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EDITORIAL

Zika on Board

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The Olympics and Paralympic games bring joy to millions of people worldwide. This year it was held in Rio de Janeiro, Brazil amidst the Zika virus epidemic. On 1 February 2016, six months leading to the Olympics, the excitement was dampened by the World Health Organization declaration of the unprecedented vector-borne Zika virus (ZIKV) infection as a public health emergency of international concern [1]. At that point in time, people in Malaysia also felt the heat but had the consolation that the epidemic occurred across the Atlantic on the other side of the world. On 27 August 2016, Singapore reported the first local confirmed case of ZIKV infection in the city-state [2]. It was only a matter of time that Malaysia reported its first confirmed case of ZIKV infection on 2 September 2016 [3]. A 58-year old woman from Klang, Selangor was diagnosed as the first ZIKV case, who had earlier visited her daughter in Singapore who was infected by the ZIKV. As of 22 September 2016, the number of confirmed ZIKV cases in Malaysia has mounted to six with both Polynesia and Micronesia strains [4]. The occurrence of the disease in our continent brings to light how rapidly globalization and free movement of population across geographical borders can accelerate the arbovirus threat across the globe.

The ZIKV is spread through the bite of infected female *Aedes* mosquitoes and evidence has shown it can also spread via sexual and blood transmission [5]. Most of the cases are asymptomatic or subclinical while the symptomatic cases are self-limiting. Other manifestations include neurological (Guillain-Barré syndrome and meningoencephalitis) and autoimmune (thrombocytopenic purpura and leukopenia) complications. More alarming is the association of the virus with infants born with microcephaly as a result of pregnant mothers infected with ZIKV with the risk of microcephaly ranges between 1-13% [6, 7], though the direct causal relationship is still under investigation.

In line with the international response, Malaysia has intensified the surveillance and management activities to control its ZIKV epidemic. These include clinical surveillance, laboratory surveillance, microcephaly and Guillain-Barre Syndrome case detection as well as preparedness and response at all ports of entry [8]. The public health delivery system in Malaysia has improved tremendously over the years following lessons learned from the emerging and re-emerging infectious diseases that affected the country over the recent years. Apart from those commendable measures; in light of this ZIKV outbreak, there are looming questions even though may appear elementary are nevertheless pertinent which the healthcare fraternity should address. Where do we go from here? What more do we need to know and do to help us manage and control this outbreak more efficiently and effectively? These questions would certainly pose a challenge to our public health especially when this arbovirus shares the same transmission vector with dengue and chikungunya i.e., *Aedes* mosquito where the authorities in Malaysia are still struggling to achieve a satisfactory control level in the country.

What shall we do? We need a paradigm shift. We need to look at the re-emergence of ZIKV in a bigger perspective and manage it accordingly. Thus, instead of reacting merely to the notified ZIKV cases, we need to start strategizing how the transmission dynamics of the arbovirus family can be altered; this possibly means to look out of the box for the solutions. The conventional measures for prevention and control should also be complemented with two other elements

which are often neglected and underestimated in most outbreak response i.e., effective communication and social mobilization [9]. We must actively engage in communication with the public to hasten the containment by using all available forms of social medium. With tons of information about the virus in the media, the message should emphasize more on health education; empowering community on the case reports, transmission routes and infection complications rather than general statements on impact and world reaction towards ZIKV [10]. Only then social mobilization, which is commonly underutilized, may help mitigate the social and economic impact during an outbreak. An informed public understands the limitation and the need for the community. Only then we will appreciate the ripple effects - they will bring the community on board, educate the community to actively participate in the outbreak management, and share the responsibility as well as the outcome. Even when the community is faced with great anxiety, an informed public would be able to understand and support any move or decision made by the authorities concerned.

Of late, the controversy which surrounded ZIKV in Malaysia involved the ethical issue in dealing with termination of pregnancy in women with possible ZIKV-related fetal brain abnormalities. This was following a statement made by the Mufti of the Federal Territory, saying that Muslim women could abort their pregnancies if they were infected by the Zika virus to avoid the adverse effect on the lives of their families or the baby itself [11]. In Malaysia, the current law does not provide for abortion for pregnant mothers infected with Zika unless the pregnancy poses a threat to the mother's life [12]. The recent Centres for Disease Control guideline does not include pregnancy termination as an option in managing suspected or confirmed Zika infection. It advocates monitoring the pregnancy with serial fetal ultrasounds in suspected or inconclusive cases and retest for ZIKV when ultrasound suggests abnormalities consistent with Zika infection and fall short in mentioning the alternative path of termination of pregnancy [13]. On the other hand, World Health Organization guideline mentions subtly on the discontinuation of pregnancy as a possible next step in the management of pregnancies with the likelihood of foetal brain abnormalities and states that women who wish to discontinue their pregnancy should receive accurate information about their options to the full extent of the law [14]. The failure to include guidelines on the option of safe, legal termination of pregnancy in Zika-response strategies is not only an issue of reproductive rights but also an issue of reproductive justice [15]. At the time of writing, it is learned that the Ministry of Health of Malaysia will hold a discussion on the matter with the National Fatwa Council regarding termination of pregnancy for women infected by the Zika virus in order to reach a consensus. Irrespective of the outcome of the *fatwa*, we are in the opinion that whether a woman who wishes to carry her pregnancy to term or discontinue the pregnancy should be offered appropriate counselling so that she, together with her partner, will be able to make a fully informed choice on the next step of action.

