The burden of human influenza in Malaysia

Jamal I-Ching Sam, MRCP, FRCPath

Department of Medical Microbiology, Faculty of Medicine, University Malaya, 50603 Kuala Lumpur

SUMMARY

Seasonal and pandemic influenza causes considerable morbidity and mortality globally, but the burden of disease is understudied and underreported in developing countries such as Malaysia. Before considering the cost-effectiveness of introducing interventions such as vaccines to control influenza, it is imperative to determine clinical and socioeconomic impact of the disease. This review summarises the main available literature on human influenza in Malaysia, the possible reasons for the lack of study and awareness of influenza, and important knowledge gaps for future study.

KEY WORDS:
Influenza, respiratory tract infections, burden of illness

INTRODUCTION

Every year, influenza causes millions of infections, and 250,000-500,000 deaths.[1] There are an estimated 28,000-111,500 deaths annually in children under 5 years attributable to influenza, most of which occur in developing countries.[2] Yet, the burden of influenza remains underappreciated and understudied in many developing countries, where there is often a perception that influenza is mainly a disease of temperate climates. The World Health Organization (WHO) strongly recommends studies of influenza epidemiology, disease burden, and vaccine effectiveness in developing countries[3] with a view to encouraging further uptake of vaccine. The purpose of this paper is to review the literature on influenza in Malaysia, the possible reasons for the relative neglect of influenza, and ultimately to increase awareness and understanding of this important disease among Malaysian clinicians.

VIROLOGY

Influenza is a respiratory tract infection (RTI) that causes disease ranging from mild upper RTI to severe pneumonia. Life-threatening complications such as secondary bacterial pneumonia, myocarditis and encephalopathy may occur. Influenza viruses are in the *Orthomyxoviridae* family, and are divided into influenza A, B and C; the latter causes only mild sporadic disease, and will not be discussed further. Influenza viruses principally infect birds, but have evolved to also affect mammals, including humans. The influenza genome consists of 8 RNA segments encoding at least 10 proteins. Two of these, haemagglutinin and neuraminidase, are key determinants of host tropism, immunity and virulence, and also form the basis for naming of influenza A strains. The current influenza A strains circulating in humans are H1N1 and H3N2. Only one human case of avian influenza has been described in Malaysia to date, that of a tourist from China who was confirmed to have H7N9 while visiting Sabah.[4]

Influenza viruses mutate at a low level, and this "genetic drift" allows influenza to continuously evolve and escape from the pressures of population immunity. This means that each individual is always susceptible to infections with new strains. "Genetic shift" occurs when a strain of influenza A virus completely replaces one or more of its gene segments with the homologous segments from another influenza A strain, a process known as reassortment. If the new segments are from an animal influenza virus to which humans have had no exposure and no immunity, worldwide pandemics may ensue. Reassortment has led to at least 3 pandemics, in 1957 (H2N2), 1968 (H3N2) and 2009 (H1N1).

INFLUENZA BURDEN IN ASIA

The literature on the burden of influenza in Southeast and East Asia is relatively limited, although influenza rates of 11-26% of outpatient fevers and 6-14% of hospitalised pneumonia cases have been reported from various countries.[5,6]

In Thailand, influenza was associated with 10.4% of hospitalised pneumonia cases over a 4 year period, and the highest incidence was seen in children under 5 years and adults over 75 years.[7] In the USA, hospitalisation rates of children under 5 years with seasonal influenza were estimated at 1.4 per 100,000,[8] and can be compared with Southeast Asian rates in Singapore (0.7-0.9),[9] Thailand (2.4),[7] Vietnam (3.9-4.7),[10] and the Philippines (4.7).[11] In Hong Kong and Singapore, influenza is associated with annual excess mortality rates of 11-14.8 per 100 000 person-years, especially affecting the elderly; again, these rates are comparable to that of the USA.[12,13]

Influenza was estimated to result in between USD23-63 million in economic costs in Thailand in 2004, with the main contribution from lost productivity due to missed work days.[14] In China, the cost of a child attending outpatients with influenza was USD127, equivalent to 30% of the average monthly household income in urban settings,[6] while the direct cost of hospitalisation of a child for influenza was USD624.[15]

Corresponding Author: Jamal I-Ching Sam, Department of Medical Microbiology, Faculty of Medicine, University Malaya, 50603 Kuala Lumpur.
Email: jicsam@ummc.edu.my

These studies indicate that in Asia, the clinical and socioeconomic impact of influenza is considerable, and is similar to that of countries in temperate climates.

SEASONAL INFLUENZA IN MALAYSIA

The Malaysia Influenza Surveillance System collects data by disease-based and laboratory-based surveillance. In the former, influenza-like illness data is collected from sentinel clinic sites around the country. For the latter, samples are sent from sentinel sites to the National Public Health Laboratory in Sungai Buloh for influenza detection. Using conventional detection methods of immunofluorescence or culture, RSV is the commonest respiratory virus detected in children with ARI, while influenza is identified in 2.0-3.2% of cases.[16-18] However, the use of more sensitive molecular methods such as PCR increases influenza detection rates to 13%,[19] indicating that the occurrence of influenza in Malaysia is underestimated.

Influenza is generally seen year-round in Malaysia, with no clear seasonal trends.[16,20] Influenza A is usually detected more frequently than influenza B, although year-to-year variation may be considerable. The southern hemisphere vaccine is recommended in Malaysia, but the limited data available shows moderate match with circulating influenza strains. For example, between 2005 and 2009, the influenza B lineage used in the trivalent vaccine matched the predominant circulating strain in only 2 out of 5 years.[21]

The incidence of seasonal influenza remains unknown. Seroprevalence rates of 22.3% for seasonal H1N1 and 14.7% for seasonal H3N2 were reported in Kuala Lumpur,[22] indicating that infection with influenza A is common in the general population. Outbreaks among schoolchildren are common.[16,23] Hospital-based studies are useful to indicate the clinical impact of influenza. In a study of 132 children admitted with influenza, 16 (12.1%) had severe disease requiring intensive care or ventilation, and 3 (2.3%) died; 9 of the cases of severe disease and one death occurred in previously healthy children with no underlying chronic illness.[24] Age <12 months was a notable risk factor for severe disease. The data above is scanty, but suggests that seasonal influenza causes endemic morbidity and mortality, and that severe disease does occur in healthy individuals.

