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Volume 11 Number 2

2008

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Cover

"Isles of White in the Sea of Red." A classical Dengue rash during the recovery phase.

Image courtesy of Dr Tan Lian Huat and Prof. Lucy Lum.

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THE MENACE OF VECTOR-BORNE DISEASES

Retneswari M

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The crux of the current health problem is the alarming increase of dengue cases in the country. Dengue fever is endemic in Southeast Asia with Malaysia seeing dengue cases surge since 2003. The Health Minister of Malaysia has reported that the acute increase in dengue cases is worrying and could hit the country's productivity, tourism industry and economy.

Despite the concerted efforts, by government agencies and other related organizations, to educate the public on maintaining clean homes and surroundings and conduct spot checks on suspected mosquito breeding areas, Malaysia seems to see a steady rise of dengue cases each year. Lately, the presentation of cases as dengue encephalitis adds to the burden of the problem. Thus, it is just timely that the article on Dengue has been addressed in this issue.

Currently, in the absence of an effective vaccine and drug, reducing the *Aedes aegypti* mosquito population remains the mainstay for the prevention and control of dengue. Community participation in eliminating breeding sites calls for social marketing in dengue prevention, extensive health education and community outreach. The Malaysian community still appear ignorant towards a clean environment and lack the insight that no amount of government initiatives alone will curb the outbreaks.

The Microbiology Laboratory in the University of Malaya must be commended for advancements in molecular diagnostic tests using two multiplex PCRs allowing detection of the virus from Day 1 of fever. This would allow earlier confirmation of the disease and treatment thus reducing morbidity and mortality.

In view of the unique multiethnic nature of the Malaysian population, the study on genotype variants of the HLA class 1 among the different ethnic groups showing diverse genetic polymorphism would not only reflect the significant role in determining the severity of the infections but also aid to identify ethnically distinct individuals with risk for either disease severity and/protection from severe disease (1).

The presence of four serotypes, problem of immune enhancement and complexity of the disease have

hindered the development of a vaccine. The success described in this paper in eliciting human immune response in humanized mice holds promise that developing a vaccine for dengue may not be too far away (1).

All three initiatives namely, government commitment, scientific advancement, and community participation cum empowerment are inseparable in the combat against dengue infections. Malaysians need to understand that newer vector borne diseases like chikungunya have been introduced into the country. This would add to the burden of morbidity and mortality due to vector-borne diseases bearing a direct impact on the health care costs. Combating one disease is bad enough, what more with a new disease to tackle.

Having just dwelled with the alarming increase of dengue cases in the country, it appears that Malaysia being in the Asian region has another burden of reemerging diseases within the country. The paper entitled 'Malaria among Foreign Workers in Selangor (2), Malaysia' clearly indicates the marked increase of malaria cases in the state of Selangor, a rapidly urbanizing state in the country. The fact that 60% of the malarial cases were contributed by foreign workers, mostly males, active age group as skilled/unskilled workers clearly depicts the apprehension that such an endemic disease could become urban. This may represent only the tip of the iceberg further compounded by the huge number of illegal workers in this country and having skipped medical screening. The high mobility of these workers coming from malaria endemic countries, living or working in densely populated areas and carrying the *plasmodium vivax* infection which causes relapses reflects the impending health issues in hand. To curb the emergence of

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such urban outbreaks and keep the disease at bay, the immigration department and the health ministry have to work closely to control the influx of illegal workers and ensure very stringent medical examinations before arrival, followed by intensive medical surveillance by FOMEMA.

The study on work-related disease or disorders noted a prevalence of 57.8% sleep disturbance among nurses in Melaka General Hospital where shift work was not associated with sleep disturbance as would have been anticipated. Nurses working in intensive unit groups (ICU, CCU, burns unit and high dependency) showed a higher prevalence of sleep disturbance compared to other unit groups which could be explained by their nature of high job demand, maintaining a high state of vigilance, responsibility, stress handling critical conditions and high expectancy while working in these areas (3).

A country is considered to have aged when 7% of its population is elderly. Malaysian is not far from reaching this status as currently it has an ageing population of 6.3% (4).

As rightfully addressed by the author on home falls and home environmental hazards among the elderly (4), falls have come to be recognized as a major threat to the safety, health and independence of elderly persons. The prevalence of home falls among the elderly was found to be 25.1% in this study, posing as a considerable threat to this group (4). Though this study is done in a particular district in Melaka, it should initiate further representative studies to prepare the country towards handling an elderly population who desire good health, independence and an opportunity to lead productive lives, the essential ingredients to a general well being of the elderly.

Apart from the review articles, three case reports on intrahepatic subcapsular haematoma complicating laparoscopic, cholecystectomy (5), intrapulmonary bronchogenic cyst (6) and congenital bilateral aplasia of vas deferens (CBAVD) are presented in this current issue (7).

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DENGUE: BREAKBONE FEVER, HEMORRHAGIA OR SHOCK

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ABSTRACT:

Dengue virus infection has been endemic in Malaysia and in the region for decades and the disease caused by the virus has led to increased morbidity and mortality each year. Dengue is now endemic in more than 110 countries worldwide with two-fifths of the world's population at risk. Dengue fever is a flu-like illness and clinical features vary with the age of the patient. Dengue haemorrhagic fever on the other hand, is characterized by high fever, haemorrhagic phenomena and in severe cases, circulatory failure. There is no specific treatment for dengue fever but careful clinical management frequently saves the lives of these patients. Vaccine development has been difficult as protection against one or two dengue viruses could actually increase the risk of more serious diseases. At present, the only method of preventing dengue is to combat the vector mosquitoes. Dengue is diagnosed by viral isolation and or serology. Current methods, some in-house and others commercial, are far from satisfactory. My laboratory has developed, evaluated and validated tests for dengue that now enable detection on the first day of illness in most cases. At the same time an important aspect of dengue prevention is protection. To this end, we have been investigating the various immune parameters such as T-cells, cytokines and antibody neutralizing activities to show that specific immune responses do occur in a selected Malaysian population which are HLA restricted, cytokine mediated and directed specifically at certain regions of the virus. (*JUMMEC 2008; 11 (2): 39-52*)

KEYWORDS: dengue, dengue haemorrhagic fever, laboratory diagnosis

Introduction and Epidemiology

Dengue and dengue hemorrhagic fever (DHF) are caused by one of four closely related, but antigenically distinct virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) of the genus *Flavivirus* (1). Infection with one of these serotypes does not cross-protect, so persons living in a dengue-endemic area can have up to four dengue infections during their lifetime. Dengue is an urban disease of the tropics and the viruses that cause it are maintained in a cycle that involves humans and *Aedes aegypti*; a domestic, day-biting mosquito that prefers to feed on humans. In some regions, other *Aedes* species such as *Ae. albopictus* and *Ae. polynesiensis* are also involved. Infection with a dengue virus can produce a spectrum of clinical illness which ranges from a non-specific viral syndrome to a severe and fatal hemorrhagic disease. Important risk factors for DHF include the strain and serotype of the virus, age, immune status and genetic predisposition of the patients (2, 3).

Dengue is the most important arthropod-borne viral disease of humans worldwide with an estimated 100

million cases of dengue fever (DF) and 250,000-500,000 cases of DHF in the world, with the average case fatality rate being 5%. Half of the world's population lives in areas at risk of infection and these are popular tourist destinations, too. For the first 5 years of the current decade, the annual average number of cases was 925,896, almost double the figure for 1990-1999 (479,848 cases) (Figure 1). All four dengue viruses are now circulating in Asia, Africa and the Americas. It is a scene that did not prevail two or three decades ago. Perhaps the only comforting news is that reported case-fatality rates have been lower in recent years than in the decades before 2000 (4). The earliest record of dengue in Malaysia was published by Skae in 1902 of an outbreak in Penang (5). Subsequently in the years 1904, 1932 and

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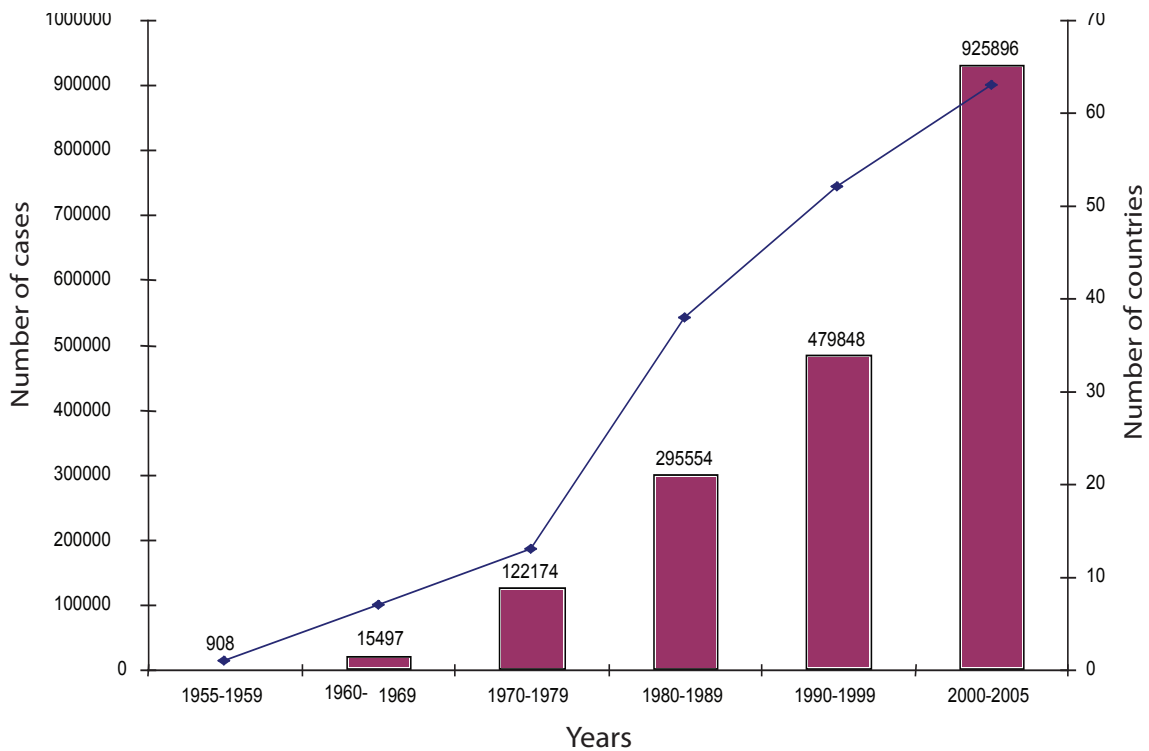


Figure 1: Average number of cases of dengue or severe dengue reported to WHO, and average annual number of countries reporting dengue from 1955 to 2005

1933, more reports were made of dengue outbreaks in various parts of Peninsular Malaysia, largely in ports and large cities (6). Dengue virus was first isolated in 1950 by Smith (7) and the first laboratory confirmation was carried out by the Institute of Medical Research in 1953. Since 1953, pockets of epidemics have occurred in urban areas of Peninsular Malaysia. In Malaysia, dengue was made a notifiable disease in April 1971 (8). From then on, increased numbers were noted and dengue fever, dengue hemorrhagic and dengue shock syndrome DF/DHF/DSS have become major public health problems. Between 1973 and 1987, the mean incidence of DF was noted to be 2-11 per 100,000 while that of DHF was 0.5-8 per 100,000. The major ethnic group affected were the Chinese with the major age group being 10-19 years. A seasonal pattern was noted with cases increasing following the rainy seasons. Most cases occurred in urban areas. Reasons cited for the various outbreaks, as well as for the increase in cases, were: the exodus of susceptibles from non-endemic to endemic areas, rapid urbanization, a disturbance in human ecology, creation of slums and squatters and living conditions that perpetuated vector breeding (9, 10). Figure 2 depicts the difference in clinical versus serologically confirmed dengue cases from 1973 (11). As can be

seen, the number of cases confirmed by serology is 11,930 as compared to the number of cases reported which is 44,189 (as of November 2007—www.moh.gov.my). The DHF case fatality rate is 3.6% while that for total dengue is 0.26%.

The reasons for this dramatic global emergence of dengue/DHF as a major public health problem are complex and not well understood. However, several important factors have been identified: ineffective mosquito control, which is virtually nonexistent in most dengue-endemic countries, and global demographic changes such as uncontrolled urbanization and concurrent population growth resulting in substandard housing and inadequate water, sewer, and waste management systems. All of these increase *Ae. aegypti* population densities, thus facilitating transmission of *Ae. aegypti*-borne disease (12). Consumer goods packaged in non-biodegradable plastic and automobile tyres, discarded into the environment, provide ideal larval habitats that lead to increased population densities of the principal mosquito vector, *Ae. aegypti*. Finally, increased travel by airplane has helped transport dengue viruses between population centers of the tropics, resulting in a constant exchange of dengue viruses and other pathogens (13).

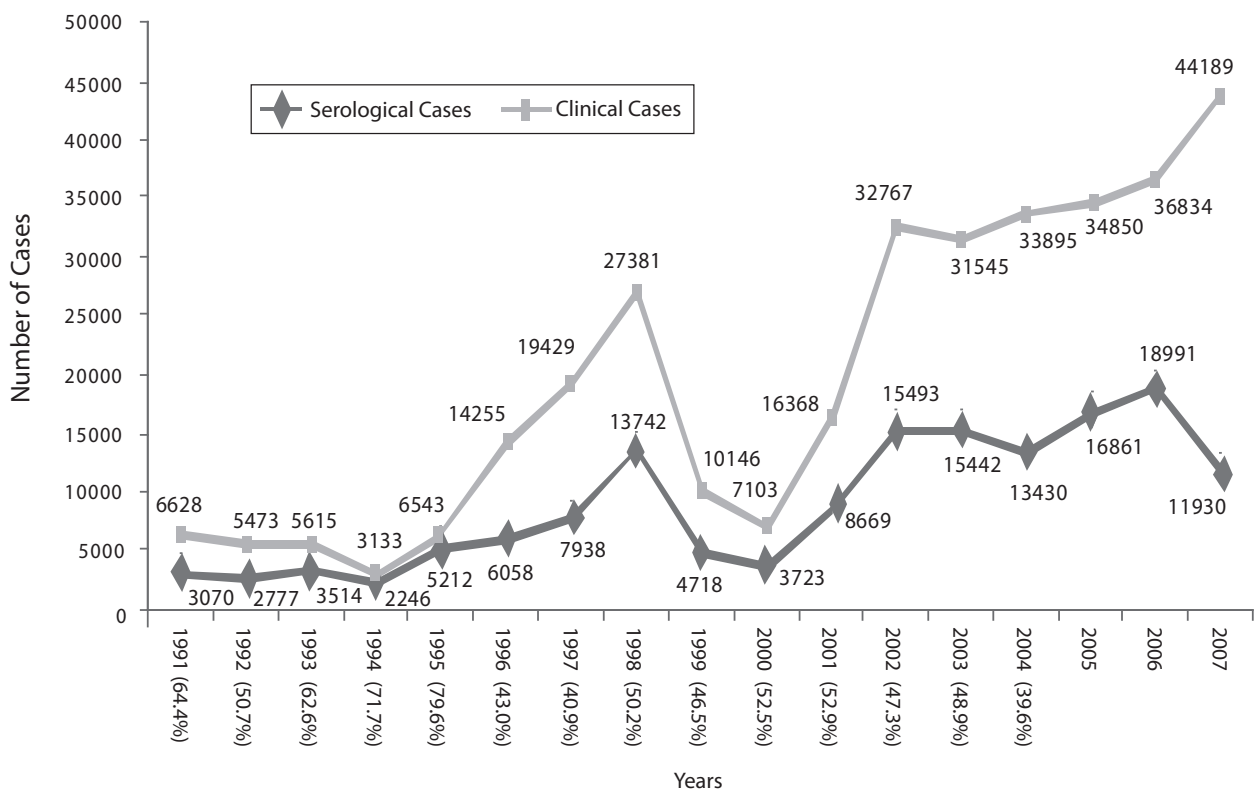


Figure 2: Distribution of Clinical and Serologically Positive Cases of Dengue in Malaysia: Source: Vector Borne Disease Division, MOH

Clinical Disease

DF may be asymptomatic or lead to a range of clinical presentations even death. Clinically, it can be confused with influenza, rubella, malaria, chikungunya, leptospirosis or typhoid. The incubation period is four to seven days (range of 3-14). The inoculation of the dengue virus to the human host starts with the bite of the infected female mosquito vector that introduces saliva containing the dengue virus into the bite site which then spreads to the possible target tissues such as lymph nodes, spleen, bone marrow and liver. The incubation period ends with an acute onset of fever, which might recur after five to eight days. During the febrile phase of the viral infection, viremia occurs and lasts for three to five days. Together with the occurrence of viremia and fever, prodromal syndromes such as malaise, chills, and headache may develop. These are followed by muscle, back, retro-orbital and joint pain. The febrile painful period of DF lasts five to seven days, and may leave the patient feeling tired for several more days. The vast majority of infections are asymptomatic or minimally symptomatic. Leukopenia and mild thrombocytopenia are frequently seen as well as hemorrhagic manifestations such as petechial rash,

epistaxis, gum bleeding, gastrointestinal bleeding, microscopic hematuria and hypermenorrhea. The more severe manifestation is DHF. Once primarily a children’s disease, it is now seen in all age groups (14, 15, 16). Most cases occur in individuals with prior dengue exposure. DHF has been classified into 4 grades according to severity of shock and bleeding. It is defined as an acute febrile illness, with minor or major bleeding, thrombocytopenia, plasma leakage, pleural or other effusions or hypoalbuminemia/proteinemia. Pathophysiologically, plasma leakage differentiates DF and DHF. A positive tourniquet, collection of exudates at pleural and abdominal cavities, a progressively decreasing platelet count and a rising hematocrit (signifying abnormal capillary permeability) indicate increased probability of impending shock (17). Once shock has set in, the fatality rate may be as high as 12-44%. Liver damage, cardiomyopathy, encephalopathy, neurological manifestations such as altered consciousness, convulsions and coma have also been described (18). The definition of severe dengue is currently under review. An immunological basis for endothelial permeability and vascular leakage is widely accepted, but definitive data to explain the mechanism is still lacking (19).