Despite being a re-emerging disease, there is still much evidence required to effectively manage and control the ZIKV outbreak. The disease behaviour remains dynamic, and a concerted effort by the health authorities and policy makers in implementing the appropriate dynamic alignment to meet the challenges is imperative. It also requires heightened public awareness of personal responsibility which is of paramount importance. The public health preventive strategies remain the cornerstone in the control of this mosquito-borne disease.

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EDITORIAL

Herd Immunity or Heard Not of Immunity?

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INTRODUCTION

The Lancet published this early report by Andrew Wakefield et al on February 28th, 1998; "*12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain….Onset of behavioural symptoms was associated, by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children*" [1].

This article flipped the concrete evidence-based success story of vaccination into an emotionally charged and debatable topic of the century. It was only after a decade of much larger studies which failed to replicate their findings that it became evident that there was no association between Measles, Mumps and Rubella (MMR) vaccination and autism. While it is well known that scientific investigations can be wrong but what is unacceptable here is the fraudulent research practice, in this case, the presentation of wrong data, and the lead author's overwhelming undeclared conflict of interest. The aftermath could not be more devastating, Lancet withdrew the paper fully and the loss of his license to practice medicine in the UK in 2010.

THE WIDER IMPLICATION

The MMR-Autism link saga to the medical world meant that more research, time and money were poured to refute the study and also to expose the fraud but the repercussions however were not only confined to the medical profession. The greatest damage was the appalling tangential increase in vaccine refusal among parents worldwide which fuelled the measles outbreak across the United Kingdom (UK), United States and Canada in the year 2008 and 2009. UK for example, saw a drop in vaccination rates from 87.4 percent to 79.9 percent in the year 2000-01 and 2003-04 respectively and not surprisingly, a dramatic increase in measles cases in the UK in the year 2007-08, which was equal to the combined total measles notifications for the past decade [2].

As the news coverage on the controversy intensified, and coupled with advancement of technology in the social media network, the public perception on vaccination has suddenly changed, the most successful health revolution in the 20th century is now at stake. Seemingly increasing public distrust and confusion over the safety of vaccination were echoed and mischievously elaborated geographically, reaching out to most of the third world countries including Malaysia causing the dreaded domino effect of declining immunisation rates in many countries including our own.

THE BLIGHT ON OUR SUCCESS

We began our free national immunisation programme for Diphteria, Pertussis and Tetanus in 1958, the vaccination for Tuberculosis, Polio and Measles were gradually added into the immunization schedule between the years 1960 to 1980s. Malaysia has done very well since, based on the latest Millenium Development Goal (MDG) report in 2015, we have reached almost full coverage for one-year-old intake of the Measles, Mumps and Rubella (MMR) vaccine. The rate of intake of this vaccine was initially 70.1% in 1990, with massive improvement to 94.3% (2008) and 95.2% in 2013 [19], validated by a recent study in 2016 from a rural clinic in Sabah at 98.5% [29].

Lurking behind this success however is the rising trend of parents refusing to vaccinate their children. We now notice an increase in the number of vaccine refusal from 470 cases in 2013 to 648 in the following year and 1292 in 2015. Among the states in Malaysia, Kedah state recorded the highest number of vaccine rejection cases with steady rise from 239 cases in 2014 to 318 cases a year later.

Why is this happening? Data from the state of Kedah health statistics suggested that the major cause for the refusal was the concern regarding the vaccine contents and their religious permissibility (*halal*). This is supported by a cross-sectional study in 2013 done in Perak that showed the main reasons for parental immunisation refusal were preference to alternative treatment (75%), assumption that vaccines have no effect (37.5%) and apprehension on the vaccine contents (25%), other reasons included not being informed regarding vaccination from health practitioners, information from family members and media, religious influence, personal belief and long waiting time in the clinic [18]. In this study the refusal rate was 8 per 10,000 children per year and immunisation defaulter rate was 30 in 10,000 children per year. Vaccine refusal could also be caused by deferral which could be due to either ill infants or parents missing the schedule or appointments [17].

The number of vaccine preventable diseases has also showed steady increment for the past few years, in tandem with the decrement of immunisation rates. Measles cases in Malaysia has quadrupled from 195 cases in 2013 (6.6 cases per million population) to 794 cases up till September 2016 (34.7 per million population). This is certainly a blight on our success and it pushes us off track from the MDG target of global measles elimination by 2015.

APPREHENSION OF VACCINE CONTENT

Certain chemicals are present as ingredients in the vaccines to ensure safety and effectiveness of the final products. These substances naturally exist in the environment and only become toxic if they reach or exceed a certain threshold.

Among chemicals used in vaccine preparation include thimerosal (mercury), which is an organic compound containing ethylmercury. Its primary role is to prevent bacterial and fungal contamination and has been used as vaccine preservative since 1930's [30].