PANDEMIC INFLUENZA IN MALAYSIA

The H1N1 pandemic in 2009 was the first global pandemic since 1968, and undoubtedly raised awareness among the public and healthcare staff that influenza is an important and relevant disease.

The first pandemic case in Malaysia was reported in May 2009. Most cases occurred during an intense 6-week period in August-September, and there were 12,307 reported cases with 77 deaths in 2009.[25] The reported cases were underestimated, as many cases were not confirmed in the laboratory. A seroprevalence study carried out before and after the pandemic in Kuala Lumpur showed a cumulative incidence of 18.1%, including almost a third of people aged <30 years,[22] suggesting that the true incidence was much higher.

In a review of 117 adult patients admitted with confirmed H1N1 in Kuala Lumpur, a third had no underlying medical conditions, 14 (12%) developed severe disease, and 7 (6%) died.[26] Bacterial co-infection was seen in 34% of patients admitted in Johor Bahru, especially in those >50 years.[27] In an important national review of 1,362 children hospitalised with pandemic H1N1, 134 (9.8%) required intensive care, and 51 (3.7%) died.[28] A high proportion of 63% had no underlying medical conditions, while the presence of at least one concurrent medical condition increased the risk of death by 4.4 times. In the most affected age group of <2 years, the hospitalisation rate was 33 per 100,000 children (0.1 pre-pandemic) and the mortality rate was 1.3 per 100,000 children (0.1 pre-pandemic).[28] About 8% of children had neurological complications, most commonly febrile seizures, but there were serious manifestations such as influenza-associated encephalopathy, acute necrotising encephalopathy, and intracranial haemorrhage, leading to 4 deaths and 3 cases of permanent disability.[29]

A single economic study has been published, showing that the total direct healthcare costs alone for each hospitalised patient with pandemic influenza was USD510.[30] This figure is 44% higher than the per capita national expenditure on health of USD353 in 2009. A comprehensive review of the full clinical and socioeconomic impact of the pandemic is not yet available, but it is clear that the burden in Malaysia was considerable. It should be noted that the H1N1 pandemic strain is now the predominant circulating seasonal H1N1, and has been the recommended H1N1 component of both northern and southern hemisphere annual vaccines since 2009. Subsequent surveillance shows that H1N1 continued to cause many cases in 2010 and 2011.[25]

REASONS FOR THE NEGLECT OF INFLUENZA

In the past, healthcare workers in Malaysia may have felt that influenza was difficult to diagnose, with no antimicrobial treatment available, and was a generally benign illness. The word "flu" is widely used by the public to refer to any mild upper respiratory tract infection, and this contributes to the perception that influenza does not cause significant disease. The pandemic in 2009 undoubtedly disabused many of that belief, and regular reports of cases and deaths were important reminders of the impact of influenza.

The lack of satisfactory and accessible diagnostic facilities has contributed to past neglect of influenza. Previously, there was a dependence on immunofluorescence and culture for diagnosis, and these could only be done in a handful of virology facilities around the country. However, immunofluorescence is relatively insensitive, while culture is technically challenging and produces results which take too long to be clinically useful. The increasing availability and falling costs of molecular assays and rapid antigen detection kits have made influenza diagnosis more accessible than ever before. However, clinicians need to be aware of the limitations of these tests; for example, the low sensitivity of rapid detection tests when major shifts of influenza strains occur.[31]

Prior to the pandemic, neuraminidase inhibitors to treat influenza (such as oseltamivir and zanamivir) were not widely available in Malaysia. This has now changed. Early treatment with neuraminidase inhibitors should now be considered as it may benefit patients at high risk of severe complications.[32] Resistance to these agents are currently very rare in Malaysia.[33,34]

KNOWLEDGE GAPS IN MALAYSIA

The WHO recommends the use of influenza vaccines to prevent influenza-associated morbidity and mortality. In resource-limited settings, the decision to introduce routine vaccines or other control and treatment measures first requires knowledge of the burden of disease.

There is a need for comprehensive national surveillance to determine population rates for influenza-associated clinic visits, hospitalisation, and mortality. Data on adults is particularly lacking. Such data is especially needed for groups at high risk for severe complications who would be the main recipients of vaccines. The socioeconomic costs of influenza need to be studied, to enable calculations of the cost-effectiveness of introducing any interventions. Determination of circulating influenza subtypes[35] and seasonality will allow more effective choice of vaccine (northern or southern hemisphere formulation) and timing. Better surveillance requires better diagnostics, and field studies to evaluate simpler, more accessible tests such as rapid antigen detection kits. Healthcare workers' awareness must be improved to reduce the misconception that influenza is uncommon in the tropics, and this can be achieved with improved diagnostics and dissemination of surveillance and epidemiological data.

CONCLUSIONS

Although the published data on influenza is relatively lacking, it is evident that influenza causes a significant and under recognised burden of disease in Malaysia. General awareness was raised after the pandemic, and should continue improving with the increasing availability of more affordable diagnostic assays. There remain numerous gaps in knowledge of the burden of influenza in Malaysia. Public health and research efforts are encouraged to fill these gaps, as there are effective interventions available, notably vaccines and antivirals.

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Conflict of interest

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