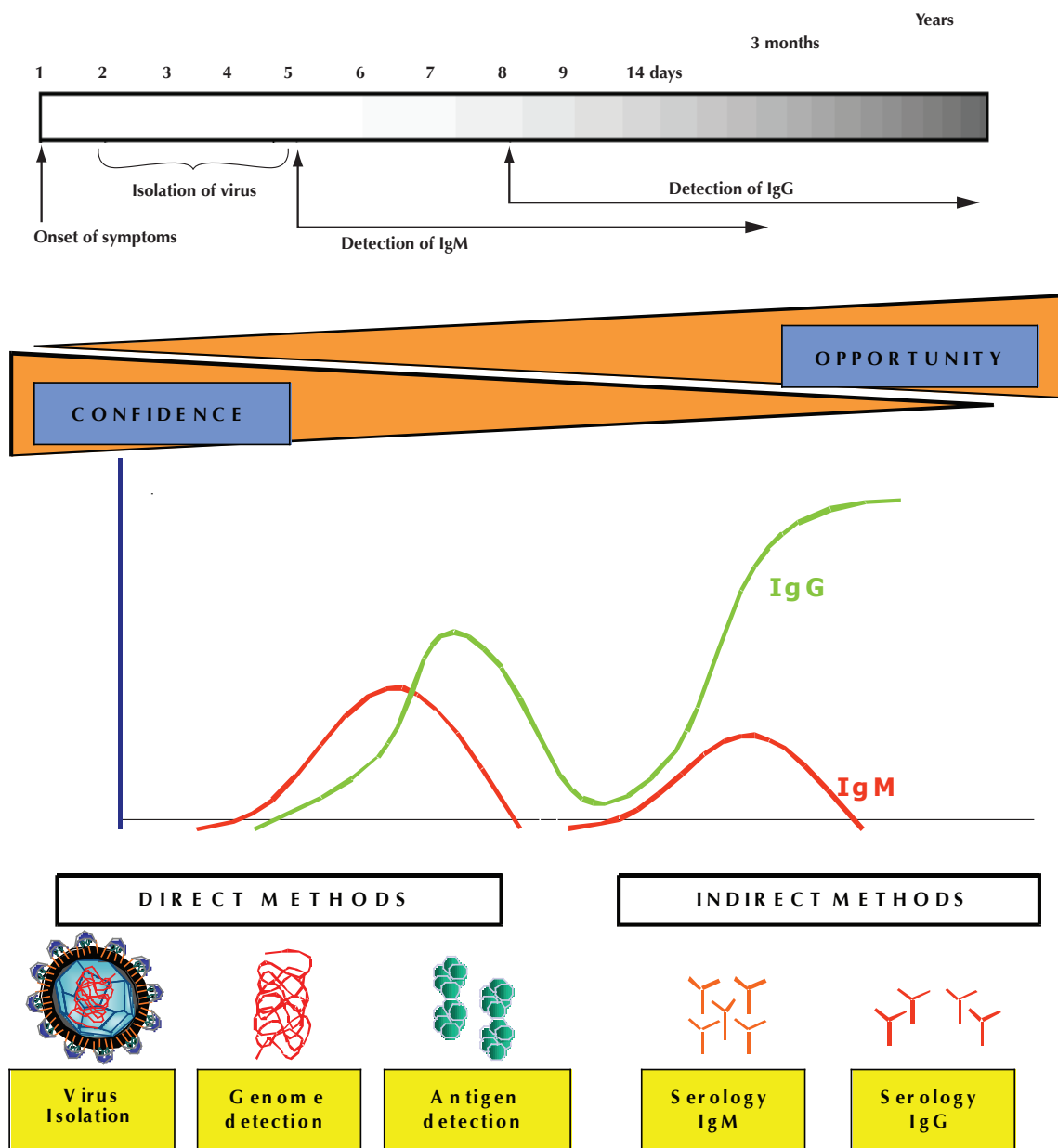


Figure 3: Suitability of dengue diagnostic assays during the course of the disease

Laboratory Diagnosis

Dengue viruses belong to the family Flaviviridae that has more than 70 viruses that cross-react in serological tests as they share group antigens, thus complicating diagnosis. Laboratory diagnosis depends on virus isolation and serologic tests (20). Circulating virus remains detectable in the blood during the febrile period after which they are rapidly cleared with the appearance of specific antibody. Virus isolation is carried out using mosquito cell lines which is then detected using an indirect fluorescent antibody test. The use of polymerase chain reaction (PCR) may

shorten the time of detection (21), but this test is still experimental and the few commercial products available have not been validated. Serological diagnosis depends on the presence of IgM antibody or a rise in IgG antibody titer in paired acute and convalescent phase sera. More than 90% of patients are IgM positive by the fourth day of illness, but the IgM antibody may be due to an infection up to 3 months earlier (22, 23). Commercial kits for the measurement of antibodies include the ELISA kits, a dipstick and a rapid dot-blot assays. These kits do not require specialized training, but their sensitivity and specificity vary. The choice of a test therefore,

depends on the availability of facilities, human resources and also time of sampling. Figure 3 shows the comparison of tests according to the assessability of the tests and their confidence. However for a diagnosis of "confirmed" dengue, the dengue virus should be identified by isolation or there could be a four-fold rise in antibody titer. Recent innovations in the development of dengue diagnostics include NS1 ELISAs (24), chemiluminescent optical biosensors for the detection of virions, natural cytotoxicity receptor immunoglobulins, recombinant proteins, microsphere based immunoassays and lab on a CD assays (25).

Pathogenesis

The risk of DHF is higher when two or more virus isotopes are circulating simultaneously. Also the presence of dengue antibodies acquired either actively by prior infection or passively via maternal antibodies in milk or *in utero* is a contributory factor. Thus, antibody actually enhances viral infectivity at non-neutralizing concentrations. During the primary infection, dengue virus attaches to the target cell via a highly sulphated glycosaminoglycan heparan sulfate. This is followed by the penetration of virus into the target cell, mediated by another secondary high affinity receptor. The identity of the high affinity receptor in dengue virus infection has yet to be resolved and further studies are required as the list of proposed and known receptors including DC-SIGN and other unidentified proteins are tremendous. In secondary infection of dengue virus, it is believed that apart from the typical infection route as demonstrated in the primary infection, dengue virus mediates its entry into target cells via Fc_v-receptors. The hypothesis known as antibody-dependant enhancement (ADE) is a process in which the virus complexed with specific antibody is taken up by mononuclear cells via a FcR mediated endocytosis (19). This mode of entry takes advantage of the host's immune system and has led to the extensive infection of the cells possessing Fc_vR such as monocytes, dendritic cells and B-lymphocytes. The infection of these cells results in release of pro-inflammatory chemokines that are implicated in the development of plasma leakages in DHF and dengue shock syndrome (DSS). Chemical mediators such as interleukin-1, interleukin-6, tumor necrosis factor and platelet activating factor from infected monocytes, gamma interferon, interleukin-2, interleukin-4, interleukin-5,

interleukin-6, and interleukin-10 produced by T-lymphocytes are suspected of playing essential roles in the vascular endothelial damage of the disease, the development of severe plasma leakage, and the hemorrhagic manifestations. But this hypothesis is not unanimous as there is a small but consistent percentage of DHF/DSS cases that are due to primary infections (26), that is, no pre-existing antibody in these individuals. Epidemiological and laboratory studies suggest also that virus strain, individual susceptibility and good nutritional status may also be important as risk factors for DHF. Therefore to ensure that a vaccine gives immunity and does not enhance immunopathology, it must give protection to all the four serotypes, give high levels of immunity and give life-long immunity. Many approaches are being taken in vaccine development such as recombinant subunit vaccine, live recombinant vaccines and live attenuated vaccines. The lack of understanding of the immunology and immunopathology of the disease and of a suitable animal model as well as the inherent dangers of using live vaccines, have made vaccine development slow. Currently, candidate attenuated vaccines are being evaluated in various parts of the world.

Prevention and Control of Dengue Infections

Prevention and control currently depends on controlling the mosquito vector, *Ae. aegypti*, in and around the home where most transmission occurs. Space sprays with insecticides to kill adult mosquitoes are not usually effective as ULV-aerosols have little impact on the adult female *Ae. aegypti* and no impact on the immature stages. The most effective way is larval source reduction that is, eliminating or cleaning water-holding containers that serve as the larval habitats in the domestic environment. The feeding habit of *Ae. aegypti*, which involves a typical pattern of high frequency-short period blood meals taken from several victims in every meal, has increased the odds for the dengue virus to spread with high efficacy. Moreover, *Ae. aegypti* prefers to live and feed in indoor domestic environment. The period for the infected mosquito to become infectious is approximately eight to twelve days after an infected blood meal. In addition to the infected female mosquito, transovarial transmission has been demonstrated in various studies (27). Studies have shown that 2.35% to 40.00% of mosquito larvae were found to be positive for dengue virus. The task might seem a simple matter of treatment and elimination of

infested containers but they are hard to sustain as they are labour intensive, requiring discipline, diligence and are intrusive. In recent years, there has been an increased focus in the role of the community in mosquito control (13). Community participation requires extensive social marketing of dengue prevention, with health education and community outreach. Government participation in the form of elimination of mosquito production sites on a larger scale and some through limited use of larvicides and adulticides are essential. In addition, active laboratory based surveillance that can provide early warning for epidemic activity is essential. Health officials should know at any point in time where dengue transmission is occurring, what serotypes are circulating and the severity of illness associated with dengue infection. Another equally important component of a sustainable prevention programme is the education of the medical community on clinical diagnosis and management of DHF cases so as to help understand the pathophysiological changes that occur in DHF and hence, keep fatalities low. Furthermore, greater research efforts looking into more effective disease prevention strategies such as new mosquito control technology, the changing epidemiology, disease pathogenesis and dengue vaccines are essential. Lastly, community-integrated programmes would certainly be useful not only for keeping dengue

epidemics at bay but also all other infectious diseases transmitted similarly and with an endemic nature.

Dengue Vaccines and Antivirals

To date, no vaccine has yet been licensed and no candidate vaccine has progressed beyond phase II clinical trials. It generally takes 15 years for candidate vaccines to advance from discovery to licensing. The presence of four serotypes, the problem of immune enhancement and the complexity of the disease are some of the factors that have impeded the development of dengue vaccine. The theoretical danger of a dengue vaccine that causes a severe disease exists unless solid immunity is afforded equally to all the serotypes. Another point to note is that the correlates of protection to dengue are poorly understood and hence, intensive studies are essential to demonstrate that any candidate vaccine induces only a protective response.

To add to this problem, the lack of a suitable animal model has hampered assessment of any developing vaccines. As such, clinical trials are important in terms of the information they provide on immunity and reactogenicity while long term evaluation is required to demonstrate lack of evidence of immune enhancement. Currently a number of vaccines are in clinical trials (Table 1): live attenuated tetravalent

Table 1: Types of Dengue vaccines being developed and their current status; Adapted from reference 55

Type of Vaccine	Key Features	Institute	Current Status
Live Attenuated	Serial passage of DEN 1,2 & 4 in PDK* cells	Mahidol University	Phase 2 Clinical Trials
	DEN-3 in vero cells and final passage in FRhL#	Aventis Pasteur, France	
Live Attenuated	DEN 1-4 Serial passage in PDK cells	Walter Reed Institute/Glaxo SmithKline, Belgium	Phase 2 Clinical Trials-Children
Chimeric	DEN 1-4 prM and E genes inserted into non structural portion of YF+ 17D vaccine	St. Louis University Acambis Cambridge Aventis Pasteur, France	Phase 2 Clinical Trials
Chimeric	DEN 1-3 prM and E genes inserted into attenuated DEN-4 backbone	NIH, USA	Volunteer Trials
Chimeric	DEN 2-4 prM and E genes inserted into attenuated DEN-1 backbone	NIH, USA	Phase 1 Trials
Chimeric	DEN 1-4 prM and E genes inserted into attenuated DEN-2	CDC, USA	In vivo (mouse)

*PDK – primary dog kidney cell line

#FRhL – fetal rhesus monkey lung cells

+YF – Yellow Fever

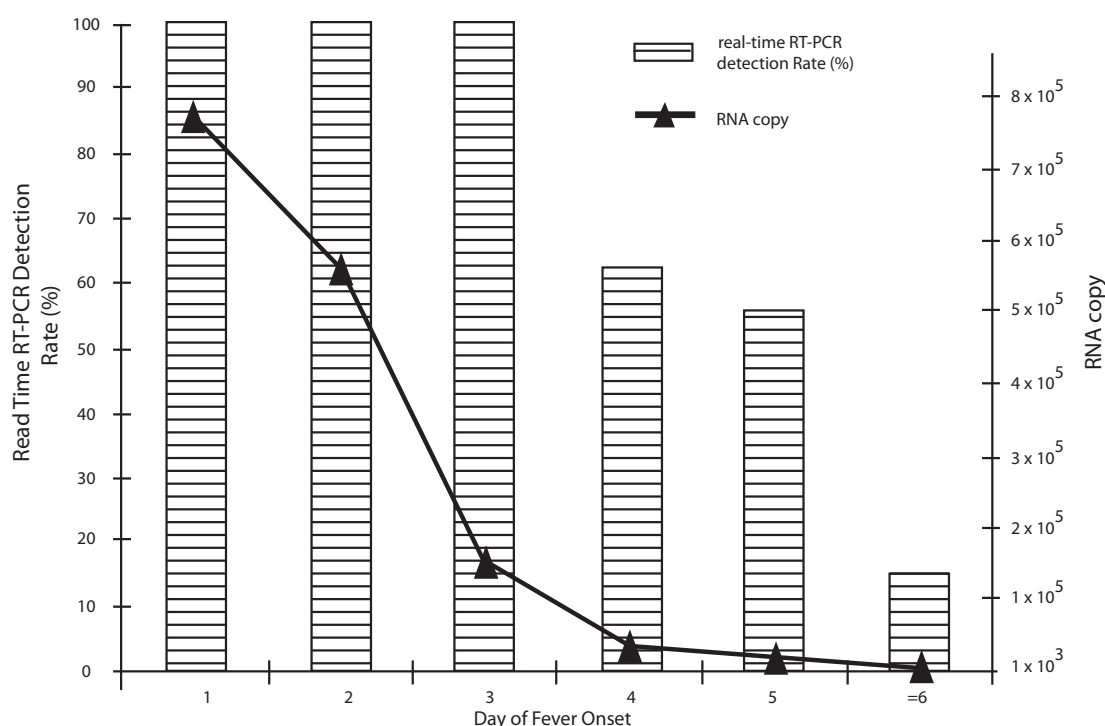


Figure 4 : Comparison between viral detection rate, day of fever onset and RNA copies

candidates utilizing classical virological techniques which are in phase II trials and recombinant vaccines (Chimerivax) that use the 17DYF vaccine as a backbone, which are also in phase II clinical trials (28). Candidate recombinants using DEN-4 as the backbone are also in phase I and II clinical trials. Alternative approaches such as DNA vaccines have demonstrated immunity in non-human primates and are now in phase I clinical trials. The most advance subunit vaccine is based on the recombinant E and NS1 produced in a *Drosophila* expression system. This, however, is currently being tested in non-human primates. A major challenge exists in that the criteria that are to be used to evaluate candidate vaccines in exposed populations as the definition of protection to dengue are not yet scientifically demonstrated. On a related note, there have also been developments in antiviral drugs and similar constraints do exist. There have been some exciting developments and drugs have been designed specifically targeting the NS3 and NS5 protein (29). Apart from these, natural products from plants have also been shown to be effective, less cytotoxic and are said to be cheaper (30).

Research

My advent with dengue virus began with the demonstration of a cellular immune response to

dengue in mice and the presence of H-2 restricted cytotoxic activity to dengue virus infections in mice (1982-1986 – PhD thesis, 31, 32, 33, 34, 35). Following that, I then went on to develop monoclonal antibodies to dengue virus (1987-1991, as a co-researcher), studied the epidemiology of dengue in Malaysia (1985-1990, 36, 37), and also investigated possible role of cytokines in dengue infections (1996-1997, 38). To address some of the questions raised above, my laboratory embarked on determining what proteins are produced in response to this virus both in the cells and in the plasma. This is with the aim of identifying early and newer biomarkers that could then be potential diagnostic reagents. Diagnostic tools were developed such as Real Time PCR assays and current tools, such as commercial serological kits and antigen assays, were evaluated. I also hoped to develop a point of care test with reasonable sensitivity and specificity for use in the future. At the same time, I also began investigations into the mechanisms of protection and began investigating HLA associations and the cellular immune response specifically to the T cells and attempted to determine the viral epitopes selected by the host in its development of specific T cells as these are essential correlates of immunity for any intracellular organism. These studies would also have an impact on vaccine assessment and development. To further address newer syndromes and

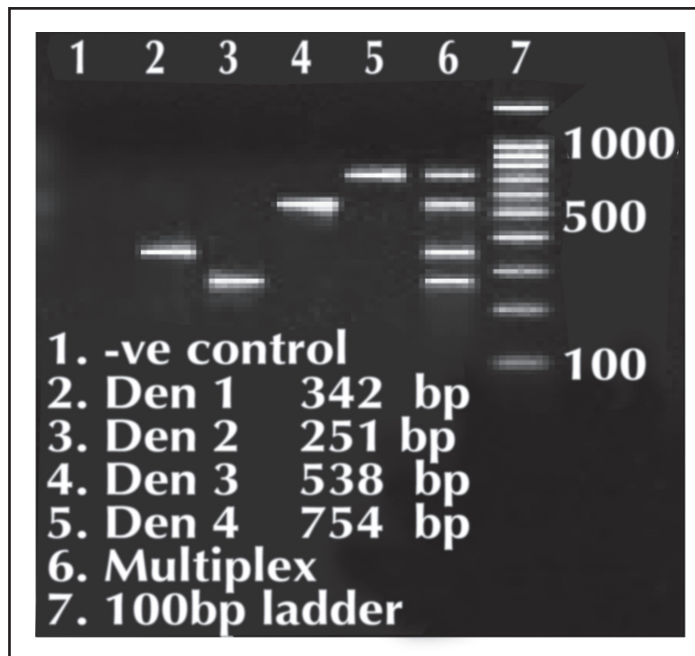
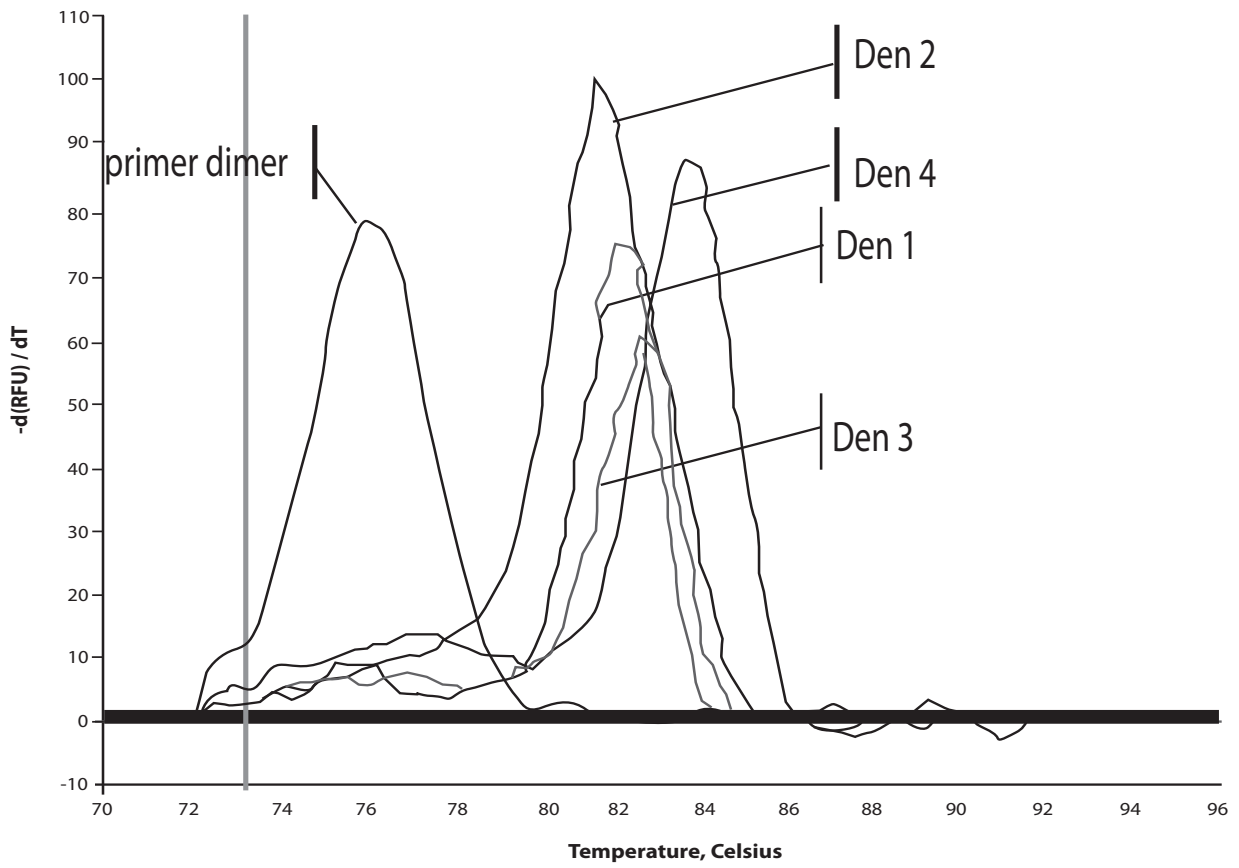


Figure 5: Multiplex RT-PCR analysis by Standard PCR and Real Time PCR

possible changes in the virus itself, sequencing of the viruses isolated in the region was carried out from time to time.