Virtually all vaccines are now mercury-free; and even if present its potential harmful effect is almost negligible as the chemical content in the vaccine is extremely low.

Aluminium is another compound used in vaccine preparation. It acts as an adjuvant to enhance the immune response to the vaccine antigen [30]. Exposure to aluminium from vaccines is well below the current minimum risk level of 2.0 mg/kg per day [30]. Interestingly, the content of aluminium is higher in breast milk compared to vaccines [31] as well in certain medications such as antacids [31].

However, another reason of apprehension that is being used as bone of contention by anti-vaccination campaigners is the permissibility (*halal*) of the vaccine contents.

THE ISLAMIC VIEWPOINT

The objectives of Islamic law (*maqasid shariah*) are the preservation of five fundamental elements in a person; religion, life, lineage, intellect and property. Correspondingly, the maxim of Islamic law (*Qawaid al Fiqh*) adheres to the principle of avoiding harm, thus taking steps towards maintenance of health and this includes vaccine administrations to prevent serious and life-threatening illnesses among children are in accordance to these principles.

As stated earlier, the main religious consternation regarding vaccination among Muslims parents revolves around the issue of permissibility (*halal*) of the vaccine contents. In this regard, many scholars in Islamic Jurisprudence have in fact issued clear ruling (fatwa) regarding the permissibility of most vaccines used as part of national immunisation programmes worldwide, including Bacillus Calmette-Guerin (BCG), Hepatitis B, Diphtheria, Tetanus, Pertussis and Rubella vaccines [20-24].

Differences of opinion however does exist among the scholars regarding vaccines that have substances derived from pork, which are forbidden (*haram*) in Islam, being used during their manufacturing process. As an example, for the production of oral polio and rotavirus vaccines, trypsin enzyme of porcine origin is used during production to

dissociate the virus from cultured cells, but it is later removed through the process of microfiltration. The use of this substance however has led the Malaysian Fatwa Committee National Council of Islamic Religious Affairs in 2008 to issue a ruling that the use of Rotavirus vaccine is forbidden, other religious considerations by the council include the availability of an alternative trypsin source and the absence of an urgent state (*darurah*) for its use. But other opinion does exist which can be considered to be more in tune with the spirit of Islam that discourages complexity in performance of religious duties, the ruling from the European Council of Fatwa & Research in 2003 led by Yusuf al-Qardhawi. He concluded that the use of oral polio vaccine was permissible based on the following reasons; the negligible amount of trypsin used in the vaccine preparation, the fact that trypsin is filtered and thus not detectable in the final vaccine, and finally what is forbidden (*haram*) is made permissible in the state of necessity. As a result of this ruling, many Muslim countries such as Saudi Arabia, Bahrain, Yemen, Qatar, Iraq, Morocco, Sudan and Pakistan [20] have incorporated Rotavirus vaccine that uses porcine trypsin in their national immunisation programmes.

THE WAY FORWARD

This requires efforts by all relevant stakeholders, government and non-government, to reverse the trend we see locally as well as worldwide. One great stride forward was the WHO approved Global Vaccine Action Plan, a framework to prevent millions of deaths by 2020 through more equitable access to existing vaccines for all peoples in all communities [30]. The aims here are to strengthen routine immunisation to meet vaccination coverage target, accelerate control of vaccine-preventable diseases as well spur research for development of new and improved vaccines [30].

Healthcare providers are undoubtedly the front liners in educating the parents and clarifying any doubts which may prohibit vaccine adherence among them. We know that counseling parents with clear information about the risks and benefits of vaccines, and taking advantage of clinical consultation visits for explanation of immunisation are among the most effective strategies suggested to achieve this [31]. In Malaysia, forums and educational talks to the general public are actively organised by the Malaysian Ministry of Health and other non-governmental organisations to reach for these parents at all levels and localities. Besides that, social media is also very effective and is a borderless educational platform to reach the community.

Finally, the history of vaccination had been a great success story of the last century, Measles vaccination alone has been estimated to have helped save 17.1 million lives in the year 2000 [27]. Lack of knowledge on the issue compounded with contradictory information in social media have led to the disruption of herd immunity that previously had been the gate keeper in protecting our children from vaccine-preventable disease. We must do all we can to ensure it remains a success.

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REFLECTIONS

Medical Education in Malaysia: The Evolving Curriculum (Part 1)

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THE TRADITIONAL CURRICULUM

Medical education in Malaysia has evolved in the past 50 years since independence. This paper highlights the various stages of curriculum development that were made to meet the needs of the developing country.

Malaya was under British rule between the 18th and the 20th Centuries. British Malaya as it was then known comprised of the Peninsular States and the Straits Settlements of Penang, Malacca and Singapore. Western medicine was introduced to the then Malaya in Singapore, with the setting up of the first medical school in 1907. It was called the Government Medical School and later became known as the King George VII College of Medicine in Singapore. In 1910 the first batch of seven male Medical graduates received their Licentiate in Medicine and Surgery (LMS) [1].

