

REVIEW

COMMUNITY CHALLENGES OF INFLUENZA INFECTION AND STRATEGIES FOR THEIR MANAGEMENT: MALAYSIAN PERSPECTIVE

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Abstract. A group of specialist physicians met on 28 February 2015 and in 2017 to review additional available evidence and put forth a consensus document regarding challenges of influenza infection and strategies for their management in the Malaysian context. The document highlighted global and Malaysian burden of influenza and challenges in influenza management. In addition, the document reported a consensus of the panelists on strategies for managing these challenges in Malaysia. Challenges facing control and management of influenza infection included lack of perception of influenza illness severity among the general population and healthcare workers, availability and affordability issues of influenza vaccine, and lack of perception of influenza vaccination as a part of obstetrics, cardiology, respiratory and geriatric specialty care. Salient strategies set out by the panelists to manage influenza infection included increasing awareness among target population, educating patients as well as the general public concerning the importance of influenza vaccination, promoting influenza vaccination among target population by providing vaccination cards, organizing talks and campaigns on the importance of influenza vaccination, introducing a mass 'Influenza Day' throughout the country, and prioritizing and delivering influenza vaccination among target population.

Keywords: influenza, Malaysia, public awareness, surveillance system, target population, vaccination

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INTRODUCTION

Influenza viruses have been responsible for seasonal epidemics worldwide, with fatal complications in up to one million people every year (WHO, 2003). In USA, influenza contributes to the greatest annual economic burden when compared to other vaccine preventable diseases (Ozawa *et al*, 2016). Development of new virus strains through re-assortment of human and animal influenza virus genes has been the cause of the pandemics in 1918, 1957, 1968, and 2009 (MOH, 2006; WHO, 2015). Recognizing the global magnitude of influenza morbidity and mortality, the World Health Organization (WHO) launched the Global Influenza Program (GIP), which provides member States with strategic guidance, technical support and coordination of activities essential to make health systems better prepared against seasonal, zoonotic and pandemic influenza threats (WHO, 2015). Many influenza-related illnesses and fatalities are preventable through increased use of available highly effective and safe vaccines (WHO, 2003).

Following a Nipah outbreak in 1999, Malaysia has put in place procedures to better prepare for epidemic challenges of influenza (MOH, 2006). However, between 2003 and 2005, six influenza outbreaks have been documented from west Malaysia mainly among students in residential schools (MOH, 2006). Malaysia National Influenza Pandemic Preparedness Plan (NIPPP) proposed in 2006 aims to facilitate an organized, coordinated national preparedness and response in the event of an influenza pandemic (MOH, 2006). In addition, the

Malaysian Society of Infectious Diseases and Chemotherapy (MSIDC) produced "Guidelines for adult immunization" detailing available influenza vaccine, target groups for vaccination, vaccination schedule, and evidences for effectiveness (MSIDC, 2014). However, despite these measures by the Ministry of Health Malaysia (MOH), there are many practical community challenges in the management of influenza infection, such as effective influenza surveillance, failure to perceive severity of influenza infection among the general public as well as healthcare workers, availability and affordability of influenza vaccine, and challenges regarding effective vaccination regimen.

Thus, a group of physicians from specialties related to influenza management reviewed these aspects of influenza infection, discussed strategies for effective management of community challenges of influenza and produced a consensus document enunciating clear insights from the Malaysian context and strategies to achieve better community outcome from influenza vaccination.

CHALLENGES OF INFLUENZA INFECTION AND STRATEGIES FOR THEIR MANAGEMENT

Burden of influenza infection

Globally, an estimated 90 million cases of influenza occur in children <5 years of age and influenza leads to 28,000-115,500 deaths (Nair *et al*, 2011; APACI, 2014). Sam *et al* (2010), in a retrospective evaluation of clinical features and seasonal pattern of influenza in hospitalized children in Malaysia over a 25-year period, noted the following: severe influenza cases in 16

children (nine previously healthy), among whom 12 (eight previously healthy) required intensive care; severe influenza was associated with children <12 months of age, females and absence of rhinitis at presentation; and mean duration of hospitalization due to influenza was 6.2 days. The data suggest influenza leads to considerable socioeconomic loss in terms of absenteeism from school and work, and thus, in Malaysia, seasonal influenza has a considerable impact on healthy children and in those with underlying medical conditions. Zamberi *et al* (2003), in an evaluation of epidemiology of respiratory viruses in hospitalized children with respiratory infections in Malaysia, reported influenza viruses (13.2%) were the third most common respiratory viruses detected in nasopharyngeal aspirates collected from these children.