Development of Molecular Diagnostic Tests

The genome of the dengue virus encodes for three structural proteins (C, preM and E) and seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5). Among the structural proteins, the E protein serves as a hemagglutinin and surface molecule. It possesses the strain determinant of the virus and is the main target of the humoral immune response. The non-structural protein 1 (NS1) is said to serve as a viral genome replicating factor associated with the negative strand of the viral RNA and it is also secreted. The function of the hydrophobic NS2a, NS4a and NS4b are still obscure, but they have been postulated to serve as anchors for viral replication complex or to inhibit the interferon response of host's cell (NS4b). NS3 together with NS2b form a serine-protease to cleave the precursor protein formed in the primary translation process. Finally, the NS5 protein serves as the RNA-dependent RNA polymerase and methyltransferase in the replication of the virus (39). With this knowledge two multiplex PCRs (Standard and Real Time) were developed to two different regions of the virus (preM-Capsid and NS5) in order to further improve diagnostics of dengue infections. Both assays have shown 100% specificity and are more than 98% sensitive, and they are able to detect/amplify virus from Day 1 of onset of fever (Figure 4 and 5). Viral antigens can be detected up to Day 7 of fever and even in the presence of high titres of circulating

Table 2: Sensitivity, Specificity and Efficiency of NS1 ELISAs as compared to RT-PCR

Assay	Sensitivity (%)	Specificity (%)	Efficiency (%)
RT-PCR	97	100	98
Biorad NS1	87	100	89
Panbio NS1	84	100	73

antibodies (40, 41). The laboratory has also evaluated two commercially available ELISA kits for the detection of NS1 and the results (Table 2) imply that it is a useful assay in the first four days of fever, but its detection rate decreases with increasing levels of antibody (24). To enhance diagnostics for dengue virus infections, we utilized two-dimensional electrophoresis, mass spectrometry and Western blot to determine the differential expression levels of proteins in peripheral blood mononuclear cells (PBMC) of patients with DF and DHF in order to identify both viral factors and host factors that may be used as either diagnostic reagents or as early diagnostic markers for disease severity. Eight proteins were identified that were up-regulated two-fold or more in patients compared to healthy controls of which at least three proteins—aldolase, thioredoxin peroxidase and alpha tubulin—are related to dengue infection. Both thioredoxin peroxidase and alpha tubulin are over-expressed in DHF patients compared to DF patients while aldolase was expressed at a higher level in DF patients as seen in Table 3 (42, 43). We are currently developing methods that will be able to detect both antigens and antibodies simultaneously so that the disease can then be diagnosed irregardless of the day of onset of fever.

Table 3: MALDI-TOF identification of differentially expressed proteins in DF and DHF patients

Proteins ID	Experimental MW/pI	Sequence Coverage	DF (% Vol)	DHF (%Vol)	Image Master 2-D Elite Software Analysis
Alpha 1 Antitrypsin	44.2 kD/5.4	16.2	0.357	0.647	2 fold in DHF vs DF
Dengue NS3	79 kD/4.5	15.7	0.235	0.502	2 fold in DHF vs DF
Dengue NS1	50 kD/6.5	17.3	0.367	0.698	2 fold in DHF vs DF
Aldolase	39 kD/8.7	25.3	0.461	0.234	2 fold in DF vs DHF
Alpha tubulin	48 kD/5.0	14.2	0.138	0.458	3 fold in DHF vs DF
Thioredoxin	22 kD/5.7	23.2	0.288	1.428	6 fold in DHF vs DF

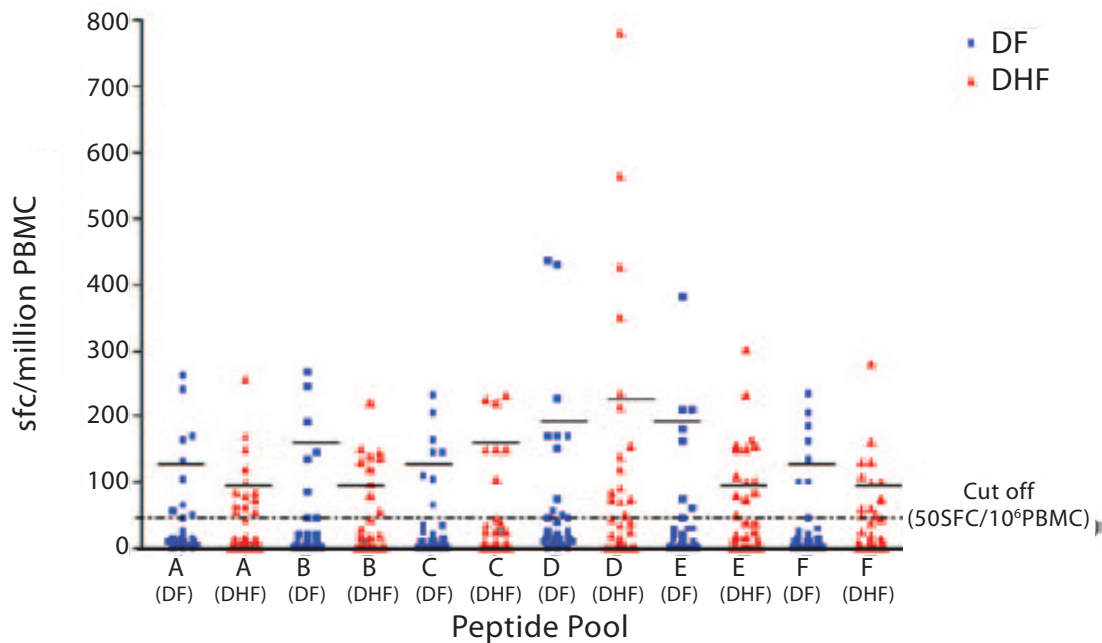


Figure 6: Spot-forming cells per million PBMC in DF versus DHF patients in response to peptide pools from various regions of the virus
 Levels of SFC in DF and DHF patients in response to peptide pools containing peptides from structural (AnC, C, PrM and E) and nonstructural (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) regions. Pool A: AnC, C, PrM and E; Pool B: E, and NS1; Pool C: NS1, NS2A; Pool D: NS2B and NS3; Pool E: NS3, NS4A and NS4B; and Pool F: NS5. The means for each peptide pool is indicated by a bar. Responses were considered significant when a minimum of 50 SFCs per 10⁶ PBMC were present per well, representing at least twice the number of SFCs in negative controls

T Cell Responses in Dengue Fever and Dengue Hemorrhagic Fever Patients in Malaysia

The magnitude of T cell responses and the involvement of cytokines and chemokines have been reported to correlate with dengue disease severity. In our study, 60 Malaysian adults with dengue viral infections were investigated for their dengue virus-specific T cell responses to 32 peptides antigens from the structural and non-structural regions from dengue virus isolate. Seventeen different individual peptides from C, E, NS2B, NS3, NS4A, NS4B and NS5 were found to evoke positive gamma interferon responses by using an in-house developed enzyme-linked immunospot (ELISPOT) assay in 13 patients with DF and DHF with the range of 50-700 SFU/10⁶ PBMC. NS3 and predominantly NS3₄₂₂₋₄₃₁ peptide were found to be important T-cell targets (Figure 6, 44). The ELISPOT analysis also revealed high frequencies of T cells that recognize both serotype-specific and cross-reactive dengue virus antigens in patients with DHF. The results strongly support the presence of high frequencies of activated CD8⁺ T cell in patients with DHF, with the highest reactivity being targeted to NS3 region. These findings indicate a need to identify as many dengue-specific T-cell peptides as possible in a larger number of dengue patients with multiple HLA backgrounds to better understand how the immune system responds

to dengue virus and contributes to pathogenesis. Preliminary data on the level of cytokines indicate a probable role for IP-10, PDGF and IL-9 as these cytokines were elevated in DHF as compared to DF patients. Currently, an attempt is being made to further define the role of pro-inflammatory cytokines in vascular leakage and to determine that which leads to endothelial leakage.

HLA-A and -B allele associations with DF and DHF patients in Malaysia.

It has been proposed that HLA alleles play a significant role in the severity of dengue viral infections. The higher frequency of several HLA alleles in dengue infected patients versus control subjects would suggest that these alleles are associated with susceptibility or protection against this viral infection. In this study, we have investigated genotype variants of HLA Class 1 (-A and -B) of 50 dengue infected Malay, Chinese and Indian patients in Malaysia using polymerase chain reaction-sequence specific (PCR-SSP) techniques. The frequency of alleles A*24, B*07 and B*40 were significantly increased in dengue infected patients (*Pc* < .05) regardless of ethnicity, suggesting that patients with these alleles might be at increased risk to dengue viral infection. Significantly higher frequency of allele B*13 in dengue infected

Malay patients suggests a probable role in susceptibility of dengue infection in this group. This finding on diverse genetic polymorphisms could serve as a prognostic tool to identify ethnically distinct individuals with risk for either disease severity and/or protection from severe disease. Further investigations are being conducted to show if this association is with a specific subtype.

Sequencing of dengue viruses isolated in the region

Preliminary study on dengue seroepidemiology in Brunei showed that from 2005 to 2006, dengue 2 was the predominant serotype followed by dengue 1. This study is the first to report the isolation and typing of dengue viruses isolated in Brunei and the extent of dengue infection in that country (45). Limited sequence analysis of the E/NS1 gene at both amino acid and nucleotide level revealed that the Brunei DEN-2 were mainly clustered in the genotype I together with the Malaysian, Indonesian, Sri Lankan and Myanmar isolates (46). Five genotypes were identified and the phylogenetic analysis of the full-length sequences places these DEN-2 isolates very near to the Indonesian and Australian strains. Nucleotide sequences showed changes occurred at 51 positions (21.2%) while the amino acid homology ranged from 91% to 100% (47). Full sequence of two isolates were recently completed. A hundred Malaysian dengue viruses (1-4) isolated from the years 1995-2005 were sequenced and compared. This work is currently ongoing.

Dengue specific receptors

It is still unclear what receptors the dengue virus recognizes on the cell surface. Many cell types express heparan sulfate, but a more specific protein receptor is thought to be required to target dengue virus to permissive cell types. To date, glycans, DC-SIGN, GAGs, CD-14 associated protein and many other potential proteins have been suggested, but not confirmed, as possible modes of entry for this virus (48, 49). The primary viral receptor and the *in vivo* target cell needs to be determined unambiguously. With the advent of a modern day tool like RNA interference (RNAi), it is possible to home in on this elusive protein(s). RNAi is an evolutionarily conserved mechanism that permits the selective post-transcriptional down regulation of target genes in eukaryotic cells. As such, RNAi has enormous potential not only as an invaluable tool in biological research and drug development but also as

a possible approach to the *in vivo* inactivation of gene products. We have designed siRNAs to silence potential targets in human cells to investigate if a putative receptor exists or if this virus utilizes something else for entry.

Protection against dengue – what determines this?

With the knowledge that pre-existing antibodies put us at risk of severe dengue infections, the question then arises as to what constitutes protection against dengue. A very large number of subclinical dengue infections are said to have occurred and this group is not accounted for in annual figures of dengue infections. These individuals have innate mechanisms of immunity that protect them. With this in mind, we have begun, firstly, to develop and establish assays that enable rapid detection of these antibodies using flow cytometry. This tool is being used to not only determine levels of neutralizing antibodies, but also to titrate the virus within 48 hours, a procedure that normally takes between seven to ten days. At the same time, the genetics of protection in this subclinically infected group will be determined. Another correlate of protection is the production of siRNAs by the host. To this end, the quaternization of siRNAs to the virus is being attempted to determine the possibility of this tool in alleviating disease pathology. However, it is also imperative to monitor untoward off-target effects as well. This technology is also especially well-suited in treating viral infections, and numerous examples have now illustrated that a wide range of viruses can be inhibited with RNAi, both *in vitro* and *in vivo*.

Primary Dengue Animal Model of human disease

Dengue viral pathogenesis and vaccine studies are hampered by the lack of an ideal animal model mimicking human disease and eliciting an adaptive human immune response. Although currently available animal models have been very useful in dissecting some key aspects of disease pathogenesis, a major limitation with these models is the lack of a human immune response. In this study, we sought to overcome this difficulty by utilizing a novel mouse model that permits multi-lineage human hematopoiesis and immune responses following transplantation with human blood forming stem cells. To generate immunocompetent humanized mice, neonatal RAG2^{-/-}γc^{-/-} mice were xenografted with human CD34⁺ hematopoietic stem

cells, resulting in *de novo* development of major functional cells of the human adaptive immune system. To evaluate susceptibility to dengue viral infection, humanized mice were challenged with DEN-2 serotype. Viremia lasting up to three weeks was detected in infected mice with viral titers reaching up to $10^{6.3}$ RNA copies/ml. Fever characteristics of dengue were also noted in infected mice. The presence of human anti-dengue antibodies was evaluated using an antibody capture ELISA. Anti-dengue IgM was first detected by two weeks post-infection followed by IgG at six weeks. Sera from some of the infected mice were also found to be capable of dengue virus neutralization. Infected mouse sera showed reactivity with the viral envelope and capsid proteins in immunoprecipitation assays. These results (as summarized in Figure 7) demonstrate for the first time that humanized mice are capable of dengue viral primary human immune responses, thus paving the way for new dengue immunopathogenesis and vaccine studies (50). This study was carried out during my sabbatical at the Colorado State University in early 2006.

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MALARIA AMONG FOREIGN WORKERS IN SELANGOR, MALAYSIA

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ABSTRACT:

The state of Selangor, Malaysia, is facing a significant rise in the number of malaria cases with the incidence varying from 20 to 90 per 100,000 persons in a population. A study was carried out to describe the distribution of malaria cases in relation to the growing number of foreign workers in Selangor. Data were reviewed using the return forms "PBV (M) 101", a summary of malaria cases in Selangor for 2006 and Annual Reports of Vector-Borne Disease Control Unit, Selangor State Department for 2001- 2005. The malaria cases in Selangor varied between 172 cases in 2001 and 90 cases in 2006. Most of the cases were contributed by foreign workers, who were predominantly male of economically active age group and came from malaria endemic countries. Most of these cases were concentrated in the urban districts. Malaria is still endemic in Selangor. Malarial infection has the potential of contributing to an urban outbreak of malaria. (*JUMMEC 2008; 11 (2):53-58*)

KEYWORDS: *malaria, incidence, foreign workers, imported, outbreak*

Introduction

Malaria is one of the re-emerging diseases in Selangor, Malaysia, and the incidence is increasing due to of several reasons such as anti-malarial drug resistance, insecticide resistance and international travel (1,2). Currently, malaria is still a public health problem in Malaysia (2, 3, 4, 5). Since the implementation of the Malaria Eradication Program in 1967 that was later converted to the Vector-Borne Disease Control Program in the 1980's, the number of malaria cases has declined significantly. Within the past 10 years, the incidence rate has declined significantly from 300/100,000 population in 1994 to 24.1/100,000 population in the year 2004 (3,4) (Figure 1).

Malaria cases were commonly reported in the rural areas (86.5%) and among the Orang Asli (33.1%) (4). However, new sources of contracting malaria have been introduced recently. The sources of infection in these areas were noted to be from foreign workers (2, 5, 6). Malaysia is highly dependent on foreign unskilled and semiskilled labourers. There were 1.7 million legal migrant workers in Malaysia in 2005 (7). Of concern, most of these foreigners came from malaria endemic countries (2, 3).

WHO reported that there were over 2 million cases of malaria in India, over 200,000 cases in Vietnam and over 100,000 cases in Myanmar and Pakistan in 1992 (2). The Ministry of Health of Indonesia reported that there were over 3 million clinical malaria cases in 1998 (8). These migrants may carry with them microbial pathogens. In addition, their cultural traditions and behavioural patterns promote disease transmission, as does living in unhealthy and crowded slum conditions (2, 6).

The incidence of malarial infection among foreign workers has been steadily increasing. Several focal outbreaks were reported among foreign workers who worked in the construction sites in the urban areas (4, 6). The total number of cases among immigrants has increased from 1,627 cases in 2003 to 2,009 cases in 2004. Some 74.2% of these cases were from

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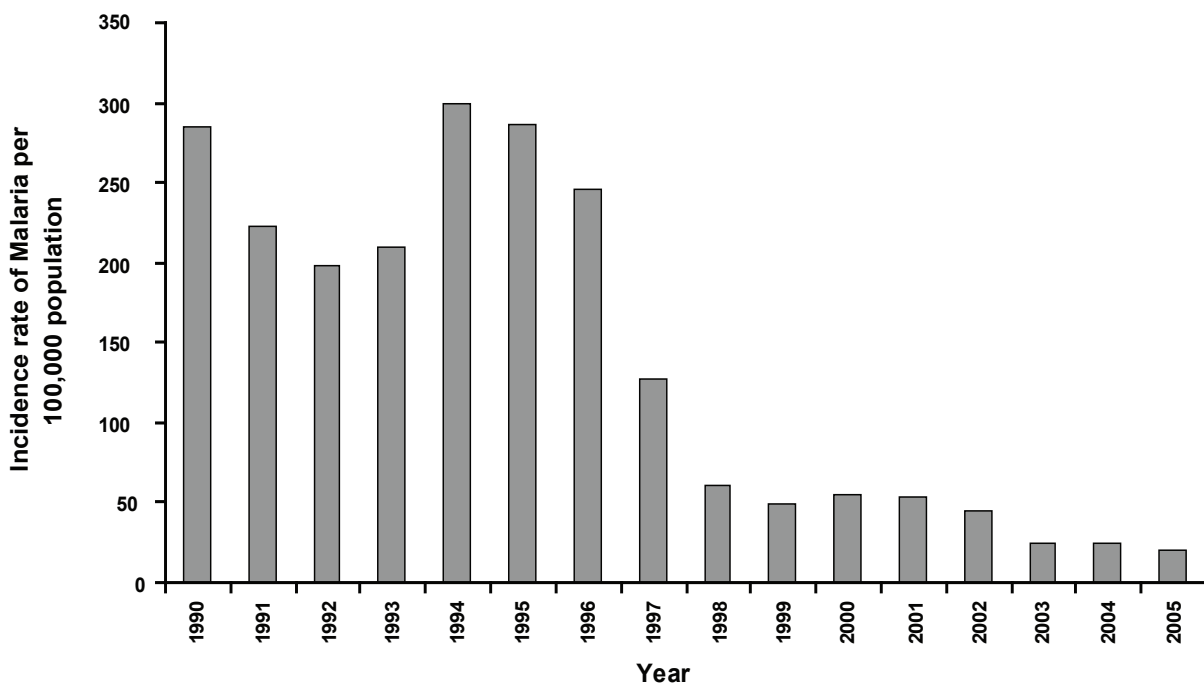


Figure 1: Incidence of Malaria, Malaysia, 1990-2005

Indonesian workers. These cases contributed to about 32.6% of the total reported cases of malaria in the year 2004 (4).