In 1949, the University of Malaya was established, based in Singapore, with a branch set up in Kuala Lumpur in 1959. In 1961, both governments of Singapore and Malaya agreed and passed legislation in Parliament to make the Kuala Lumpur Campus an autonomous body known as the University of Malaya; with its own medical school and teaching hospital. Thus in 1962, the government approved the setting up of the University of Malaya Medical Faculty, together with its teaching hospital, in the Klang Valley. The Faculty became fully functional in 1964 with the first intake of 64 medical students. After the hospital was built, the whole complex was named the "University of Malaya Medical Centre (UMMC)", with facilities for undergraduate medical teaching, hospital services, the nursing school and other ancillary services put in place [2].

Professor Thumboo John Danaraj who was then Professor of Medicine in the Medical Faculty at the University of Singapore, was appointed as Founding Dean of the Medical Faculty, University of Malaya in Kuala Lumpur [3]. With his appointment, the process of "head hunting" and appointment of academic staff began together with the selection of potential students for the first academic session.

It was mandatory that the Faculty get relevant and competent professionals to start the ball rolling. These medical academicians came from different parts of the globe, including Sri Lanka, Canada, Singapore and the UK (Figure 1).

Front Row: Professor Winifred Danaraj, SPM (2nd from left), Professor TJ Danaraj, Dean (5th from left), Professor Loke, Biochemistry (6th from left)
Back Row: Professor Chan Kok Ewe, Pharmacology & other Professors (from left to right)

Figure 1 The founding teachers: Faculty of Medicine, University of Malaya, 1965 (Courtesy of the late Prof. TJ Danaraj).

With these academicians on board, the toiling of planning and designing of the medical curriculum started since the first batch of medical students was scheduled to enter the medical school in 1964.

Globally, the medical curriculum followed the traditional didactic teaching of basic sciences comprising of anatomy, physiology and biochemistry

in the first year of undergraduate medical course. In the second year, the subjects of pathology, pharmacology, medical microbiology and parasitology were introduced. This was interspersed with topics on communicable diseases and principles of social and preventive medicine (SPM). The thrust of the undergraduate curriculum then was in the various aspects of issues related to social and preventive medicine. This was deemed to be important because the newly formed Malaysia, for the most part, was still mostly rural.

Professor Danaraj, having had experience as an academician in Singapore, felt that the didactic teaching of "dry" basic science subjects may not be perceived as interesting and relevant by the medical students. Thus, early on in the undergraduate medical curriculum, he introduced the clinical correlation classes (CCC) with clinical cases brought to the auditorium to demonstrate the physical signs and correlate them with basic science topics that were learnt during the previous week (Figure 2). This made the preclinical students understand the importance of basic medical science subjects in order to be able to explain the symptoms and the development of physical signs when disease occurs.

Figure 2 Clinical Auditorium, University of Malaya Medical Faculty. Clinical integration with patients starts in year 1 (CCC) (1967) [Courtesy of the late Prof. TJ Danaraj].

This was perhaps the earliest change in the curriculum to facilitate the teachers to think about possibilities of making basic science "dry topics" more interesting to the students. This gradual introduction of clinical medicine into basic science "preclinical years" and *vice versa* in the clinical years was perhaps the beginning of integrated teaching and the evolution of the undergraduate medical curriculum in Malaysia in the late 1980's.

The clinical years begin from years 3 to 5 with rotations in general medicine, surgery, paediatrics orthopedics and obstetrics and gynaecology. In the clinical years, the integration of basic sciences in the form of clinico-pathological case (CPCs) discussions in the final year, sets the stage for future developments in the undergraduate curriculum. The clinical postings and the CPCs were meant to expose the students to develop their critical and analytical thinking skills during their clinical clerkships. Thus, learning to make reasonable diagnoses based on patho-physiological processes that had occurred, with minimal investigative procedures. This was meant to prepare them for their general medical service as medical officers in the rural areas, and also providing them with the basics for future career development.

NATIONAL STRATEGIES TO IMPROVE HEALTH CARE FOR THE POPULATION

Let us now look at the needs of the country then, and how the medical schools were tasked by the Government to contribute towards improving the health services in the then rural Malaysian society.

During the British Administration of the then Malaya, the legacy left behind by the British was a network of health services that extended to the really remote parts of Peninsular Malaya [4], as depicted in Figure 3.

When Malaya had her independence in 1957, the health programs were somewhat coordinated although there was a gross deficiency of doctors to run the district hospitals and the general hospitals. Healthcare then was provided at best by the hospital assistants (now known as medical assistants, MA).

