004. 6(4): p. 500-504.
34. Siva SR, Chong ST, Tan CT, Ten year clincal and serological outcomes of Nipah virus infection Neurol J Southeast Asia, 2009. 14: p. 53-58.
35. Chong HT, Kamarulzaman A, Tan CT, Goh KJ, *et al*, Treatment of acute Nipah encephalitis with Ribavirin Ann Neurol, 2001. 49: p. 810-813.
36. Steffen DL, Xu K, Nikolov DB, Broder CC, Henipavirus mediated menraine fusion, virus entry and targeted therapeutics. Viruses 2012. 4(2): p. 280-309.
37. Mungali BA, Schopman NC, Lambeth LS, Doran TJ, Inhibition of Henipavirus infection by RNA interference. Antiviral Res, 2008. 80(3): p. 324-331.
38. Chong HT, Tan CT, Relapsed and late-onset Nipah encephalitis, a report of three cases. Neurol J Southeast Asia, 2003. 8(109-112).
39. Abdullah S, Chang LY, Rahmat K, Goh KJ, Tan CT, Late-onset Nipah virus encephalitis 11 years after the initial outbreak: A case report. Neurol J Southeast Asia, 2012. 17(1): p. 71-74.
40. Yob JM, Field H, Rashdi AM, Morrisy C, *et al*, Nipah virus infection in bats (order Chiroptera) in Peninsular Malaysia. Emerg Infect Dis, 2001. 7: p. 439-441.
41. Chua KB, et al, Isolation of Nipah virus from Malaysian Island flying-foxes. Microbes Infect, 2002. 4: p. 145-151.
42. Chua KB, Chua BH, Wang CW, Anthropogenic deforestation, El Nino and the emergence of Nipah virus in Malaysia. Malaysian J Pathol, 2002. 24(1): p. 15-21.
43. Chua KB, Nipah virus outbreak in Malaysia. J Clin Virol, 2003. 26(265-275).
44. Hossain MJ, *et al*, Clinical presentation of Nipah virus infection in Bangladesh. Emerg Infect Dis, 2004. 10(12): p. 2082-2087.
45. ICDDRB, Outbreaks of Nipah virus in Rajbari and Manikgonj. Health and Science Bulletin, 2008. 6(1): p. 12-13.
46. Chadha MS, *et al*, Nipah virus-associated encephalitis outbreak, Seliguli, India. Emerg Infect Dis, 2006. 12: p. 235-240.
47. Arankalle VA, Bandyopadhyay BT, Ramdasi AY, Jadi R, Patil DR, Rahman M, et al, Genomic characterisation of Nipah virus, West Bengal, India. Emerg Infect Dis, 2011. 17: p. 907-909.
48. Hsu VP, Hossain MJ, Parashar UD, *et al*, Nipah virus encephalitis re-emergence, Bangladesh Emerg Infect Dis, 2004. 10: p. 2082-2087.

49. Harit AK, Ichpujani RL, Gupta S, *et al,* Nipah/Hendra virus outbreak in Siliguri, West Bengal, India in 2001. Indian J Med Res, 2006. 123(553-560).
50. Harcourt BH, Lowe L, Tamin A, Liu X, Bankamp B, et al, Genetic characterisation of Nipah virus, Bangladesh. Emerg Infect Dis, 2004. 11: p. 1594-1597.
51. Rahman MA, *et al*, Date palm sap linked to Nipah virus outbreak in Bangladesh, 2008. Vector Borne Zoonotic Dis, 2012. 12: p. 65-72.
52. Montgomery JM, *et al*, Risk factors for Nipah virus encephalitis in Bangladesh. Emerg Infect Dis, 2008. 10: p. 1526-1532.
53. Luby SP, Hossain J, Gurley E, *et al*, Recurrent zoonotic transmission of Nipah virus into Humans, Bangladesh, 2001-2007. Emerg Infect Dis, 2009. 15(8): p. 1229-1235.
54. Chang LY, Tan CT, Nipah virus infection in Viral infections of the Nervous System, J. AC, Editor. 2013, Springer Basel: Canada. p. 317-336.
55. Chong HT, Hossain MJ, Tan CT, Difference in epidemiologic and clinical features of Nipah virus encephalitis between Malaysian and Bangladesh outbreaks. Neurol J Southeast Asia, 2008. 13: p. 23-26.
56. Quddus R, *et al* A report of 4 patients with Nipah encephalitis from Rajbari district, Bangladesh in the January 2004 outbreak. Neurol J Southeast Asia, 2004. 9: p. 33-37.
57. Sejvar JJ, Hossain MJ, Saha SK, *et al*, Long-term neurological and functional outcome in Nipah virus infection. Ann Neurol, 2007. 62(3): p. 235-242.
58. O'Sulivan JD, Allworth AM, Paterson DL, *et al,* Fatal encephalitis due to novel paramyxovirus transmitted from horses. Lancet, 1997. 349: p. 93-95.
59. Field H., Hendra virus infection risks. Neurol J Southeast Asia, 2009. 14: p. 77-78.
60. Playford EG, McCall B *et al,* Human Hendra virus encephalitis associated with equine outbreak, Australia 2008. Emerg Infect Dis, 2010. 16(2): p. 219-223.
61. Field H, Young P, *et al,* The natural history of Hendra and Nipah viruses Microbes Infect, 2001. 3: p. 307-314.
62. Wong KT, Robertson B, Ong BB, Chong JW, *et al,* Human Hendra virus infection causes acute and relapsing encephalitis. Neuropathology and Applied Neurobiology, 2009. 35: p. 296-305.
63. Chong HT, Abdullah S, Tan CT, Nipah virus and bats. Neurol J Southeast Asia, 2009. 14: p. 73-76.
64. Lehlé C, Razafitrimo G, *et al*, Henipavirus and Tioman virus antibodies in Pteropodid Bats, Madagascar. Emerg Infect Dis, 2007. 13(1): p. 159-161.
65. Chua KB, The discovery of Nipah Virus: A personal account. Neurol J Southeast Asia, 2004. 9: p. 59-63.