Malaria is a vector borne disease transmitted to man by the bite of an infected anopheline mosquito. The causative agent of malaria is a protozoan of the genus *Plasmodium*, and four species affect humans, i.e. *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae* (9, 10, 11).

If severe cases of malaria were not managed properly they would lead to complications, such as cerebral malaria or death (11, 12). The case fatality rate for malaria in Malaysia has increased from 0.33% in 2003 to 0.58% in 2004 (4). Therefore, there is a need for information on the characteristics of malaria cases to help in the control of this disease.

Selangor is one of the most developed and rapidly urbanising states in Malaysia. It covers 7960.84 km² area with a population of about 4.7 million in the year 2005 (13). However, Selangor still faced a significant number of malaria cases with the incidence rate of malaria fluctuating from 20 to 90 per 100,000 populations between 1996 and 2006. Of concern, these cases were commonly reported in urban districts such as Petaling, Hulu Langat and Gombak, which have high population densities (Figure 2)

This study described the epidemiology of malaria in Selangor with special reference to foreign workers.

Methods

This was a descriptive study mainly to describe the trend of malaria cases for the past six years. The characteristics of malaria cases in 2006 were obtained from reviewing secondary data, such as the malaria returns forms "PBV (M) 101," summary of malaria cases in Selangor for the year 2006 and Annual Reports of Vector-Borne Disease Control Unit (2001-2005) from the Selangor state health department.

The PBV (M) 101 or Malaria Case Registry form contains information about the malaria cases from a particular district or state. Information reported in this form include socio-demographic characteristics of the patients, investigation and treatment aspects of each malaria case.

The case definition for malaria in this study was "any foreign worker with or without symptoms or signs of malaria who shows laboratory confirmation of parasitaemia" (14). Based on the criteria set by the Ministry of Health, "Imported A" was defined as "any malaria infection where the source of the infection was imported from outside this country". The patient must have contracted the infection within

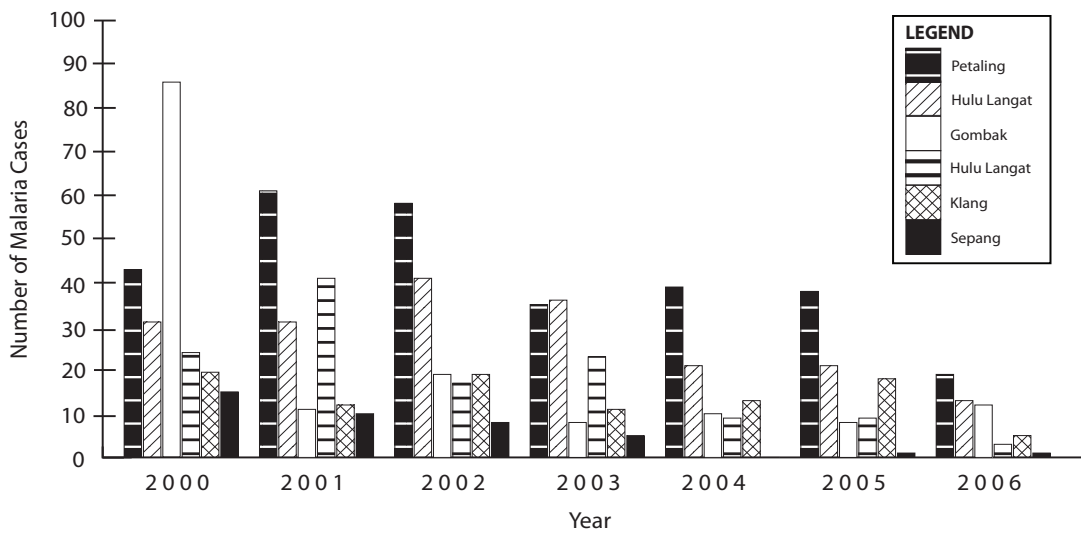


Figure 2: Distribution of Malaria Cases by Selected Districts, Selangor, 2000-2006

three months of staying in Malaysia and his/her place of stay in Malaysia is a malaria risk area.

The variables included for this study were age, gender, citizenship status, type of infection, source of infection and reporting district. Data were analysed using the statistical package for social science (SPSS) 12.0 for Windows (15). After the data entry, data cleaning was conducted. This involved checking the frequency of all the variables. All data were shown as numbers and proportions.

Results

Malaria cases were still endemic in Selangor. The number of malaria cases in Selangor varied between 172 cases in 2001 and 90 cases in 2006. On further analysing the distribution of these cases, it was evident that there was a significant contribution from foreign workers to the total number of cases. The proportions of foreign workers have increased from 57% to nearly 75% out of the total number of malaria cases in Selangor in the years 2001-2006 (Figure 3).

The workers were predominantly male (92.7%). The median age was 26 years old (interquartile range: 23-31) (Figure 4).

The distribution of these cases according to countries of origin showed that most of the cases were from Indonesia (17 cases) and Myanmar (16 cases), followed by India (8 cases) and Pakistan (7 cases) (Figure 5).

The source of infection (89.1%) was imported from other countries based on the criteria set by the Ministry of

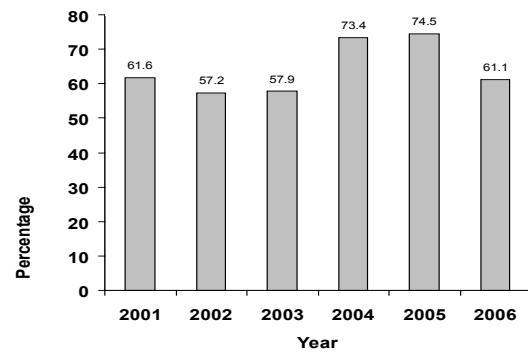


Figure 3: Proportion of Malaria Cases Contributed by Foreign Workers, Selangor, 2001-2006

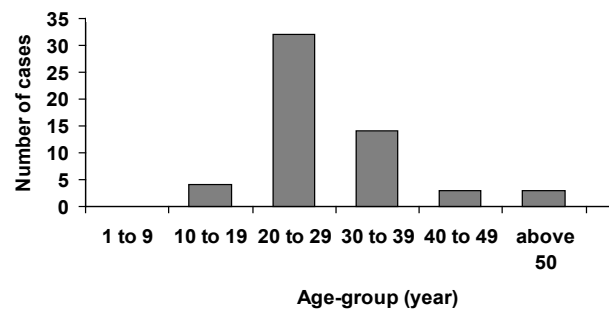


Figure 4: Distribution of Malaria Cases (Foreign Workers) by Age Groups, Selangor, 2006

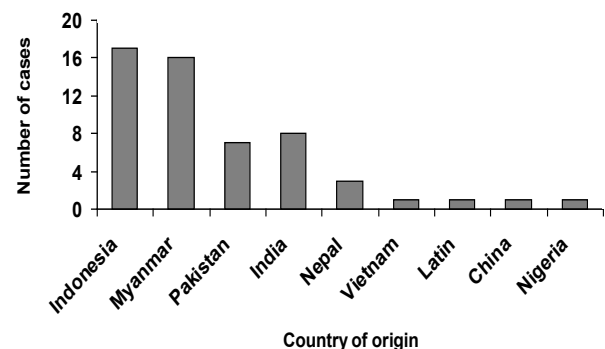


Figure 5: Distribution of Malaria Cases (Foreign Workers) by Countries of Origin, Selangor, 2006

Health (imported A). Most of them were infected by *Plasmodium vivax* (70.9%), followed by *Plasmodium falciparum* (27.3%) and *Plasmodium malariae* (1.8%). Distribution of the cases according to districts in the state of Selangor, Malaysia showed that most of them were from Petaling (36.5%), Hulu Langat (23.1%), Gombak (23.1%), Klang (9.6%), Hulu Selangor (5.8%) and Sepang (1.9%).

Discussion

Overall, this study showed that malaria cases still exist in Selangor despite the fact that it is one of the most urbanised states in Malaysia. About 60% of the malaria cases reported in Selangor were significantly contributed by foreign workers who were predominantly males of economically active age group. Many of these workers came to Malaysia to work as unskilled and semi-skilled labourers.

An important point to note is that these cases came from malaria endemic countries such as Indonesia, India, Vietnam, Myanmar and Pakistan (2,16). Since these workers are young, active, and highly mobile, they have the potential to transmit infections to others.

The proportion of cases actually corresponded with the distribution of migrant workers in Malaysia: Indonesian workers were the highest (68.9%), followed by others such as Nepalese (9.9%), Indian (6.9%) and Myanmar (4.6%) (16). Previous studies have also shown that a significant proportion of migrant workers in referral hospitals (5,17). A retrospective survey in the University Hospital Kuala Lumpur in 1998 showed that out of 134 malaria patients who were admitted throughout the period 1983-1992, foreigners made up 32.8% of all the malaria cases. Indonesian workers contributed 16.4% of all these cases (5).

Another survey, which was carried out in the University Hospital Kuala Lumpur showed that out of 81 cases of malaria which were admitted to that hospital, 49% of them were imported malaria (17).

The Foreign Workers Medical Examination Monitoring Agency (FOMEMA) stipulated a set of laboratory examinations that are mandatory to be carried out on foreign workers. The laboratory examinations include tests for HIV, hepatitis B, malarial parasites and others.

Those who failed the medical tests were deported and their work permits were revoked (7). However, these examinations may not have detected the incubating or dormant states of malarial infection because the examination was conducted by testing blood film for malarial parasite (BFMP) (2, 18, 19).

In addition, since the commonest infection detected in these foreigners was *Plasmodium vivax* that has the tendency to relapse, these cases might not have been detected during the screening examination. In this type of infection, relapse can occur months or years after exposure due to the presence of latent parasites in the liver (10, 20).

On top of that, there was also no examination conducted on illegal workers, who were believed to be present in a significant number, who might be having this infection and transmitting this disease to others (7).

This finding is consistent with the distribution of malaria cases in Malaysia, which showed *Plasmodium vivax* as causing the highest infection, i.e. 51.6% of the cases. On top of that, Asia is one of the regions that is contributing to the largest number of vivax malaria cases in the world (20).

One of the new techniques that is available to detect malarial infection in the latent or recrudescence stage of disease is polymerase chain reaction (PCR), which is capable of detecting parasites at a density of 1 per microlitre or less compared to a microscope, whose threshold of detection is around 10-50 parasites per microlitre. It is an expensive test. However, in the long run it may be more cost effective in detecting malaria cases.

Of concern, these malaria cases were commonly reported in the urban districts of Selangor that have a higher density of population, such as the Petaling, Gombak and Hulu Langat districts. This was because these districts have a lot of work opportunities for the migrant workers either in the factories, housing area or plantation sites. Therefore, the potential threat of urban outbreak of malaria cannot be ignored.

Study Limitations

There were limitations of this study that need to be considered while interpreting the results. Firstly, the

study was a review of surveillance data. The captured information was aggregated and not the individual characteristics of the cases.

In this study, the incomplete information included occupation and entry status of the foreign worker (legal or illegal). The entry status is crucial to ensure that medical examination has been conducted prior to entry. The observation seen in this study might be only the tip of the iceberg and the actual number of cases might be more because illegal migrants never turned up for treatment.

Recommendation

Decisions and actions to control the potential spread of malarial infection by migrants must be based on properly collected data. The malaria returns form should include further detailed history such as district of origin, duration of stay in Malaysia and status of the migrant (legal or illegal). The past medical history should include history of malarial infection, history of contact to malaria cases, drug history and history of examination by FOMEMA.

It is important to have earlier detection and notification of these cases so that epidemiological investigations can be done to ascertain the source. This study only looked at the descriptive epidemiology of malaria in Selangor. Further study is needed to look into risk factors for malaria transmission among these foreign workers and comparing them with factors for local population.

Conclusion

Malaria is still endemic in the state of Selangor, Malaysia. This is actually due to imported malarial infection. Infections among the foreign workers have the potential of spreading the malaria diseases to urban areas and in contributing to an outbreak. Knowing the risk factors that lead to transmission of infection in these migrants could contribute significantly to the prevention of malaria in this country.

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SOCIODEMOGRAPHIC AND FOETAL CHARACTERISTICS OF MOTHERS WITH PREMATURE DELIVERIES IN HOSPITAL TUANKU JAAFAR SEREMBAN, NEGERI SEMBILAN, MALAYSIA

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ABSTRACT:

This is a retrospective case control study conducted between 1 January 2005 and 30 June 2006 at the Hospital Tuanku Jaafar, Seremban, Malaysia. The objective was to study the maternal sociodemographics and foetal characteristics associated with premature delivery. There were 387 cases selected universally and 387 controls selected by using systematic random sampling involving every 13 cases. The patients were women who had delivered their babies before 37 completed weeks, while the control were women who had term deliveries during the same period. Data were collected using structured questionnaire through secondary data. Results showed that having multiple pregnancies (OR=8.33, 95% CI: 2.91, 23.84), congenital abnormality (OR=4.6, 95% CI: 0.98, 21.84) and intrauterine growth retardation (OR=15.59, 95% CI: 3.69, 65.82) were the risk factors of premature delivery. Being an ethnic Indian also raised the odds (OR=1.67, 95% CI: 1.14, 2.43) but this was not significant in the multivariate analysis. Other sociodemographic characteristics did not contribute significantly to the risk factors for premature delivery in this sample. In conclusion, foetal characteristics were found to be significantly associated with premature delivery after adjustment for other confounding factors. (*JUMMEC 2008; 11 (2): 59-65*)

KEYWORDS: *Premature delivery, maternal sociodemographic and foetal characteristics*

Introduction

Premature delivery is a leading cause of perinatal mortality in the United States and all over the world. Infants born before 37 weeks of gestation are also at a higher risk of contracting infections and of having neuro-developmental problems (1). WHO defined premature delivery as infants born before 37 completed weeks as calculated from the first day of the last menstrual period. Premature delivery is a cause of 75% of perinatal morbidity and of mortality world wide (1). It is of public health importance as premature delivery contributes to 12.2% of perinatal mortality in Malaysia and 73.2% of perinatal mortality occurred in the first week of life (2). A study by Boo showed that 95.7% out of 329 premature babies had low birth weight, which was high risk for perinatal mortality (3)

Most causes of premature delivery are unknown. In Malaysia, the prevalence of premature delivery was 10% in the year 1998 (4). There were no published findings on maternal characteristics and foetal characteristics of premature deliveries. Therefore, it is important to look for the causes of premature delivery.

The objective of our study was to look at the maternal sociodemographic and foetal characteristics among mothers presented with premature delivery.

Methodology

The study was conducted in Hospital Tuanku Jaafar, Seremban, between 1 January 2005 and 30 June 2006. The study design was a retrospective case control study. Secondary data of the cases and controls were extracted from the medical records in the hospital. The patients were defined as women who delivered at less than 37 completed weeks while control was defined as women who delivered after 37 weeks period of gestation. Measurement of period of gestation was based on ultrasound and the last normal menstrual period.

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Table 1: Frequency Distribution of Maternal Sociodemographic Characteristics

Sociodemographic characteristic		Premature N=387 N (%)	Term N=387 N (%)	p value
Age (years)	Mean s.d	30.93 5.93	30.62 5.07	
Parity/ number of children	Median s.d	3 1.47	3 1.49	
BMIkg/m2	Mean s.d	25.12 3.7	24.65 3.83	
Ethnicity				0.00
Malay		259 (49.0)	270 (51.0)	
Chinese		32 (37.6)	53 (62.4)	
Indian		88 (61.5)	55 (38.5)	
Others		8 (47.1)	9 (52.9)	
Age group in years				0.45
<27		108 (49.1)	112 (50.9)	
28-31		107 (47.8)	117 (52.2)	
32-35		84 (48.8)	88 (51.2)	
>36		88 (55.7)	70 (44.3)	
Mothers' education				0.31
Primary		9 (69.2)	4 (30.8)	
Secondary		306 (50.3)	302 (49.7)	
Diploma/degree		72 (47.1)	81 (52.9)	
Marital status				0.56
Married		386 (50.1)	385 (49.9)	
Divorced		1 (33.3)	2 (66.7)	
Mothers' occupation				0.31
Professional & Management		34 (39.5)	52 (60.5)	
Skilled worker		15 (48.4)	16 (51.6)	
Semiskilled worker		80 (51.6)	75 (48.4)	
Unskilled worker		27 (56.3)	21 (43.8)w	
Businesswoman		17 (60.7)	11 (39.3)	
Housewife		214 (50.2)	212 (49.8)	

There were 12,015 deliveries during the study period. All mothers with premature delivery were selected as cases, while mothers with term delivery were selected as controls. The exclusion criteria were primigravida, cases referred from other states, non-Malaysians and mothers with intrauterine death.

A total of 774 respondents which consisted of 387 cases and 387 controls were selected into this study. The sample size was calculated by using EPI_INFO version 12 with $\alpha=0.05$, power=80%, and a prevalence of maternal smoking of 12% with OR=1.8 which was based on the study by Ahern *et al* (5).

A structured questionnaire was prepared to extract the data from the medical records. The questionnaire recorded sociodemographic characteristics of mothers such as age, ethnicity, education level, marital status, occupational status, smoking status, parity, and Body

Mass Index (BMI). Foetal characteristics such as sex, twin delivery, congenital abnormality and intrauterine growth retardation were also recorded using the same questionnaire.

Data Analysis

Data was entered and analysed in SPSS Windows version 11.5. Significant level was preset at 0.05 and 95% C.I. was reported where appropriate. Logistic regression was used to investigate the association of maternal sociodemographic and fetal characteristics on premature delivery. Variables with $p \leq 0.25$ were entered into the multivariate logistic regression model. The final model consisted of variables with $p < 0.05$.

Results

Table 1 shows the frequency distribution of sociodemographic characteristics of the mothers. The

Table 2: Association between Maternal Sociodemographic and Characteristics with Premature Delivery

Maternal Sociodemographic characteristic	Crude OR	95% CI	p value
Ethnicity			0.004
Malay	1.00	-	
Chinese	0.63	0.39,1.01	
Indian	1.67	1.14,2.43	
Others	0.93	0.34,2.43	
Age group in years			0.45
<27	1.00	-	
28-31	0.95	0.65,1.38	
32-35	0.99	0.66,1.48	
>36	1.30	0.86,1.97	
Education			0.31
Primary	2.51	0.75,8.57	
Secondary	1.14	0.80,1.63	
Diploma/ Degree	1.00	-	
Marital Status			0.56
Married	1.00	-	
Divorced	0.50	0.05,5.52	
Maternal Occupation			0.31
Professional & Management	1.00	-	
Skilled worker	1.43	0.63,3.28	
Semiskilled worker	1.63	0.96,2.78	
Unskilled worker	1.96	1.04,4.02	
Businesswoman/ self employed	2.36	0.98,5.66	
Housewives	1.52	0.96,2.47	

mean age of the mothers with premature delivery was 30.93 ± 5.93 years, while for the control was 30.62 ± 5.07 years. The average number of children for both groups was 3. There was a slight difference in terms of mean BMI for both groups. The mean BMI kg/m^2 was 25.12 ± 3.7 for the cases and 24.65 ± 3.83 for the controls.