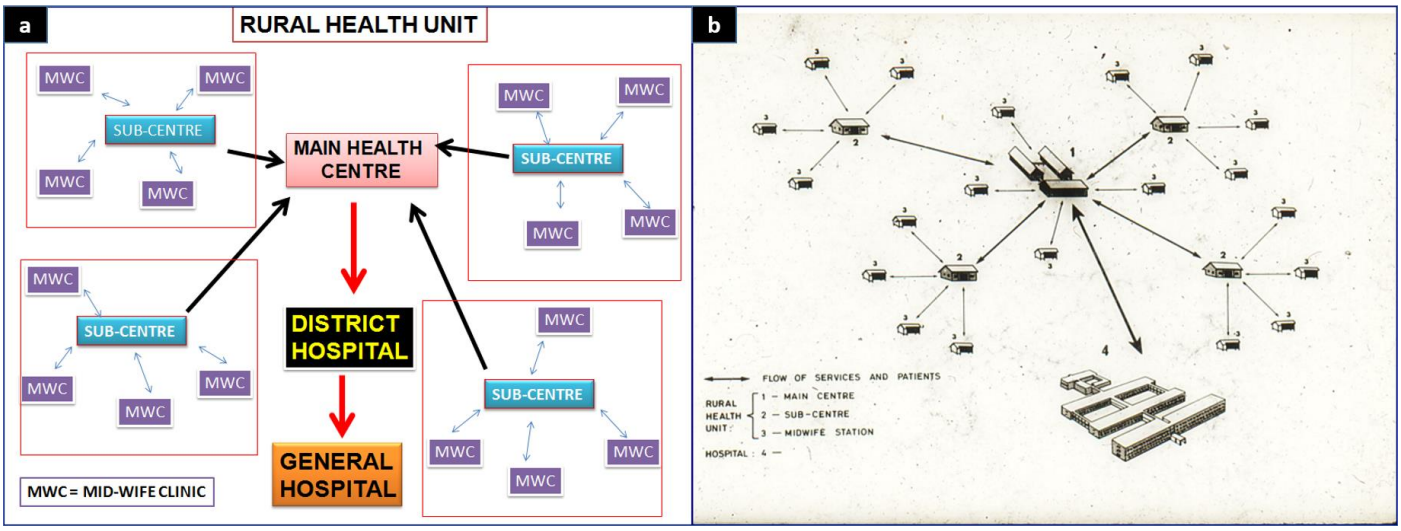

Figure 3 Network of Government run Health Care Services (Legacy from the British Rule of Malaya). a) Rural health unit. b) Replica of the original photo (Courtesy of the late Prof. TJ Danaraj).

During this period the teaching of medicine closely followed the British medical education system that was practiced in the UK. In those early days, the teaching of medicine was by apprenticeship with some knowledge of basic sciences to explain the symptoms.

Then came the didactic (traditional); and scientific discipline model. This preceptor-ship had advantages especially when there was as yet no formal structured curriculum mapping. To this day, clinical mentoring and preceptor-ship is practiced to some extent in the clinical ward rounds with bedside teaching. The concept of mentoring and development of clinical acumen was very apt in clinical practice; both during the undergraduate days and continues in the world of medical academia to this day. This is an art that is slowly dying with the advent of investigative medical practices.

While doctors have to know how to use modern investigative tools, clinical acumen is still required, to be able to make reasonable diagnosis and institute treatment; to be able to determine what investigations are appropriate and when referrals are necessary. This is so because government-sponsored medical graduates face compulsory service that may be in rural areas where there is scarce advanced investigative tools to aid them in making the diagnosis.

In the 1990's with the inevitable trend of producing more specialists, it was deemed necessary for the Ministry of Health to ensure that there will be enough primary care providers and general physicians who would approach patients in a holistic manner. This was tasked to the universities to take the lead to develop programs to train medical officers as generalists and family and primary care physicians.

Medical schools in Malaysia, in developing their medical curriculum, need to address these issues and tailor-make the curriculum to suit the healthcare needs of the country.

To be continued in Part 2: The Blended Curriculum

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CASE REPORT

Invasive Pneumococcal Pneumonia with Massive Empyema: A Case Report

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ABSTRACT

Although the use of appropriate antibiotics has significantly improved the outcome of pneumonia, severe complications are still encountered. We report here of a case with invasive pneumococcal pneumonia with massive empyema. A 2-year-4-month old girl presented with fever for 8 days and intermittent cough for 2 weeks. On examination, reduced air entry with dullness on percussion was noted on the left lung. Chest ultrasound revealed moderate to gross pleural effusion with septations, for which left thoraco-centesis with insertion of pigtail tube was performed. *Streptococcus pneumoniae* was detected via polymerase chain reaction (PCR) test in the pleural fluid. Intravenous (IV) benzylpenicillin and ceftriaxone were given together with one course (5 days) of intrapleural urokinase to breakdown the septations. Timely and appropriate management of pneumonia including the use of thrombolytic agent is vital to ensure optimal outcome and reduce the need of invasive procedures in cases with massive empyema. Public awareness of pneumococcal vaccination is also essential as a part of preventive measures.

KEYWORDS: Pneumococcal, pneumonia, empyema

INTRODUCTION

Worldwide estimates of the yearly incidence of pneumonia in children aged <5-years range from 120 to 160 million, with more than 99% occurring in resource-limited nations [1]. Pneumonia is one of the commonest causes of admission in children and a significant contributor to morbidity and mortality in both developed and developing countries [2]. Although the use of appropriate antibiotics has significantly reduced the number of complications arisen from bacterial pneumonias, severe invasive complications such as cavitary necrosis, abscess formation, pleural effusion or empyema are still encountered in clinical practice [3, 4].