Premature deliveries were significantly more common ($p=0.004$) among the Indian mothers (61.5%) as compared to Malays (49%), Chinese (37.60%) and others (47.10%). Mothers in the age group of more than 36 years old were more commonly found to have premature deliveries compared to mothers from other age groups.

About half of the mothers in the cases group received secondary level of education (50.3%), while about half of the control group received tertiary education (52.90%). Half of the mothers in the cases' group were married and about 60% of them were businesswoman/self-employed. A majority of the

Table 3: Association between Foetal characteristic with Premature Delivery

Foetal Characteristic	Crude ratio	95% CI	p value
Twin			<0.001
No	1.00	-	
Yes	8.33	2.91,23.84	
History of congenital abnormality			0.05
No	1.00	-	
Yes	4.60	0.98,21.84	
Baby sex			0.77
Male	1.00	-	
Female	1.04	0.78, 1.38	
History of intrauterine growth retardation			< 0.001
No	1.00	-	
Yes	15.59	3.69,65.82	

controls were professionals and/or worked in managerial positions. About two-thirds of the cases smoked compared to the controls.

The association between maternal sociodemographic characteristics with premature delivery for all cases and controls are presented in Table 2. The odds of premature delivery was 1.67 (95% CI 1.14, 2.43) times more likely in Indian mothers compared to Malay or Chinese mothers. However, variables such as age group ($p=0.45$), education status ($p=0.31$) and marital status ($p=0.56$) were not significantly associated with premature delivery. The association between maternal parity ($p=0.88$) and smoking status ($p=0.41$) with premature delivery were not significant. The association of BMI group was marginally significant ($p=0.06$).

Table 3 shows that history of twin delivery was a significant risk factor for premature delivery ($p<0.001$). The odds of premature births was 8.33 times higher in twin delivery compared to single pregnancy (95% CI 2.91, 23.84). Congenital abnormality was also marginally significantly associated with premature delivery ($p=0.05$). The odds of premature delivery was 4.6 times higher in congenital baby compared to a normal baby (95% CI 0.98, 21.35).

The association of foetal sex was not significant with premature delivery ($p=0.77$). The odds of premature delivery was 15.59 times higher in intrauterine growth

retardation baby compared to a normal weight baby (95% CI 3.69, 65.82).

Multivariate Analysis

In the final model of logistic regression (Table 4), history of twin pregnancy, congenital abnormality and intrauterine growth retardation were significantly associated with premature delivery. Mothers with twin delivery were 18.8 times more likely to have premature deliveries compared to controls (95% CI 6.30, 56.16). Mothers with congenital abnormalities were 6.70 times more likely to have premature delivery compared to controls (95% CI 1.28, 35.18), while mothers with intrauterine growth retardation babies were 25.46 times more likely to have premature delivery compared to controls (95% CI 5.55, 116.79).

Table 4: Final Predictors Model of Risk Factors For Premature Delivery

Predictors	Crude OR	95 % CI	Adjusted OR	95 % CI
History of twin pregnancy				
No	1.00	-	1.00	-
Yes	8.33	2.91, 23.84	18.80	6.30, 56.16
History of congenital abnormality				
No	1.00	-	1.00	-
Yes	4.60	0.98, 21.35	6.70	1.28, 35.18
History of intrauterine growth retardation				
No	1.00	-	1.00	-
Yes	15.59	3.69, 65.82	25.46	5.55, 116.79

Discussion

Maternal Socio-demographic characteristics

Maternal age was found to be a significant risk factor for premature delivery in many studies. Maternal age of less than 20 years and more than 35 years is a risk factor for premature delivery and perinatal mortality. However, this factor is not found to be a significant risk factor for premature delivery in this study. This could be due to the different age classification groups that might have contributed to non-significant findings. The exclusion of primigravida in the study might also have affected the results. Primigravida was excluded in this study because these mothers have no history of previous premature delivery and no history of

miscarriage as required in this study. Similar negative findings were found in other studies (6, 7, 8).

Many studies found that Black ethnicity with low social income received less medical care and had a higher risk of premature delivery compared to the White ethnicity (9, 10, 11, 12). In this study, being of Indian ethnicity was a significant risk factor for premature delivery in the univariate analysis with an odds ratio of 1.67 (95% CI 1.14, 2.43). However, it became insignificant in the multivariate analysis after adjustment for other risk factors. This could be due to the difference in inclusion and exclusion criteria where preterm birth was excluded in most of the studies indicated (7, 15, 16).

Occupation could be a risk factor for premature delivery. Strenuous activity, stressful work, physical fatigue, prolonged standing could lead to inadequate rest and subsequently maternal and foetal morbidity (17). A few studies have found that fatigue at work or stress could lead to premature delivery (14, 17). However, there were also contradicting findings in the relationship between occupation with the risk of premature delivery (9, 12, 16).

In the univariate analysis, there was a significant association between unskilled worker (OR=1.96, 95% CI: 1.04, 4.03) and businesswoman or self-employed women (OR=2.36, 95% CI: 0.98, 5.66) with the risk of premature delivery. However, it became insignificant after adjustments were made for other risk factors. This difference could be due to different inclusion and exclusion criteria, and different occupation classification groups. This finding is similar to those found in other studies (9, 12, 16).

Few studies have associated divorced or widowed mothers as a risk factor for premature delivery (8, 12, 16). However, the risk factor also depends on the mothers' income. Mothers with higher income will not be affected by broken marriages. In this study, marital status was not a significant risk factor for premature delivery (p=0.56). Other studies have also showed similar negative results (7, 17).

Maternal Characteristics

The association between parity with premature delivery is controversial. Some studies showed significant association between premature delivery with parity (13, 14, 18). However, some studies showed

contradicting findings between parity with premature delivery (16, 17). High parity was not a significant risk factor for premature delivery in this study with an odds ratio of 1.01 (95% CI 0.61, 1.68). The reasons for this finding could be due to differences in classification group, exclusion of primigravida, difference in inclusion and exclusion criteria where, in this study, indicated preterm birth was included besides difference in study population.

In one meta analysis on smoking mothers, the odds of premature delivery was 1.27 (95% CI 1.21, 1.33) with an evidence of a dose response relationship (12). However, smoking was not found to be a risk factor for premature delivery with an odds ratio of 1.50 (95% CI 0.25, 9.05) in this study. Similar findings were found in other studies (18, 19). The reason for our finding could be due to the small number of smoking mothers in our study.

Maternal nutritional status is associated with premature delivery. Some studies showed significant association between BMI and premature delivery (13, 14, 20). A study by Feresu *et al* (7) found that there was a significant association between mother's BMI (< 19.8 kg/m) with the risk of premature delivery with an odds of 1.82 (95% CI 1.11, 2.99). Obesity was also associated with premature delivery (14). In the Cardiff Birth Survey, it was found that women with weight of < 45 kg was associated with premature delivery with 2.27 times higher risk compared to women with normal weight (95% CI 1.23, 4.19) (13). Similarly, mothers with maternal weight of <50 kg had a higher risk of premature delivery (OR=2.72) compared to those with normal weight (9, 13).

However, Kramer *et al* (21) had contrasting findings. He found that there was a difference in determining the actual weight gain. Most of the studies take the average weight gain in a year instead of tissues weight gain. According to Kramer *et al*, the maternal weight gain was defined as tissues or cells weight gain instead of average weight gain. Besides that, some of his study subjects included mothers who had induced delivery.

However, our study did not find a significant association between maternal BMI > 30kg/m² with premature delivery ($p=0.06$) OR=1.10 (95% CI 0.47, 2.80) This

could be due to a difference in the classification group of maternal weights. Some studies used maternal weight of < 45 kg, (13) or weight of <50 kg (20) as the cut-off points for maternal nutritional status, while some studies used BMI < 18.5kg (7). There was also a difference in determining the actual weight gain. Most of the studies take the average weight gain in a year (7, 14). The maternal weight gain was defined as tissues or cells weight gain instead of average weight gain (5, 21). Besides that some studies included induced delivery and excluded congenital abnormality or twin pregnancy. In our study BMI > 30 kg/m² was used with reference to maternal BMI < 18.5 kg.

Foetal characteristics

Twin pregnancy, congenital abnormality and intra-uterine growth retardation are known as risk factors associated with premature delivery. Twin pregnancy is normally associated with premature delivery. It is due to the overstretching of the uterus which promotes preterm labour. Some studies showed association between twin pregnancy with premature deliver (14, 15). Twin pregnancy is a significant risk factor for premature delivery in this study with an adjusted odds ratio of 18.80 (95% CI 6.30, 56.16). However, others have shown negative finding (22). This could be due to the selection criteria where only mothers with previous twin pregnancy were included (22).

The foetus itself could be the cause of premature delivery. If the growth was retarded or malformed, the foetus was prone to be born prematurely (23). Some studies showed significant association between congenital abnormal babies and premature delivery (23, 24). Others noted that infants with congenital abnormality had a premature birth risk of 2.7 times higher than normal; and those with multiple congenital abnormality had a risk as high as 35 times more than normal babies (24).

In this study, foetal congenital abnormality was a significant risk factor for premature delivery. Mothers with history of foetal congenital abnormality were 6.70 times more likely to have premature delivery compared to mothers with no history (95% CI 1.28, 35.18). This finding is similar to other studies (15, 23).

Limitations Of The Study

Information gathered for the study was secondary data extracted from medical records. Not all variables could be found in the medical record files. Information on maternal income, fathers' smoking status, interpregnancy interval, history of drug abuse or alcohol, history of psychological problems such as depression, pre-pregnancy weight, history of occupational hazards was not available. Therefore, this study could not assess the mothers' characteristics as above. It is recommended that future study should be conducted in a prospective manner. In addition, the exclusion of primidgravida in this study could be another limitation.

Conclusions

Maternal sociodemographic characteristic was not a significant risk factor for premature delivery. Foetal characteristic was found to be significant in this study after adjusting for twin pregnancy, congenital abnormality and intrauterine growth retardation. It is recommended that antenatal mothers should have good antenatal and prenatal care for maternal medical problems since premature delivery could not be prevented.

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PREVALENCE OF SLEEP DISTURBANCE AMONG NURSES IN A MALAYSIAN GOVERNMENT HOSPITAL AND ITS ASSOCIATION WITH WORK CHARACTERISTICS

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ABSTRACT

The objective of this study was to determine the prevalence of sleep disturbance with work characteristics among nurses in the Melaka Hospital, Malacca, Malaysia. This was a cross sectional study conducted in Melaka Hospital. Universal sampling was conducted and a Malay version of the Pittsburgh Sleep Quality Index (PSQI) questionnaire was used in data collection. Socio-demographic characteristics such as age, marital status, number of children and work characteristics such as type of work schedule and duration were also enquired. Factors associated with poor sleep quality were compared between those nurses with good sleep quality by using logistic regression. There were 607 nurses who completed the questionnaire with a response rate of 73.1%. There was a moderate prevalence (57.8%) of poor sleep quality (PSQI > 5) in all study subjects. The prevalence of sleep disturbance was more widespread among nurses who worked shifts (62.0%) compared to non-shift working nurses (41.5%) $p < 0.001$. A logistic regression analysis showed that age, marital status and unit group were the major associating factors of poor sleep quality. Sleep disturbance decreased with increasing age (OR = 0.42, 95% CI 0.25, 0.73) while married nurses (OR = 2.3, 95% CI 1.42, 3.82) and those in the category of intensive group (OR = 2.1, 95% CI 1.1, 4.1) were more prone to have sleep disturbances. In conclusion, this study revealed moderate prevalence of sleep disturbance among nurses working in Melaka Hospital but it was not associated with the work shifts. Age, marital status and work environment especially in the intensive group unit seemed to be factors associated with reduced global sleep quality among nurses in this study. (*JUMMEC 2008; 11 (2): 66-71*)

KEYWORDS: *sleep disturbance, shift work, nurses*

Introduction

Sleep is a natural periodic state of rest for the mind and body, in which the eyes usually close and consciousness is completely or partially lost, so that there is a decrease in bodily movement and responsiveness to external stimuli (1). The amount of sleep each person needs depends on many factors, including age. Infants generally require about 16 hours a day while teenagers need about nine hours on average and for most adults, seven to eight hours a night is enough although some people may need as few as five hours or as many as ten hours of sleep each day (2). When human beings do not obtain enough sleep, people will think and move slowly and make more mistakes. The consequences of sleep deprivation include susceptibility to common viral illnesses, diabetes, obesity, heart disease, and depression (3).

The causes of sleep disturbance are many and varied.

For a variety of reasons, nurses are particularly prone to sleep disturbance. Nurses face many problems that may negatively affect sleep quality, including work schedule. Within the health care services, the need for 24-hour nursing care requires nurses to work on shift systems. Shift work is used to describe as a variety of working time arrangements, including: (a) working outside daytime hours such as night shifts; (b) overtime work; or (c) irregular or rotational work patterns (a system in which staff are required to work a combination of day, afternoon and night shifts) (4). Nonshift schedule refers to working during the hours which an

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office is normally open for business or consultation or in other words, following a standard work day/office hours (8.00 to 5.00 p.m.) or a permanent/fixed time/hour day.

In a study of sleep disturbance among 817 hospital staff workers, 29.7% of health staff scheduled for rotating daytime shifts experienced disrupted sleep occurring two nights or more per week. These workers also reported significantly more difficulty in initiating sleep than fixed daytime workers (20.1% and 12%, respectively) (5).

A study among nurses in Thailand showed that there was a high prevalence (73%) of poor sleep quality and the prevalence was more widespread among nurses working in shifts (76.7%) than nonshift nurses ($p < 0.0002$). That study also showed that poor sleep quality was inversely related to age ($p < 0.001$) (6). Prevalence of insomnia among shift-working nurses (29.2%) was three to four times higher than that in the general population in a study conducted in Japan (7). Beside shift work, other factors affecting sleep quality are age, marriage, number of children and duration of work predisposed to sleep disturbance (3, 6, 8). In Malaysia, the prevalence of sleep disturbance among nurses or other factors contributing to sleep disturbance have not been well studied. The objectives of this study were to determine the prevalence of sleep disturbance among nurses in the Melaka Hospital and the association between sleep disturbance and work characteristic of the nurses.

Materials and Methods

This study was a cross-sectional study conducted in Melaka Hospital in Malaysia. The study population were nurses who worked in the Melaka Hospital. The sampling method was universal and data were collected from June to October 2006. All nurses who worked in Melaka Hospital and fulfilled the inclusion criteria (had worked more than two months in the hospital and was registered with the Ministry of Health, Malaysia) during the data collection period were invited to participate in the study. From 926 nurses, 830 nurses fulfilled the criteria. Out of these, 679 nurses were working on rotational shifts and 151 were on nonshifts. Work units were divided into four categories: Medical, Surgery, Intensive and Ambulatory Groups.

The study instrument used the Malay version of Pittsburgh Sleep Quality Index (PSQI). PSQI was developed by Buysse *et al* (9) and the source of the questionnaire was cited from The Hartford Institute for Geriatric Nursing, Division of Nursing, New York University. The PSQI is a self-rated questionnaire that is useful in determining whether a person has a significant sleep disturbance over the previous month. Nineteen individual items generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction. A PSQI total score greater than five is diagnostic of sleep disturbance and differentiates between nurses that have sleep of good quality from those with poor quality sleep. A pre-test was performed among 38 nurses in the Alor Gajah Hospital, Kedah to test and to verify that the questionnaire was easily understood by the respondents. The data were entered into a computer using the SPSS Version 13.0 software. Data were cleaned and checked before analysis. These data were coded appropriately according to the type of variables. Univariate significance between various factors and sleep disturbance were identified using binary logistic regression. Multivariate logistic regression was used to examine the association of various factors with sleep disturbance while simultaneously controlling for potential confounders. The significance of association and its precision was determined by the 95% confidence interval and the magnitude was determined by the crude odds ratio.

Results

Out of 830 nurses, 607 (73.1%) answered the questionnaire. Out of those who responded to the questionnaire, 71.3% were shift nurses and 80.4% were nonshift nurses.

Malays formed the largest ethnic group (87.3%) (Table 1). About half of the nurses (56.2%) had college/university education, and most of them were married (85.5%). 79.7% of the nurses worked on the shift schedule. About 82% were staff nurses while 12.5% were community nurses. Nurses from Surgery were the majority (44.2%) followed by the Medical group (37.4%).

Out of the 607 respondents who answered the questionnaire, our study showed that 351 nurses had

Table 1: Sociodemographic and Work Characteristics of Respondents

Characteristics	n (%)
Ethnicity	
Malay	530 (87.3)
Chinese	59 (9.7)
Indian	12 (2.0)
Others	6 (1.0)
Marital Status	
Single	81 (13.3)
Married	519 (85.5)
Widow/Divorced	7 (1.2)
Education level	
Secondary	266 (43.8)
College/University	341 (56.2)
No of children	
0	151 (24.9)
1 – 2	254 (41.8)
3 – 4	167 (27.5)
> 4	35 (5.8)
Type of work	
Non shift	123 (20.3)
Shift	484 (79.7)
Job rank	
Matron/Sister	21 (3.5)
Staff nurse	498 (82.0)
Community nurse/Midwife	76 (12.5)
Assistant nurse	12 (2.0)
Unit group	
Medical	227 (37.4)
Surgery	268 (44.2)
Intensive	60 (9.9)
Ambulatory	52 (8.6)
Job duration	
1 month- 5 years	265 (43.7)
6-10 years	149 (24.5)
11 – 15 years	51 (8.4)
16 – 20 years	46 (7.6)
21 – 25 years	38 (6.3)
>26 years	58 (9.6)

(n = 607)

sleep disturbance (57.8%) (Table 2). The prevalence of sleep disturbance was significantly highest among Malay nurses ($p=0.021$). Age was inversely related to sleep disturbance ($p=0.002$) where nurses aged 50 to 59 years old has the least sleep disturbance with the lowest 95% CI (OR = 0.41 (0.24, 0.67) compared to young nurses. Married nurses were more prone to have sleep disturbances (OR 1.98 95% CI 1.23, 3.18)

Table 2: Association between Sleep Disturbance and Socio Demographic Characteristics among Respondents

Characteristics	No Sleep Disturbance (n=256) n (%)	Sleep Disturbance (n=351) n (%)	OR 95% CI	p value*
Ethnicity				0.021
Malay	211 (39.8)	319 (60.2)	0.45 (0.26, 0.78)	
Chinese	35 (59.3)	24 (40.7)	0.66 (0.21, 2.08)	
Indian	6 (50.0)	6 (50)	0.33 (0.06, 1.82)	
Others	4 (66.7)	3 (33.3)		
Age				0.002
20 – 29	91 (38.7)	144 (61.3)	1.09 (0.72, 1.64)	
30 – 39	62 (36.7)	107 (63.3)	0.83 (0.53, 1.31)	
40 – 49	50 (43.1)	66 (56.9)	0.41 (0.24, 0.67)	
50 – 59	53 (60.9)	34 (39.1)		
Marital Status				0.018
Single	46 (56.8)	35 (43.2)	1.98 (1.23, 3.18)	
Married	207 (39.9)	312 (60.1)	1.75 (0.37, 8.34)	
Widow/Divorce	3 (42.9)	4 (57.1)		
BMI				0.406
Under weight	11 (30.6)	25 (69.4)	0.55 (0.27, 1.15)	
Normal	149 (44.5)	186 (55.5)	0.65 (0.30, 1.4 0)	
Over weight	72 (40.4)	106 (59.6)	0.62 (0.26, 1.50)	
Obese	24 (41.4)	34 (58.6)		
Education Level				0.104
Secondary School	122 (45.9)	144 (54.1)	1.31 (0.95, 1.81)	
College/ University	134 (39.3)	207 (60.7)		
No. of children				0.176
0	74 (49.0)	77 (51.0)	1.56 (1.03, 2.34)	
1 – 2	97 (38.2)	157 (61.80)	1.27 (0.81, 1.98)	
3 – 4	72 (43.1)	95 (56.9)	1.63 (0.76, 3.47)	
> 4	13 (37.1)	22 (62.9)		
No.of dependent				0.0927
0	47 (48.5)	50 (51.5)	1.13 (0.71, 1.79)	
1 – 2	138 (45.5)	166 (54.6)	1.74 (1.05, 2.89)	
3 – 4	60 (35.1)	111 (64.9)	2.07 (0.89, 4.82)	
5 – 6	1031.3)	22 (68.8)	1.88 (0.17, 21.4)	
> 6	1 (33.3)	2 (66.7)		

* χ^2 test

compared to single nurses. BMI, education level, number of children and number of dependants were not significant factors in this study.

Shift nurses had 2.3 times higher risk of haing sleep disturbance with OR 2.30 (95% CI 1.54, 3.44) compared to nonshift nurses (Table 3). The unit group was significant in this study (<0.001). The crude OR for

Table 3: Association between Sleep Disturbance and Work Characteristics among Respondents

Characteristics	No Sleep Disturbance (n=256) n (%)	Sleep Disturbance (n=351) n (%)	95% CI	p value*
Type of work				0.0001
Nonshift	72 (58.5)	51 (41.5)	2.30 (1.54, 3.44)	
Shift	184 (38.0)	300 (62.0)		
Job rank				0.180
Matron/Sister	12 (57.1)	19 (42.9)	1.99 (0.82, 4.80)	
Staff Nurse	200 (40.2)	298 (59.8)	1.33 (0.50, 3.53)	
Com Nurse	38 (50.0)	38 (50.0)	1.33 (0.32, 5.54)	
Assistant Nurse	6 (50.0)	6 (50.0)		
Unit group				0.0001
Medical	92 (40.5)	135 (59.5)	0.81 (0.64, 1.320)	
Surgery	114 (42.5)	154 (57.5)	1.97 (1.16, 4.30)	
Intensive	14 (23.3)	46 (76.6)	0.32 (0.16, 0.58)	
Ambulatory	36 (69.2)	16 (30.8)		
Job duration				0.011
0 - 5 yrs	110 (41.5)	155 (58.5)	1.29 (0.85, 1.95)	
6-10 years	53 (35.6)	96 (64.4)	1.20 (0.64, 2.22)	
11 - 15 years	19 (37.3)	32 (62.7)	1.21 (0.63, 2.31)	
16 - 20 years	17 (37)	29 (63.0)	0.46 (0.23, 0.93)	
21 - 25 years	23 (60.5)	15 (39.5)	0.50 (0.28, 0.89)	
>26 years	34 (58.6)	24 (41.4)		

* χ^2 test

nurses who worked in the Intensive group was highest (OR = 2.24, 95% CI 1.16, 4.30) while the Ambulatory group was noted to have the least sleep disturbance (OR = 0.32, 95% CI 0.16, 0.58). Job duration was significantly associated with sleep disturbance ($p=0.011$) while the job rank was not significant.

Table 4 shows the multiple logistic regression analyses performed on all significant predictors that had meaningful association on the outcome on sleep disturbance. The findings showed that the factors associated with sleep disturbance were marital status, age and unit group. Age between 50 to 59 years had least sleep disturbance compared to other age groups. Married nurses was twice more common to obtain sleep disturbance compared to single nurses. Similar to those nurses who worked in the Intensive Group, they were twice more prone to experience sleep disturbance as compared to other unit groups.

Table 4: Predictors of sleep disturbance among respondents

Characteristics	Crude OR	Adjusted OR	95% CI
Marital status			
Single	1.00	1.00	1.42, 3.82
Married	1.98	2.33	0.56, 14.55
Widow/Divorced	1.75	2.87	
Age group			
20 - 29	1.00	1.00	0.65, 1.51
30 - 39	1.09	0.99	0.51, 1.34
40 - 49	0.83	0.83	0.25, 0.73
50 - 59	0.41	0.42	
Unit group			
Medical	1.00	1.00	0.64, 1.34
Surgery	0.81	0.93	1.08, 4.10
Intensive	1.97	2.11	0.19, 0.75
Ambulatory	0.32	0.38	

Discussion

More than half of the nurses in this study had sleep disturbance during the month before completing the questionnaire and met the PSQI criteria for "poorer sleep." The percentage of nurses in the current study who scored global sum of PSQI more than 5 points (considered to have sleep disturbance) was 57.8% and the prevalence was higher for shift nurses compared to nonshift nurses. Most studies showed a lower prevalence of sleep disturbance than this study. However, there are studies that showed a prevalence of sleep disturbance of more than fifty percent (6, 8). After the statistical adjustments, the current study did not find a significant effect of work schedule on sleep quality. Similar findings were found elsewhere (10, 11).

In this study, marital status was strongly associated with sleep disturbance where married nurses were twice more likely to develop sleep disturbance. A study among 128 nurses had shown that higher prevalence of sleep disturbance was found among married nurses (97.54%) compared to single nurses (83.33%) (8). It was noted in the current study that most married nurses had children. Family and domestic work would lead to fatigue or stress that affected sleep quality (12, 13). A few studies had shown that being married and having children lead to less sleep and less time for free-time activities (14, 15).

Age showed significant association with sleep disturbance in this study. Age between 50 to 59 years had the least sleep disturbance compared to other age group. This study is similar to other studies where age is inversely related to sleep disturbance (6, 16). In our current study, nurses in the Intensive group showed a higher prevalence of sleep disturbance compared to other group units. Similar to findings from Ruggiero *et al*, nurses who work in intensive or critical care units such as ICU, CCU, burns unit and high dependency ward have higher prevalence of sleep disturbance (6, 17).

Conclusion

In conclusion, our findings showed that working on shift work schedule did not always lead to the presence of sleep disturbance. Other factors that predisposed nurses to develop sleep disturbance were age, marital status and work environment. Work related characteristic such as work load may lead them

to develop sleep disturbance or sleep deprivation as well. In light of the present findings, there is a need to do more research and further investigation to determine other factors that may be related to sleep disturbances among nurses.

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HOME ENVIRONMENT AND FALL AT HOME AMONG THE ELDERLY IN MASJID TANAH PROVINCE

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ABSTRACT

The aim of this study was to determine whether the home environment was a risk factor for falls occurring at home among the elderly in the Masjid Tanah community, Malaysia. An analytical cross-sectional study conducted from early June 2006 until May 2007 in six randomly selected villages in Masjid Tanah Province. A total of 516 participants were included in this study. Overall prevalence of falls among the study participants was 27.3%. Home falls accounted for 66.7% of the total falls. In conclusion, there was no association between home environment and home fall in this study. Logistic regression analysis showed that having a depressive mood was the main determinant for home falls among the elderly in this study. (*JUMMEC 2008; 11 (2): 72-82*)

KEYWORDS: *elderly, falls, home environment, risk factors*

Introduction

Aging is inevitable and it is also known to be the most sensitive stage of one's life. Kazutomo defined aging as "regression of physiological function accompanied by advancement of age" (1). It is important to realize that aging is an irreversible process that occurs over a period of time. In the Policy for the Elderly in Malaysia, the elderly is defined as "the decrease in the ability of being in consistency with environmental factors" and the policy defines those above 60 years of age as old by adopting the criteria set at the First World assembly on Aging in Vienna in 1982 (2). Globally, older people make up a large and increasing percentage of the population. In 2000, there were about 600 million people aged 60 and above. It was estimated that in 2025 there will be 1.2 billion of elderly people and this will increase to 2 billion by 2050 (3). In almost every country in Asia the populations are aging. A country is said to be aging when at least 7% of the population are elderly (4). In Malaysia, the decline in fertility and mortality as well as improvement in life expectancy are said to be responsible for the ageing population by the year 2020. In Malaysia, currently, out of a population of 26 million (2005), 1.4 million (6.3%) are aged over 60 years. It is projected to increase to 3.3 million out of 33 million (10%) by 2020 (5).

Falls has been identified as one of the most prevalent public health problems facing older adults (6, 7). Around 40 to 60% of falls lead to injuries: 30 to 50% of these being minor injuries, 5-6% being major injuries

excluding fractures and 5% being fractures (8, 9, 10). Up to 1% of falls among the elderly resulted in hip fractures which has a significant morbidity, mortality and cost to health services (8, 9, 11).

Studies had been done to investigate why the elderly fall and these have concluded that a combination of several factors contributed to a fall, including the presence of certain 'intrinsic' or 'extrinsic' factors (11, 12, 13) which increased the risk of falls. Risk factors that have been identified include health status, medication use, impaired vision and hearing as well as environmental hazards. Information on occurrences of falls among the elderly and their associated risk factors in Malaysia are lacking. Furthermore, studies done in other countries showed that the role of environmental hazards in falls risk factors for elderly was uncertain. Investigation of the relationship between environmental hazards and falls in general population had shown mixed results (14, 15). However, it was noted that home environmental modifications had appeared to increase the effectiveness of multi-factorial interventions for reducing fall risk, and was recommended as part of a comprehensive fall prevention strategy (16, 17, 18). Therefore, factors affecting falls among the elderly and

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the occurrence of environmental hazards in our local setting should be investigated. The aims of this study were: (1) to determine the prevalence of overall falls and home falls among the elderly population in Masjid Tanah Province, in the state of Malacca, Malaysia (2) to explore the prevalence of environment hazards and other risk factors; and (3) to determine associations between home falls and these environment hazards.

Methodology

This was an analytical cross sectional study conducted from June 2006 until May 2007. The study started with a sampling of eligible study subjects from the target population. The participants were interviewed for history of fall at home and followed by home assessment to identify environmental hazards at home. This study was conducted in the Masjid Tanah Province. According to the village safety committee (JKKK) profile in 2006, the total population in this province was 15,956 people. Out of this, 11,892 were people above 65 years old (19). Main economic activities in this area are agriculture and tourism.

The target population in this study was all non-institutionalized older people above 60 years who were living in the community of Masjid Tanah Province. The sampling method used in this study was two stages cluster sampling. In the first stage, six out of 12 villages (clusters) were randomly selected by drawing six sealed envelopes containing the villages' name from a box. All houses with eligible occupants, 60 years and above, were included at this stage. In the second stage, cluster was sampled based on the number of elderly occupants in each houses. The first cluster consisted of houses with single elderly occupant while the second cluster consisted of houses with more than one elderly occupant. The eligibility criteria was the elderly who were living in their homes or leasing similar accommodations and who consented to this study. The elderly were excluded if they were diagnosed with psychiatric illnesses or if they were bedridden or if they were not able to walk. Persons with physical lower limb deformity were also excluded.

The sample size calculation was carried out by using PS Power and Sample Size Programme version 2.1.31. The type I error rate (alpha) was fixed at 0.05 and power at 80%. Previous studies showed that the prevalence of fall in elderly ranged from 20% (21) to 30% (21) and

that the prevalence of home environmental hazards among the non-faller group was about 30% (22). On the basis of this information, an estimated minimum sample size required in this study to detect a risk of 1.5 or greater for the fallers was 931 persons.

The dependent variable of interest in this study was a history of falls at home during the past 12 months. The definition for fall in this study was based on ICD 9 classification where "fall is an unexpected event where a person falls to the ground from an upper level or the same level" (23). This variable was determined during the interview. The perceived cause of fall and circumstances related to falls were determined from each faller.

The independent variable in this study was the presence of potential hazardous home environment in the participants' homes. This was also determined during the interview. Environmental hazards were defined as features of their homes or their residences that may contribute to a fall. Features such as poor lighting, slippery floors, clutter and handrails are part of the hazards that might have a role in causing falls among the elderly. The safety behaviors of the participants in the home environment were also considered as potential hazards. These components were determined by using two sets of screening tools. The Home-screen scale (HSS) was specifically designed as a nurse-administered instrument to identify environmental and behavioral risks that alert nurses to the need for action to reduce fall risks in the home (24). This instrument is a ten-item scale with two subscale categories: the home safe subscale and home behavior subscale. Each item was rated from 1 to 10 with intervals of 1. A score of 10 represented that all rooms were free from clutter for the home safe subscale and safe for the home behavior. Total subscales score range from 5 to 100. The safety house checklist (SHC) was adopted following a review of literature by Carter *et al* (25). This tool assessed the presence of hazards in each room or areas most frequently utilized by the elderly or in areas which they spend most of their time. Hazards which are thought to increase the risk of falling, slipping or tripping and the absence of safety devices which may prevent falls made up the majority of items in the house checklist. A decision was made about each item and a "hazard" scored if a potential hazard was present or a safety device was absent. If a hazard item area was not there to be assessed then the hazard

item was scored as "not applicable." A hazard score was calculated for each home as well as for individual rooms and areas. The reliability of this checklist was assessed by means of kappa statistic which were adjusted for prevalence and bias and showed significant inter-rater agreement on all items (at $p=0.05$) (25). Other variables that were collected include the socio-demographic pattern, housing characteristics, medical conditions, medication, depressive mood, impaired cognitive function, decline in activities of daily living (ADLs), visual acuity, increased body mass index and impaired in balance and gait performance.

Permission to carry out the study was obtained from the relevant committee and departments, and from the participants. A face-to-face interview guided by a structured questionnaire was carried out on each participant. During the interview, socio-demographic information, medical and medication history, housing characteristics, occurrence and circumstances of falls events as well the Geriatric Depression scale 15 items (GDS 15), Elderly Cognitive Assessment Questionnaire (ECAQ) and Barthel index (BI) were completed. The home assessment was performed at the same setting. The physical assessment of participants was conducted within one week from the interview day in the nearby Health Clinic based on an appointment system. This assessment included measurements of weight, height and visual acuity as well as balance and gait test.

The completed questionnaires were double-checked for completeness at the end of every interview and physical assessment session as well as before storage. Incomplete information in the questionnaires especially on the physical examination variables (weight, height, BP and visual acuity) was obtained from available medical records from the nearest health clinics. Participants with no medical records available were re-invited to the nearest health centre for completion of these measurements. After completing the variables, data capturing was done using the Microsoft Excel software.

As this study design involved two stages of cluster sampling methods, Intercooled Stata statistical software version 9 was used for complex survey analysis. The analysis was performed in two stages. First, the frequency and prevalence of each variable was calculated. Second, univariate logistic regression analyses were carried out with home falls as the

dependent variable and each of these variables as the independent variable. The results were presented as odds ratios (OR) with 95% confidence intervals (95% CIs).

Results

Study population

Out of 1,049 people who were eligible, only 530 participated (50.5%) in this study. The others either refused to participate or were not at home during the interview. Out of those 530 participants, 14 were excluded from the study, because two were bed bound, four were on wheelchair, three had either rays amputation or below knee amputation and five participants had incomplete home assessment. Thus, only 516 participants were included for analysis. A total of six villages were randomly selected in this study, namely Kampung Tanjung Bidara (200 elderly), Kampung Masjid Tanah (300 elderly), Kampung Durian Daun (89 elderly), Kampung Padang Kamunting (80 elderly), Kampung Pengkalan Balak (280 elderly) and Kampung Seri Tanjung (100 elderly). Sampling design and participants are summarized in Table 1.

Socio-demographic distribution

About 45% of the study population were between the age of 66 years and 75 years old, and 39% were between 60 and 65 years old, while another 16% were older than 75 years. The mean age of study participants was 68.7 years (95% CI 67.9, 69.6). Sixty-seven percent (67%) of study population were female and only 33% were male. The majority of the elderly interviewed were Malays (98.3%). Only a small proportion who were interviewed were Chinese (1.0%) and Indians (0.7%) in this study. More than half (68.4%) of them had no formal education while only 31.6% received any form of formal education. Most of the participants were either unemployed or housewives (73.5%), while small proportions were retired public servants (16.7%), small-medium industry entrepreneurs (6.0%) and farmers/fishermen (3.8%). Their mean monthly household income was RM419.3 (95%CI RM321.5, RM517.0). Sixty percent (60%) were married and another 40% were widowed, divorced or single. The majority of the participants stayed with their spouses (57.4%), while 27.7% stayed with their own children. Another 3.5% of these elderly stayed with other relatives or friends and about 11.4% were living alone. It was noted that more

Table 1: Distribution of Mean Age, Gender and Ethnicity of Study Participants by the Participating Villages, in Masjid Tanah Province (n=516)