Recently, an increasing number of invasive pneumonia cases caused by *Streptococcus pneumoniae* have been reported in children [5-6]. *Mycoplasma pneumoniae*, on the other hand, has also been reported to cause para-pneumonic effusion, and empyema in children [7]. Currently in Malaysia, nationwide exact figures of invasive pneumonia cases in children have not been established. Nevertheless, hospital-based studies had been performed and showed that *Streptococcus pneumoniae* was the most common responsible pathogen [8, 9]. This report highlights the importance of accurate clinical management to improve the outcome in invasive pneumococcal pneumonia with massive empyema in children. It also highlights the fact that despite the availability of antibiotics, readily available treatment and prevention programmes we still encounter cases with severe complications of pneumonia. There is a need for increase public awareness of the availability of pneumococcal vaccination.

CASE PRESENTATION

A 2-year-4-month old Chinese girl was referred from a private medical centre with the complaints of fever for 8 days and intermittent cough for 2 weeks. Fever was high grade, ranging from 38.5 ˚C to 40 ˚C. Cough was

productive, worse at night and associated with post-tussive vomiting. Oral intake and urine output were both reduced. Both her father and babysitter had history of cough. On examination, she was slightly pale and irritable. Her weight was 10 kg (just below 3rd centile), temperature 38.4˚C, pulse rate 188 beats per minutes, blood pressure 96/60 mmHg, respiratory rate 46 breaths per minutes without recessions, and blood oxygen saturation (SpO_2) 100% under nasal prong oxygen 2L/min. Reduced air entry and dullness on percussion were noted over the left lung. Right lung examination was normal.

Her initial investigations revealed haemoglobin (Hb) 10.8 g/dl, total white cell count (WCC) $24.17x10^9$/L, (neutrophil 56.8%, lymphocyte 26.7%), and platelet $599x10^9$/L. C-reactive protein (CRP) was 26.20 mg/dl on admission. *Mycoplasma pneumoniae* antibody level was noted to be high with 1:320 titre via particle agglutination test. Sputum for acid fast bacilli (AFB) was negative for 3 consecutive days. Adenovirus, influenza A & B, parainfluenza 1, 2, and 3, and respiratory syncytial virus (RSV) were not detected from the naso-pharyngeal aspirate (NPA) and no growth was obtained on sputum culture. Serum glucose, renal and liver functions were all normal.

Chest radiograph (CXR) on admission, which revealed homogeneous opacity on the left with obliteration of left costophrenic angle and mediastinal shift, was shown in Figure 1.

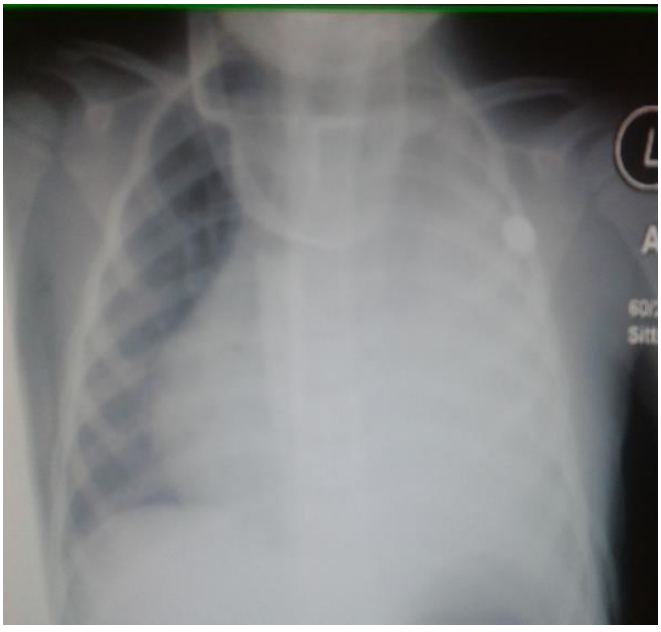

Figure 1 Chest x-ray on admission

She was started on IV benzylpenicillin 100,000 U (100,000U/kg/dose) 6 hourly and IV ceftriaxone 500mg (50mg/kg/dose) 12 hourly to ensure adequate gram positive as well as gram negative coverage. Chest ultrasound revealed moderate to gross pleural effusion with septations on the left lung, for which left thoraco-centesis with pigtail tube insertion was performed. A total of 150ml pus was drained on the first day, and continuously draining for the next 12 days. The exudative fluid was macroscopically cloudy with occasional pus cells under microscope; however, no organism was seen on gram stain. Cell count showed RBC: 10 cell/mm³, WBC: 20 cell/mm³ (predominantly: polymorphs) with no growth on culture. Pleural fluid cytology showed inflammatory cells with neutrophils predominant and no atypical cells. *Streptococcus pneumoniae* was detected via polymerase chain reaction (PCR) test for *Streptococcus pneumoniae* genome in the pleural fluid.