Villages	Kampung Tanjung Bidara	Kampung Masjid Tanah	Kampung Durian Daun	Kampung Padang Kamunting	Kampung Pengkalan Balak	Kampung Seri Tanjung
Mean age* (years)	67.8 [66.5, 69.2]	68.3 [67.9, 68.8]	69.4 [68.7, 70.2]	70.3 [68.7, 71.6]	68.9 [68.0, 69.8]	70.1 [69.1, 71.2]
Gender*						
Male	35.6 [28.3, 43.7]	29.1 [23.2, 35.8]	33.9 [21.3, 49.3]	30.5 [17.3, 47.9]	39.4 [30.7, 48.9]	25.0 [15.5, 37.6]
Female	64.4 [56.3, 71.7]	70.9 [64.2, 76.8]	6.6.1 [50.7, 78.7]	69.5 [52.1, 82.7]	60.6 [51.1, 69.3]	75.0 [62.4, 84.5]
Ethnicity*						
Malays	98.9 [97.7, 99.4]	97.3 [96.3, 98.0]	100	98.3 [96.2, 99.2]	97.8 [88.0, 99.6]	100
Chinese	0	0.9 [0.7, 1.2]	0	1.7 [0.8, 3.8]	2.2 [0.4, 12.0]	0
Indians	1.1 [0.6, 2.3]	1.8 [1.3, 2.5]	0	0	0	0
Marital status*						
Single	1.1 [0.6, 2.3]	0	0	0	0	0
Married	57.5 [28.2, 82.3]	57.3 [44.2, 69.4]	74.6 [58.0, 86.2]	54.2 [21.2, 83.9]	66.4 [34.9, 87.9]	51.6 [31.0, 71.6]
Divorced	0	0.9 [0.7, 1.2]	1.7 [1.0, 3.0]	1.7 [0.8, 3.8]	0	1.6 [1.0, 2.4]
Widowed	41.4 [17.4, 70.3]	41.8 [30.0, 54.7]	23.7 [12.9, 39.4]	44.1 [15.7, 76.9]	33.6 [12.1, 65.1]	46.9 [27.6, 67.1]
Level of education*						
None	37.9 [31.3, 45.1]	31.8 [28.4, 35.4]	13.6 [7.6, 23.1]	40.7 [26.0, 57.2]	32.8 [25.0, 41.8]	21.9 [16.7, 28.1]
Primary	59.8 [51.7, 67.3]	53.6 [46.6, 60.6]	78.0 [63.2, 87.9]	57.6 [40.0, 73.5]	61.3 [52.6, 69.4]	64.1 [55.2, 72.1]
Secondary	2.3 [1.1, 4.6]	13.6 [10.0, 18.3]	6.8 [3.8, 11.7]	1.7 [0.8, 3.8]	5.8 [3.5, 9.5]	12.5 [9.2, 16.8]
Tertiary	0	0.9 [0.7, 1.2]	1.7 [1.0, 3.0]	0	0	1.6 [0.1, 32.2]
Household income*						
Mean total income (RM)	326.2 [261.6, 390.7]	349.2 [334.2, 364.1]	390.0 [352.3, 427.7]	412.3 [266.9, 557.7]	551.9 [502.9, 600.7]	490.4 [421.0, 559.8]
Less than RM500	87.4 [80.3, 92.2]	90.0 [86.5, 92.6]		81.4 [46.8, 95.6]	68.6 [56.8, 78.4]	82.8 [74.2, 89.0]
RM500-RM1000	12.6 [7.8, 19.7]	9.1 [6.7, 12.2]		16.9 [3.2, 55.5]	27.0 [15.6, 42.6]	12.5 [6.4, 22.9]
More than RM1000	0	0.9 [0.7, 1.2]		1.7 [0.8, 3.8]	4.4 [1.8, 10.2]	4.7 [3.0, 7.3]
Housing type*						
Single storey	48.3 [37.4, 62.1]	40.9 [35.2, 46.9]	37.3 [27.7, 48.0]	16.9 [7.2, 35.0]	30.7 [19.5, 44.7]	32.8 [24.1, 42.9]
Double storey	51.7 [37.9, 65.3]	58.2 [52.1, 64.0]	62.7 [52.0, 72.3]	83.1 [65.0, 92.8]	68.6 [55.2, 79.5]	67.2 [57.1, 75.9]
Shops house	0	0.9 [0.7, 1.2]	0	0	0.7 [0.3, 1.7]	0
Living*arrangement						
Spouse and children	55.2 [27.6, 79.9]	54.5 [40.8, 67.6]	52.5 [31.3, 73.1]	55.9 [23.1, 84.3]	66.4 [44.1, 83.2]	50.0 [29.1, 70.9]
Children only	33.3 [16.4, 56.1]	23.6 [17.2, 31.5]	35.6 [21.7, 52.5]	27.1 [11.0, 52.9]	24.8 [14.0, 40.1]	31.3 [19.2, 46.5]
Other	3.4 [1.7, 6.9]	4.5 [3.4, 6.1]	0	5.1 [2.2, 11.1]	2.9 [1.2, 6.8]	3.1 [2.0, 4.9]
Alone	8.0 [3.9, 15.9]	17.3 [12.7, 23.1]	11.9 [6.6, 20.3]	11.9 [6.6, 20.3]	5.8 [2.4, 13.5]	15.6 [9.9, 23.9]

*Wald Design-based F test, $p > 0.05$

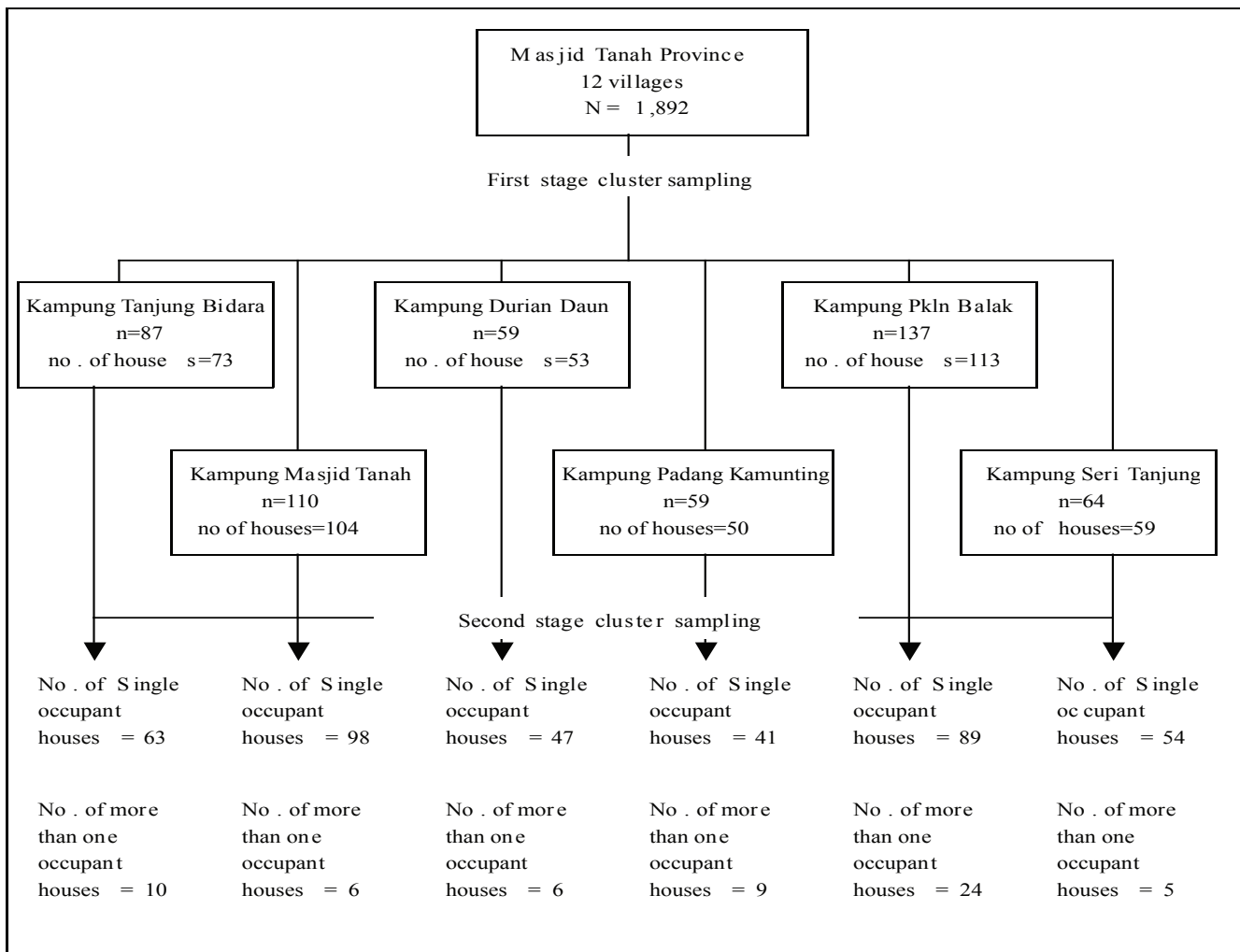


Figure 1: Summary of sampling design and participants

women (91.4%) were living alone compared to men (8.6%).

There were no significant variations in socio-demographic characteristics between the elderly studied in each village. This was demonstrated by the Wald Design-based F test which showed that the *p* values were >0.05 for each characteristic (Table 1).

Overall falls

A total of 141 faller participants (27.3%) reported 210 falls; 74.5% had experienced one episode of fall, 12.8% had two episodes of falls and another 12.8% had three or more falls in one year. Fall occurrence was highest in the younger elderly group (60-70 years) which accounted for 59.6% of total falls followed by the elderly in their 70's (32.7%) and only 7.8% of elderly more than 80 years fell during the past 12 months. Women accounted for three quarters of the falls in this study. More than half (55.3%) of these fallers did

not suffer any injury and about 38.3% sustained mild or soft tissue injuries only, including, bruises, abrasions and haematoma. Only about 6.4% of them sustained either joints dislocations or fractures. No information on utilization of medical facilities or hospitalization were gathered. On exploring the perceived cause of falls among the participants, 39% perceived their fall events was due to having slipped, 25.5% due to being tripped and another 17.0% of falls occurred due to bodily imbalance. Giddiness and weakness of lower limbs were thought to be the cause for falling by 7.1% and 3.5% of participants respectively. Most falls occurred in the evening (40%) and at night (19.9%) followed by at dawn (16.3%) and in the morning (6%). Another small proportion of fallers were unable to remember the circumstances that led to their falls. In this study, it was found that most falls occurred inside the homes (66.7%); 19.1% outdoors and another 14.2% occurred while away from their homes and surroundings. For further evaluation of the relationship

Table 2: Crude Odds Ratio for the association between study characteristics with home falls among the elderly in Masjid Tanah Province

Characteristics	Home Falls (n=516)		Crude OR	95% CI
	Yes	No		
Age				
60-65years*	0.24	0.76	1.0	-
66-75 years	0.25	0.75	1.1	[0.7, 1.8]
More than 75 years	0.27	0.27	1.2	[0.6, 2.5]
Gender				
Male*	0.19	0.81	1.0	-
Female	0.28	0.72	1.7	[0.9, 2.9]
Ethnicity				
Malays*	0.25	0.75	1.0	-
Chinese	0.48	0.52	1.1	[0.1, 22.2]
Indians	0.54	0.46	1.6	[0.4, 6.1]
Marital status				
Married*	0.23	0.77	1.0	-
Widow/Single/Divorced	0.29	0.71	1.4	[0.7, 2.5]
Education level				
None	0.26	0.74	1.1	[0.4, 2.5]
Primary	0.24	0.76	0.9	[0.3, 3.1]
Tertiary/Secondary*	0.26	0.74	1.0	-
Total household income				
Less than RM500	0.27	0.73	3.3	[0.7, 15.3]
RM500-RM1000	0.21	0.79	2.3	[0.5, 10.9]
More than RM1000*	0.098	0.90	1.0	-
Living arrangements				
Spouse and children*	0.23	0.77	1.0	-
Children only	0.28	0.72	1.3	[0.7, 2.3]
Alone	0.26	0.74	2.6	[0.7, 9.5]
Others	0.44	0.56	1.2	[0.6, 2.4]
Diabetes mellitus	0.26	0.73	1.1	[0.7, 1.6]
Hypertension	0.25	0.75	0.9	[0.5, 1.8]
Heart disease	0.29	0.71	1.2	[0.4, 3.4]
Epilepsy	0.38	0.62	1.8	[0.4, 7.8]
Stroke	0.33	0.67	1.5	[0.6, 3.8]
Knee osteoarthritis	0.34	0.66	1.6	[0.9, 3.1]
Medication				
Less than 4 types	0.27	0.73	1.1	[0.5, 2.3]
More than 4 types	0.23	0.77	0.9	[0.4, 2.2]
Depressive mode	0.33	0.67	1.9	[1.1, 3.3]
Cognitive function				
Borderline case	0.32	0.68	1.6	[0.8, 3.4]
Probable case	0.34	0.66	1.8	[0.9, 3.7]
Activity daily living				
Need assistance	0.20	0.80	0.7	[0.2, 2.4]
Body mass index (BMI)				
Underweight	0.27	0.73	1.1	[0.7, 1.7]
Overweight	0.25	0.75	0.9	[0.6, 1.6]

Row proportions

OR – Odds Ratio [95%CI – 95% Confidence Interval]

*Reference category

between home environment and other independent characteristics with occurrence of fall, only home falls were considered in the analysis.

Home falls

In this study, home falls were defined as a history of fall which had occurred inside and in the immediate surroundings of the elderly’s home within the past 12 months. It was found that the prevalence of home falls among the elderly in this study was 25.1%. Home falls occurred more commonly in females (66.8%) than in males (33.2%) and most home fallers were in the age range of 60-70 years old (54.3%). Within the home, falls commonly occurred in the living room/hallway (33.9%), bathroom/toilet (29.9%), dining room/kitchen (12.7%) and bedroom (3.1%) while outdoor falls accounted for only about 20.4%.

Home environment

In this study, the home environment was assessed by using two instruments.

Home screen scale (HSS)

In the home safe subscale, the characteristics of five hazards were assessed. Based on the cut-off points of each subscale items at the 25th percentile of this study population, it was found that about 19.4% of houses had unsafe clutter present and 16.2% had unsafe floor covering, at least in one of the areas assessed. Inadequate daylight illumination was observed in 30.5% of the homes, while 19.3% homes had insufficient night lighting. It was also found that 21.5% of these elderly homes had hazards present in their toilet. Further analysis to look for the association between home environment and study characteristics found that mean age ($p=0.01$) and cognitive function ($p=0.014$) were significantly associated with the

presence of hazards in the home environment. This step was performed in order to look for possible confounders statistically.

Safety house checklist (SHC)

This scale was designed to look for hazards in specific areas used most frequently by the elderly inside their homes. From all the areas observed, the bathroom was the most common site which has at least one hazard. This was found in nearly 40% of the homes visited. The other sites that were surveyed were the hallway, the living room, the dining room, and the kitchen. Thirteen percents (13.0%), 8.3%, 9.4% and 12.8% of homes were found to have at least one hazard in each area respectively. It was also noted that in about 4% of these homes the bedrooms occupied by the participants were hazardous.

Risk factors for home falls

Table 2 describes the relationship between study variables and home falls among the elderly.

Home environment and home falls

Crude and adjusted association between home environment and home falls among the study participants are shown in Table 2a and 2b. Based on the home safe subscale of home screen scale (HSS), there was no association between falls at home and the home environment. The crude odds ratio was 1.0. The odds ratio adjusted for age, gender, depressive mood and cognitive function remains insignificant (Table 2a).

The same relationship was also observed when the safety house checklist scale was used to classify home environment. The classification was based on the cut-off value at the 75th percentile of the study population composite score. Houses with a total score of more or

Table 2a: Relationship Between Home Fall Among the Elderly and Home Environment Based on Home Safe Subscale of HSS (Johnson M et. al. 2001) $n=516$

Home environment	Home falls		Crude OR [95%CI]	Adjusted OR [95%CI]*
	Yes	No		
Potential hazardous (score <= 40)	24.6 [13.7, 40.3]	75.4 [59.7, 86.3]	1.0 [0.3, 2.8]	1.0 [0.4, 2.7]
Safe (score>40)	25.2 [15.5, 38.1]	74.8 [61.9, 84.5]		

Key: row percentages [95% confidence intervals for row percentages] *Adjusted for age, gender, depressive mood and cognitive function

equal to six was categorized as potentially hazardous. It was found that there was an association between home environment and home falls (OR 1.1, 95% CI 0.9, 1.2). However, this relationship was not significant (Table 2b).

Further exploration of the individual elements of home environment assessed in the study with occurrences of home falls found that for exposure to more or equal to one hazards per room, the odds ratio adjusted for age, gender, depressive mood and cognitive function were 2.1 (95% CI 1.1, 4.0) for the bedroom, 1.4 (95% CI 1.1, 2.1) for the bathroom, 1.1 (95% CI 0.6, 1.7) for the kitchen, 1.1 (95% CI, 0.3, 4.9) for the living room, and 0.5 (95% CI 0.1, 2.7) for the hallway.

Discussion

Background characteristics of study population

In this study, almost all the participants were Malays (98.3%) while Chinese and Indians were represented by small proportions of 1.0% and 0.7%, respectively. The proportion of contributions by ethnic group differs from the background population. However, this distribution was closer to the ethnics' distribution of each selected village (cluster) where most Chinese and Indians were found in areas with economic activities and in town areas for example, in Kampung Masjid Tanah and Kampung Pengkalan Balak. The rest of the clusters were mostly Malay rural residential areas (19). More females were interviewed in this study. This was reflective of the gender distribution of older people in Masjid Tanah where 54% of elderly above 65 years were females (19). Furthermore, it was reported that women tend to live longer than men, so the disproportion between males and females also increased with ageing (5). It was also noted that this group of participants had never received any formal education (68.4%). This was similar to the national elderly population's pattern

of education level. A review on national policies and program has reported that the present cohort of Malaysian older persons are not well educated (1991 Census) due to the limited educational opportunities during the nation's economic development in the early decades of the twentieth century. Some 63% of older persons had not received any formal education at all (26). Findings suggested that more women were living alone than men. This finding was similar to the study done by Davis MA *et al* among 7,651 adults, aged 45 to 74 years in the National Health and Nutrition Examination Survey (NHANES I) in the United States (27). They found that the proportion of women who were living alone were higher than men and for women, this proportion increased with age.

Occurrences and consequences of falls

The prevalence of falls in this study was found to be much lower than occurrences reported by the Western studies (6, 21, 28, 29). This could be due to the fact that older people were often reluctant to report falls occurrences or that they simply forgot about the events.

A part of studying falls would not be complete without the consideration of fall sequels. Only types of injuries were captured in this study, the prevalence of needing medical attention and hospitalization were not captured. Falls had other consequences besides injuries. Long periods of being bedridden and fear of falling were common consequences that needed further consideration.

Home environment and home falls

In the whole group, the presence of home hazards did not increase the risk of falls during the past 12 months. After an adjustment for possible confounders (age, gender, depressive mood and cognitive function),

Table 2b: Relationship Between Home Fall Among the Elderly and Home Environment Based on Safety House Checklist (Carter E *et al* 1997) n=516

Home environment	Home falls		Crude OR [95%CI]	Adjusted OR [95%CI]*
	Yes	No		
Potential hazardous (score >= 6)	26.6 [16.2, 40.4]	73.4 [59.6, 83.8]	1.1 [0.5, 2.7]	1.1 [0.9, 1.2]
Safe (score < 6)	24.7 [15.9, 36.3]	75.3 [63.7, 84.1]		

Key: row percentages [95% confidence intervals for row percentages]
*Adjusted for age, gender, depressive mood and cognitive function

there was no change of risk. This could be due to that "variable" home hazards might have been eliminated or changed before the home assessment was performed. Furthermore, this study collected retrospective history of home falls. It has been shown that hazards were removed or changed following a fall (30). Another possibility for this lack of association was inadequate power of the study. Retrospective calculation revealed that this study was only 54% powered.

Risk factors for home falls

This study demonstrated that having depressive symptoms was a significant risk factor for fall among the elderly. This was also consistent with many other studies (31, 32, 33, 34). The risk increased from 50% to almost three-fold from the non-depressed elderly. This variation reflects the methodological difference in study design, sample size, study population, duration of assessment as well as the study instruments used in the various studies.

Limitations

The results in this study could possibly be subjected to selection bias as not all of the elderly in the selected cluster participated in this study. This was due to the fact that the interview was performed mainly during the daytime when most of the elderly were not at home. In addition, some elderly had refused to participate in this study. This would also contribute to the issue of lack of evidence of generalizability. As the true reasons for non-response could not be investigated and the characteristics were not determined, it was unclear as to what extent the sample studied is representative of the whole elderly population.

This study relied on self report of falls, which was known to have some systematic reporting bias because of retrospective recall. This was supported by Cumming *et al* where they reported that 13% to 32% of older adults who had fallen previously have forgotten about their falls (15).

Recommendations

Multiple risk factors were found to have associated with fall. These risk factors could be assessed simply, briefly and inexpensively in primary care setting. High risk patients could be advised to participate in a

multi-factorial intervention program or they could be referred to a physicians or physiotherapists to optimize their medical and physical conditions.

Conclusions

There was no association between home environment and home falls in this study. However, further analysis found that hazards present in bedroom and bathroom would increase the likelihood of home falls two fold and 40% of the elderly, respectively. Logistic regression analysis showed that having a depressive mood was the main determinant for home fall among the elderly in this study.