The above two antibiotics were continued for 2 weeks and then changed to syrup cefuroxime for another 4 weeks (a total of 6 weeks antibiotic treatment). Syrup clarithromycin 75mg (7.5mg /kg/dose) twice a day was also given for 1 week, started from day 3 of admission, after obtaining the positive serology result of *Mycoplasma pneumoniae*. One course (5 days) of intrapleural urokinase 40,000 units in 40 ml of normal saline 12 hourly was also administered to breakdown the septations. She was also prescribed syrup multivitamin 2.5ml OD, folic acid 250mcg (2.5ml) OD, and ferrous ammonium citrate 3ml OD in view of low Hb level, and hypochromic microcytic anaemia with pencil shaped cells seen on peripheral blood films. Low serum iron level with high total iron binding capacity was also suggestive of iron deficiency anaemia.

Repeated chest ultrasound on day 10 of hospitalization revealed residual left pleural fluid collection measuring 0.5cm x 0.9cm in maximal depth, with echogenic debris and strands within it. CXR on day 10 post treatment showed improvement with residual left pleural effusion (Figure 2). The repeated CRP and WCC also showed marked reduction. The pigtail tube was hence removed on day 12 of admission and she was discharged with oral antibiotics. She was regularly followed up in our

outpatient clinic and was last seen 2 months ago with full recovery and no residual findings.

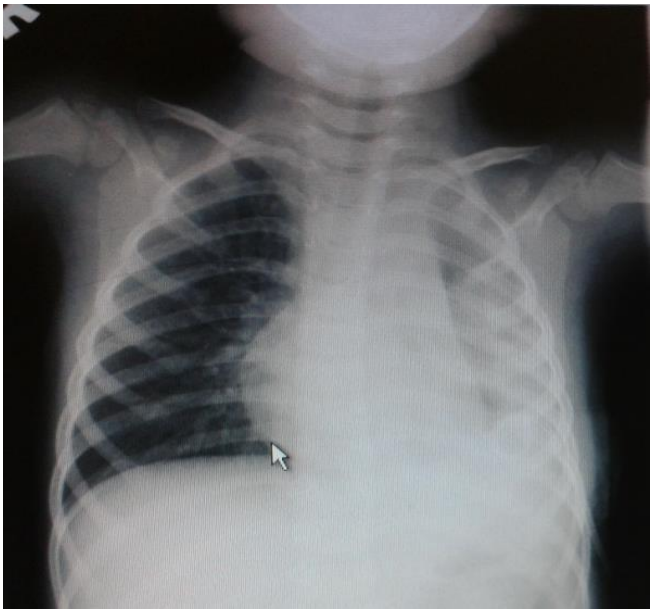

Figure 2 Chest x-ray on day 10 of treatment

DISCUSSION

Invasive pneumococcal disease (IPD) is defined as an acute and a serious communicable infection confirmed by the isolation of *Streptococcus pneumoniae* from a normally sterile sites (eg, blood, cerebrospinal fluid, pleural fluid, joint fluid or pericardial fluid)[10]. Children with IPD present severely ill as a consequence of pneumonia, septicaemia and meningitis. The commonest pathogen to cause community-acquired bacterial pneumonia in children is *Streptococcus pneumoniae*. A recognised and common complication of pneumococcal pneumonia is pleural effusion and empyema[11]. Our patient showed evidence of the presence of *Streptococcus pneumoniae* antigen in her pleural fluid which fullflled the criteria for invasive pneumococcal pneumonia, complicated by empyema.

An increase in complications of pneumonia has recently been recorded in children's population, with *Streptococcus pneumoniae* being the predominant cause[5,8,12,13]. However, there was a recent case report on a large pleural effusion with empyema caused by *Mycoplasma pneumoniae* requiring chest tube drainage for more than a week[14]. Clinicians should be aware of the potential complications of these causal organisms while treating children with pneumoina, so that early diagnosis and appropriate therapy can be instituted. Typically, the clinicians should alert the possible complications of pneumonia such as pleural effusion and empyema if there is a persistent fever after 48 hours of proper antibiotics, together with a change in physical signs. In our case, patient had high fever with productive cough for more than 1 week and had received treatment in a private medical centre. However, her condition did not improve necessitating suspicion of the presence of complications. Therefore, appropriate investigations including blood investigations, CXR and chest ultrasound are warranted, as early as possible, to confirm the possibility of developing parapneumonic effusion and empyema.

Parapneumonic effusions are more frequent compared to true empyema. Parapneumonic effusions could be under-diagnosed and empyema can occur within 7 days of the initial fluid collection[15]. Empyema is, by definition, the collection of pus in the pleural space. According to American Thoracic Society, it has been divided into 3 stages.They are: (1)Exudative – in which a sterile exudate accumulates in the pleural space with low white cells; (2)Fibrino-purulent - where pus is present with an increase in cellular counts; and (3) Organised - in which the pleural space is filled by a thick exudate with heavy sediment and there is a formation of thick peel due to fibroblast proliferation[16,17].

Investigations, at initial cannulation, should include white cell counts, CRP levels, serological testing for mycoplasma and blood culture for any gram positive as well as gram negative organisms. Repeated blood testing should be considered for cases with persistent fever, or if there is a concern of patient not responding to appropriate treatment. Pleural fluid should be sent for microscopy, culture including *Mycobacterium tuberculosis*, PCR test of suspected organisms such as *Streptococcus pneumoniae* and cytology. Chest ultrasound is the investigation of choice to be performed for all children with doubtful para-pneumonic effusion and empyema. A computerised tomography (CT scan) of thorax should be considered for cases; if children have failed to respond to proper treatment, or if there is any doubt of different pathologies[18].

Choice of antibiotics should also adhere with the national guidelines and hospital policy. According to Infectious Diseases Society of American (IDSA) guidelines, benzylpenicillin is the drug of choice for *Streptococcus pneumoniae* with minimal inhibitory concentrations (MIC) for penicillin ≤ 2.0 ug/mL and ceftriaxone or cefotaxime should be given for those with MIC ≥ 4.0 ug/ml and resistant to penicillin[19]. According to Paediatric Protocols for Malaysian Hospitals, benzylpenicillin is to be given as a first line drug in hospitalised cases with pneumonia and cefuroxime or cefotaxime as a second line antibiotic[20].

As a general guideline, benzylpenicillin and ceftriaxone are not often combined but our aim of using ceftriaxone in this case was to cover for other gram negative organisms although it can also be used for *Streptococcus pneumoniae*. There are other reports in the literature where this combination has been used to treat complicated pneumonia with effusion and empyema [21,22]. In severe cases of pneumonia, parenteral therapy combining second or third generation cephalosporins and macrolides should be administered[20,23]. The mortality was lower (p 0.004) for those who received a β-lactam–containing combination regimen as compared for those who received a β-lactam as monotherapy among critically ill patients with bacteraemic pneumococcal illness [23].

A high index of suspicion for *Staphylococcal* infection is also required due to rapid deterioration and significant risk of mortality. If radiological features such as multilobar consolidations, pneumatoceles and spontaneous pneumothorax are present, high dose of cloxacillin (200 mg/kg/day) for a longer period should be given to cover for *Staphalococcal aureus*[20]. Upgrading to second or third line antibiotics needs to be considered especially in cases with no signs of recovery, and patients remain ill with spiking temperature after 48 - 72 hours of initial treatment[20].

All children with empyema should be ideally managed by, or in discussion with, respiratory paediatricians together with paediatric surgeons and transferred to a tertiary paediatric centre, if feasible. The infusion of intrapleural fibrinolytics such as urokinase or tissue plasminogen activatorthrough chest drains can shorten the hospital stay in comparison with chest drain alone[24].

Fibrinolytics act by breaking down fibrin bands causing loculation of the empyema; and hence, drainage of the infected material is improved through the chest tube and thereby pleural circulation can be re-established[24]. Our case markedly improved by pigtail chest tube drain together with intrapleural fibrinolytic therapy using urokinase and prolonged use of appropriate antibiotics. She did not require any invasive surgery like open thoracotomy or video assisted thoracoscopic surgery (VATS) which should be considered if no clinical improvement.

Several interventions to reduce community acquired pneumonia include frequent hand-washing, promoting breastfeeding, reducing exposure to other children, avoiding tobacco smoke, and immunization[25]. The widespread use of pneumococcal immunization has reduced the incidence of IPD[26]. Currently, three types of conjugate vaccine are available, such as 7-valent Pneumococcal Conjugate Vaccine (PCV7), PCV 10 (Synflorix) and PCV 13 (Prevenar 13). PCV7 can prevent the seven different serotypes 14, 6B, 19 F, 23 F, 18 C, 4, 9V. Synflorix (PCV10) constitutes the seven serotypes in PCV7 plus the serotypes 1, 5 and 7F, whereas, Prevenar 13 (PCV13) includes the serotypes of PCV10 in addition to serotypes 3, 6A, and 19 A.

In Malaysia, 19F is the most common serotypes of *Streptococcus pneumoniae* causing IPD followed by 19A, 14 and 6B [9,27,28,29]. Hence, pneumococcal vaccination, by using these vaccines, can reduce the risk of developing IPD cases in Malaysia. These vaccines are available in the private medical centres and have not been introduced in the national immunisation schedule to date. However, discussion to add this vaccine into the national immunisation programme is currently ongoing. In many developed countries, pneumococcal vaccines have already been included in the national immunization schedule to reduce the incidence of IPD in infants and children [30, 31, 32, 33, 34]. Our patient did not receive the pneumococcal vaccine due to the lack of awareness of availability of the vaccine although recommendations for pneumococcal vaccination, even in children without underlying

medical illnesses, are usually made to parents to reduce such complications.

CONCLUSIONS

In conclusion, although the use of appropriate antibiotics has significantly improved the outcome of pneumonia, severe complications such as massive empyema are still encountered. Timely and accurate management including the use of thrombolytic agent is vital to ensure the optimal outcome and reduce the need of invasive procedures if it has developed. Public awareness of pneumococcal vaccination in infants and children is also essential to reduce such complications.

Conflict of Interest

Authors declare none.

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Authors' contribution

TNL initiated the idea for the paper and wrote the initial draft, and both authors (TNL & NSMN) were involved in editing and finalising the paper.

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