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INTRAHEPATIC SUBCAPSULAR HEMATOMA COMPLICATING LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

A 65-year-old lady with cholelithiasis underwent an elective laparoscopic cholecystectomy (LC) and was discharged on post-operative day 2. She was re-admitted after five days with right hypochondriac pain and fever. Investigations revealed a drop in hemoglobin. Computed tomography showed a large intrahepatic subcapsular collection without intra-abdominal collection. She was treated with intravenous antibiotics. Percutaneous aspiration of intrahepatic subcapsular collection under ultrasound guidance revealed old blood. Hence diagnosis of intrahepatic subcapsular hematoma (ISH) was made. She improved and was discharged after a two weeks' hospital stay. Follow-up ultrasonography examination two months later revealed complete resolution of the hematoma. We report this case due to its rarity and review the previously documented cases of this complication. (*JUMMEC 2008; 11 (2): 83-85*)

KEYWORDS: *laparoscopic cholecystectomy, intrahepatic subcapsular hematoma*

Introduction

Laparoscopic cholecystectomy (LC) is a well-accepted modality in the treatment of gallstone disease. Laparoscopic procedures are associated with faster recovery, earlier return to daily life and the cosmetic benefit of smaller scars. Post-operative hemorrhagic complications of LC are uncommon, and when bleeding does occur, it usually results in hemoperitoneum or an intra-abdominal collection. Development of an intrahepatic subcapsular hematoma (ISH) without intraperitoneal bleeding is unusual.

Case report

This is a 65-year-old lady with underlying hypertension who was on atenolol and nifedipine. She was initially admitted with gallstone pancreatitis two years ago during which an endoscopic retrograde cholangio-pancreatogram (ERCP) with sphincterotomy was performed. She was then scheduled for LC six months later. However, due to unforeseen circumstances, elective LC was only carried out two years after the pancreatitis attack. Intra-operatively, the liver appeared normal and the operation was completed uneventfully without any immediate complications. No bleeding was noted at the end of the procedure. Following delivery of the gall bladder out of the abdomen, a single stone was noted within. Histopathology of the gall bladder showed chronic inflammation. She was discharged two days after surgery.

The patient was readmitted on post-operative day five with right hypochondriac pain and spiking temperature of up to 38.5°C. Her abdomen was soft with slight tenderness over the right hypochondrium. Bruises were noted below her infra-umbilical port site and right flank. Her vital signs were stable. Full blood count revealed a drop in hemoglobin from 14.5 g/dL pre-operatively to 10.3 g/dL and a white cell count of $10.8 \times 10^9 / L$ (white cell count was raised as compared to her baseline result pre-operatively). The liver function tests were unremarkable. Clinical impression of intra-abdominal biliary collection or hematoma was made. Computed tomography was arranged because it has a higher sensitivity as compared to ultrasound. It revealed a 6 cm x 10 cm subcapsular liver collection in segment V and VI which were slightly enhanced with contrast. No extravasation of contrast was seen and there was no free fluid in the peritoneal cavity. The patient was started on sulperazone 1 g thrice a day intravenously. Despite the antibiotics, she still had spiking temperature and a clinical diagnosis of infected subcapsular biloma or hematoma was

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made. Percutaneous aspiration of the intrahepatic subcapsular collection under ultrasound guidance was performed using a 21G needle after three days of antibiotics. The procedure revealed old blood from the aspiration and further drainage was impossible due to clotted old blood. Diagnosis of an ISH was made.

As she continued to have spiking temperature, imipenem was started on day seven of admission. Blood cultures which were taken three times were all negative. The patient improved and was discharged after completing two weeks of imipenem. Follow-up ultrasonography examination two months later revealed complete resolution of the hematoma.

Discussion

Postoperative bleeding is an uncommon complication of LC. A survey of 77,604 cases done in the United States in 1993 found the incidence rate to be approximately 0.08–0.2% (1). Post-operative bleeding most commonly occurred at the gallbladder fossa, the abdominal wall puncture site, the cystic artery, and the falciform ligament. An ISH without hemoperitoneum occurring after LC is extremely rare.

A literature search on ISH without hemoperitoneum revealed only five cases. Out of these, the cause of ISH was identifiable only in one case which the surgeon attributed to an instrument stab wound (2). In the other four cases, the surgeons postulated that ISH was due to:

1. excessive bending and wrinkling of the liver capsule during retraction and dissection of the gallbladder (3)
2. injury to a pre-operatively unidentified intrahepatic hemangioma (4)
3. administration of Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), used for perioperative analgesia might have induced an antithrombotic state through its effect on thromboxane production and platelet aggregation. which possibly aggravated some minor subcapsular bleeding induced by liver retraction (5)
4. injury to the hepatic parenchyma by the guidewire used during ERCP (6)

However, the cause of ISH in our case remains unclear. The operation itself seemed uneventful. Therefore, a high index of suspicion is needed in diagnosing post-LC ISH. In patients who do not recover as expected or have a decrease in haemoglobin post-operatively, low threshold for imaging increases the chances of early detection of an ISH.



Figure 1: Intrahepatic Subcapsular Hematoma (H = hematoma)

In our case, the ISH was of moderate size. It was drained percutaneously and the patient was protected with antibiotics. Follow-up imaging was performed till the hematoma was resolved completely. Similar management was noted from our literature search, whereby stable patients with a small, nonexpanding ISH were treated conservatively with closed clinical monitoring (7). On the other hand, percutaneous drainage under ultrasound guidance was performed for cases with moderate to larger-sized hematomas.

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INTRAPULMONARY BRONCHOGENIC CYST: SINGLE CASE REPORT

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ABSTRACT

Intrapulmonary bronchogenic cyst is a rare congenital lesion originating from abnormal budding of the embryonic foregut. It is less common than mediastinal bronchogenic cyst. We describe a case of intrapulmonary bronchogenic cyst and discuss the treatment of this condition. (JUMMEC 2008; 11 (2): 86-88)

KEYWORDS: Intrapulmonary bronchogenic cyst, treatment

Case Report

A 51-year old man, who was an ex-smoker, was admitted in August 2003 with two months' history of productive cough and an episode of haemoptysis. There was no history of fever, loss of weight or appetite. He had similar complaints five years ago which were successfully treated with antibiotics. He denied having any contact with tuberculosis patients. Clinical examination was unremarkable except for minimal crepitations at the base of the left lung.

Upon admission, the patient's full blood count, renal and liver function tests were within normal limits. His erythrocyte sedimentation rate was 21 mm/h and random blood sugar was 11.4 mmol/l. Subsequently, fasting showed that his blood sugar level was normal. Three consecutive sputum samples were negative for acid-fast bacilli. Sputum for bacterial culture did not grow any organism. Chest radiograph showed a thin-walled cyst in the left lower lobe with an air-fluid level and surrounding pneumonic changes (Figure 1a).

He was treated as having lung abscess with intravenous cefotaxime (1 gm daily) and metronidazole (500 mg eight hourly) for ten days. Oral tranexamic acid was also given for hemoptysis. His symptoms improved after completing antibiotics for ten days and he was discharged with instructions to take oral cephalixin (250 mg four times daily) and metronidazole (400 mg twice daily) for two weeks.

However, the patient returned to the clinic a month later with worsening cough. A second chest radiograph showed minimal improvement of the air-fluid level

and of the pneumonic changes (Figure 1b). Sputum culture was repeated and *H. influenzae* resistant to cefotaxime was isolated. He was given oral amoxicillin-clavulanic acid (625 mg twice daily) for one month. Despite this, his cough persisted. He subsequently underwent bronchoscopic examination which showed purulent secretion within the left lower lobe bronchus. Broncho-alveolar lavage fluid grew *Pseudomonas aeruginosa*. Amoxicillin-clavulanic acid was replaced with pefloxacin, which was continued for two weeks. However, this failed to improve his condition. A trial of anti-tuberculous drug therapy was thought to be appropriate at this juncture. This anti-tuberculosis drug therapy was continued for two months but this too did not alleviate the symptoms. Computerised tomography (CT) of the thorax was performed at this stage. It showed a thin-walled cyst in the left lobe with an air-fluid level and surrounding pneumonic changes (Figure 2a and b). There was no communication with the tracheobronchial tree. Subsequently, he underwent thoracotomy for excision of the cyst and plication of the cyst wall. Histology of the excised lesion showed changes consistent with bronchogenic cyst. He remained asymptomatic 12 months after the operation.

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Figure 1: (a) and (b) Bronchogenic cyst. (a) Chest radiograph demonstrate a thin-walled cyst in the left lower lobe with an air-fluid level and surrounding pneumonic changes.

(b) Post-antibiotics. There was no significant change of the lesion except for the slightly decreased air-fluid level and pneumonic changes surrounding the cyst.

Discussion

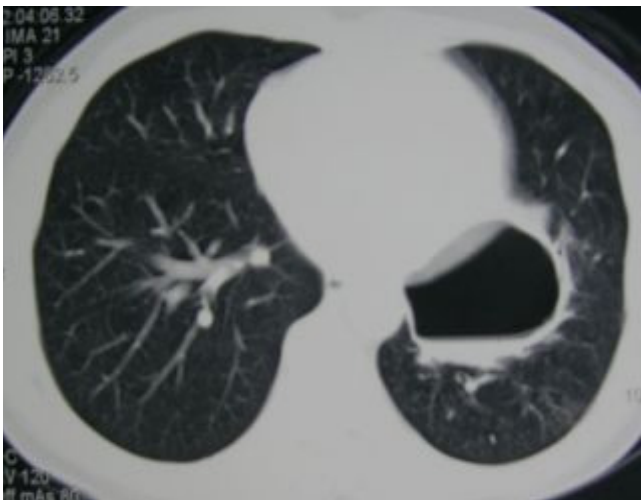
Bronchogenic cysts are congenital lesions arising from the abnormal budding of the ventral foregut that occurs between the twenty-sixth and fortieth days of gestation (1). The cyst is lined by ciliated columnar or cuboidal epithelium and is surrounded by cartilage, smooth muscle, elastic tissue and mucous gland. Intrapulmonary cyst is formed if the budding occurs later in embryonic life. In contrast, early budding results in mediastinal cyst. It is very rare for this to occur in the neck, retro-peritoneal and subdiaphragmatic spaces. It can present itself at any age group and antenatal diagnosis is possible.

Intrapulmonary cyst constitutes 10-29% of all bronchogenic cysts (1, 2, 3). Out of 11 patients reported by Mc Adam *et al* (1) and Yoon *et al* (3), six of the patients were asymptomatic on presentation. Thirty six percent had pulmonary infection and showed symptoms of fever and cough. One patient had chest pain. Hemoptysis was present in only one patient. Another patient had rupture of the infected cyst which caused pneumothorax.

The appearance of intrapulmonary bronchogenic cysts on chest radiographs and CT films can be confused with acquired cysts caused by infection or other pathological etiologies such as lung abscesses, hydatid cysts, giant bullae or lobar emphysema (1, 2, 3). Patients were frequently treated as having lung abscess, especially in the presence of air-fluid level (2). Thickness of the cyst wall is the main differentiating point between benign bronchogenic cysts and other infection-related cysts. In chest radiographs, bronchogenic cysts are thin-walled and have smooth outline. If the cyst is infected or contained secretions, it may appear as a solid tumor or it may demonstrate an air-fluid level with surrounding pneumonic changes. The cyst contents are homogenous and do not get enhanced with radiological contrast (1). In certain cases as reported by Yoon *et al*, the cyst walls were not visible on both enhanced and un-enhanced CT thorax in 80% of intrapulmonary bronchogenic cysts (3). In these patients, attenuation values of the cysts on CT thorax were between 9 to 40H. Yoon *et al* also noted areas of mosaic low attenuation with band-like linear attenuation in the surrounding lung parenchyma of the cysts on high resolution CT scans which represent



(a)



(b)

Figure 2: (a) Mediastinal and (b) Lung window. CT demonstrates a thin-walled cyst in the left lobe with an air-fluid level and surrounding pneumonic changes. There was no communication with the tracheobronchial tree.

areas of emphysema, bronchiolisation and fibrosis on histology. Air-fluid level, as seen in our case, was seen only in one of their patients. Not infrequently, the cyst may be completely filled with air (1).

Despite several radiological imaging, a definite diagnosis of bronchogenic cyst cannot be established without histological diagnosis. About half of the

patients with bronchogenic cyst had other diagnosis before surgical resection (4). Cartilage on the cyst wall is an important histology to differentiate bronchogenic cyst from other acquired cyst (1). In general, there is no specific recommendation for the management of intrapulmonary bronchogenic cyst. Most of the authors advocated surgical removal of the cysts even in asymptomatic patients as complications eventually developed in the majority of the cases (1, 2, 3, 4). Some of the complications may be life threatening for example, resulting in fatal air-embolism and pneumothorax (2, 5). Furthermore, cases of complications were associated with operative difficulties and higher post-operative morbidity (2, 4).

In conclusion, intrapulmonary bronchogenic cyst is a rare congenital abnormality that requires surgical removal especially in patients with complications.

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CONGENITAL BILATERAL APLASIA OF VAS DEFERENS (CBAVD): A REMINDER TO CLINICIANS

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ABSTRACT

Male factor infertility which accounts for 30-50% of infertility is a major problem faced by married couples. Congenital absence of the vas deferens, though uncommon, remains the most common abnormality seen in extratesticular ductal and ejaculatory system, accounting for 1-2% of male infertility. It may be unilateral or bilateral. Association with renal abnormality has also been reported with congenital absence of vas deferens (1). The patients are asymptomatic and the congenital abnormality is usually detected when investigation for infertility is carried out. We present a case of an unusual presentation of congenital bilateral absence of vas deferens (CBAVD). (JUMMEC 2008; 11(2):89-90)

KEYWORDS: absent vas deferens, renal agenesis, infertility

Introduction

Male factor infertility which accounts for 30-50% of infertility, is a major problem faced by any couple. Congenital absence of the vas deferens though uncommon, remains the most common abnormality seen in extratesticular ductal and ejaculatory system abnormalities accounting for 1-2% of male infertility. It may be unilateral or bilateral. It was first described by John Hunter in 1737 in a cadaver. We report a case of a young man who is not considering conception with congenital bilateral aplasia of vas deferens (CBAVD).

Case Report

A 20-year-old single man with no previous illnesses was admitted with 2 years' history of reduction in ejaculatory volume and reduction in consistency of the ejaculatory content. Bilateral testes and epididymis examinations were normal, but bilateral vas deferens was not palpable. The semen analysis revealed 1.7 ml of ejaculate, which was acidic in nature (pH 6.8) and demonstrated azoospermia. His hormonal profile, including FSH, LH, prolactin and testosterone were normal. An ultrasound of the scrotum confirmed the absence of bilateral vas deferens with normal testes and epididymis. Intravenous urogram (IVU) also showed an absent left kidney (Figure 1). The patient was reassured and advised to proceed with further investigation and potential *in-vitro fertilization* (IVF) when considering conception.

Discussion

Congenital bilateral absence of vas deferens is an uncommon anomaly contributing to 1-2% of male infertility (1, 2). It was first described by John Hunter in 1737 in a cadaver. Absence of vas may be unilateral or bilateral (3, 4). Absence of vas deferens can be associated with various congenital anomalies such as renal anomalies (i.e. agenesis, malrotation, ectopia, fusion, or polycystic disease), inguinal hernias, varicoceles or cryptorchidism. Renal agenesis in association with absence of vas deferens has been reported to be around 10-30% (unilateral and bilateral absence of vas deferens), though one report claimed up to 80-90% of unilateral absence of vas deferens is associated with ipsilateral renal agenesis (2, 3). Congenital absence of vas deferens has also been found to be associated with cystic fibrosis, an autosomal recessive disorder. Genetic screening for cystic fibrosis transmembrane conductance regulator (CFTR) is advised in those with congenital absence of vas deferens. The role of CFTR screening in patients with renal agenesis is debatable, as various reports by Schelegel *et al*, Augarten *et al* and

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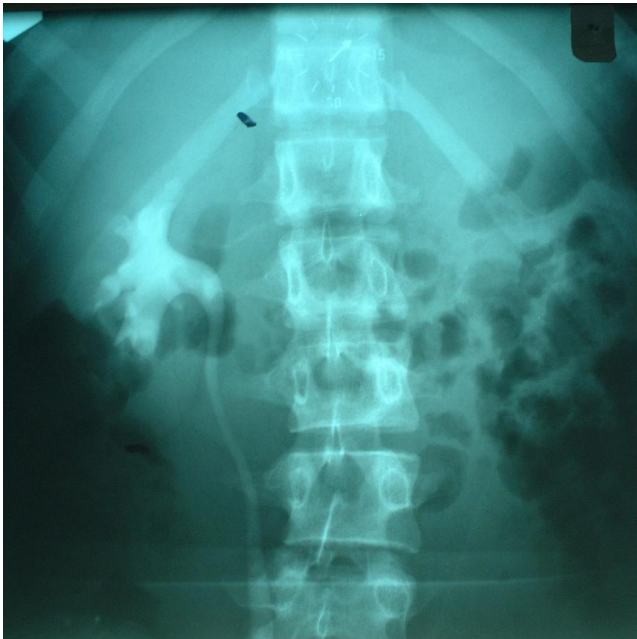


Figure 1: Intravenous Urogram showing absence of the left kidney

Dumur *et al* observed that there was no detectable CFTR mutations in patients with renal agenesis associated with congenital absence of vas deferens. Thus, it was suggested that those with congenital absence of vas deferens with renal agenesis do not usually have a genital form of cystic fibrosis (2, 5, 6). The currently recommended management of couples with infertility owing to CBAVD is sperm retrieval combined with IVF using intracytoplasmic sperm injection (ICSI) after appropriate genetic testing and counseling of the couple regarding the risk of cystic fibrosis.

A majority of the patients with CBAVD are asymptomatic and the congenital abnormality is usually detected present during the investigation for infertility. We present a case of an unusual presentation of a single man with symptoms of reduction in semen volume and consistency, as the first presentation of CBAVD.

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ERRATA IN VOL 11(1)

The text below was missing from the article titled "Sudden Visual Loss in Acute Leukaemia" by Tengku Kamalden TA, Nurliza K, Haris AR (*JUMMEC 2008; 11(1): 30-32*). We regret this error.

Case report

A 17-year-old Chinese girl complained of a sudden painless loss of central vision of the right eye during induction chemotherapy for acute lymphoblastic leukaemia. She was first presented to University of Malaya Medical Centre with a one-month history of per vaginal bleeding, weight loss, epistaxis and lethargy. There was also symptomatic anaemia. She denied history of trauma. On admission, she was pale with hepatosplenomegaly and had skin bruising on the lower abdomen. There was no jaundice. Blood investigations showed anaemia with severe thrombocytopenia (Hb 43 g/L, platelet $10 \times 10^9/L$). The white cell count was normal. Differential count showed presence of circulating blast cells (45%), NRBC (7/100WBC) and metamyelocytes (1%). Coagulation profile was within normal range (INR 1.2, PT ratio 1.17). Bone marrow aspiration confirmed pre-B acute lymphoblastic leukaemia.

While in the ward, she was observed to have non-productive cough. A few days after admission, she started to complain of a slight blurring of vision in the right eye, which suddenly worsened to a central visual loss. Upon examination by the ophthalmologist, visual acuity was counting fingers in the right eye, and 6/6 in the left. External examination of the both eyes were unremarkable, and no haematoma or bruising was noted. There were no subconjunctival haemorrhages or hyphema observed. Dilated fundus examination of the right eye revealed a large, dense, loculated subhyaloid haemorrhage almost covering the entire macula, measuring 8.25 mm horizontally and vertically (Figure 1). The left fundus showed scattered retinal haemorrhages along the major retinal vessels, sparing the macula (Figure 2). In both eyes, Roth's spots were scattered peripherally.

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