Annual influenza epidemics account for 290,000-650,000 deaths every year globally (WHO, 2018). According to estimates by the Centers for Disease Control and Prevention, from October 1, 2019 through January 25, 2020, there have been 19,000,000-26,000,000 flu illnesses and 10,000-25,000 deaths due to influenza in the United States (CDC, 2020). However, data regarding influenza-related mortality rates in the tropical regions is scant (Chow *et al*, 2006). Influenza-related disease burden in tropical and subtropical climatic zones is similar to that in temperate zones. In Singapore, a tropical country, and Hong Kong, a subtropical country, influenza associated circulatory and respiratory mortality rates per 100,000 population among people ≥ 65 years of age and among all age groups are similar to that noted in the US, a temperate zone country (Jennings, 2013).

Influenza surveillance system in Malaysia

Given that influenza viruses

constantly undergo antigenic changes, virologic and disease surveillance are essential to identify new virus variants and provide information for appropriate selection of influenza vaccine components. Disease surveillance enables healthcare providers and policy makers to identify individuals at high risk of being infected, to determine effectiveness of current prevention strategies and to make appropriate changes in the annual vaccine and antiviral therapeutic regimen (Budd *et al*, 1996). It is also paramount that healthcare workers (HCWs) and surveillance personnel promptly report influenza A virus infections so that the viruses can be promptly identified and characterized, and implementation of effective public health responses can be initiated (Budd *et al*, 1996). Together, improved real-time surveillance and prompt reporting provide signals of an emerging pandemic outbreak and enable policy makers to act appropriately (Knobler *et al*, 2005).

The Malaysia Influenza Surveillance System (MISS) initiated by MOH in 2004 comprises both epidemiology- and laboratory-based surveillances. Initially, only cases of influenza-like illnesses (ILIs) are included; however, following the H1N1 pandemic in 2009, surveillance for severe acute respiratory infection (SARI) cases was initiated (unpublished, Disease Control Division, MOH).

Beginning with Epid Week 1/2016, the Malaysia Influenza Surveillance Protocol (MISP) was implemented replacing MISS 2004. Development of MISP was guided by WHO Global Epidemiological Surveillance Standards for Influenza 2013, which describes revised global standards for a minimal basic respiratory disease surveillance system for monitoring of influenza. MISP also has two major

components, namely, epidemiology- and laboratory-based surveillances, the former collects influenza-like illness (ILI) and severe acute respiratory infection (SARI) data and the latter samples from identified sentinel sites, such as government health clinics and hospitals nationwide (unpublished, Disease Control Division, MOH).

Throughout 2016, influenza surveillance in Malaysia did not show any seasonal variation for the occurrence of influenza (unpublished, Disease Control Division, MOH). For ILI surveillance, highest (4.4%) ILI consultation rate is during Epid Week 27/2016 while lowest (1.7%) rate during Epid Week 45/2016 (Fig 1). The commonest age group affected with ILI ranges 20-59 years of age followed by 10-19 years of age; age groups >60 years old are least affected. Baseline activity for SARI admission rate ranges 2.3-4.7%, with the majority of SARI cases <13 years of age (Fig 2).

The National Public Health Laboratory, Sungai Buloh and the Institute of Medical Research, Kuala Lumpur received 3,662 influenza samples for testing in 2016, of which 9.8% tested positive for influenza (unpublished, Disease Control Division, MOH Malaysia). Among these, 43.4 and 56.6% of samples tested positive for influenza A and influenza B, respectively (Fig 3).

Due to a lack of local data, burden of disease could be gleaned from the data of influenza-related hospital admissions in pilgrims returning from Hajj and Umrah. Liaison with laboratories such as Lablink Medical Laboratory could also provide important information on influenza-related hospital admissions.

Challenges of influenza infection management: general and in Malaysia

Challenges generally associated with

influenza infection management are viral, clinical and community.

Viral challenges. Viral challenges associated with influenza infection include antigenic shift and drift (Zambon, 1999). Antigenic shift occurs following co-infection of a single host by two different viruses, each possibly from a different host species. A new virus with elements from both the original viruses is created by genomic segment re-assortment and this new virus has unpredictable pathogenicity and pandemic potential due to the absence of human immunity to some of the viral antigens. The pandemic strain created may further change its virulence as it replicates and adapts to the host. Antigenic drift occurs when genes that encode for the viral surface antigens, hemagglutinin (HA) and neuraminidase (NA), undergo stepwise mutation.

Clinical challenges. Influenza is associated with high mortality in infants, elders and in people with chronic diseases (Taubenberger et al, 2008). Patients with diabetes, cardiac disease or chronic pulmonary disease are susceptible to develop severe complications from influenza A viruses, such as hemorrhagic bronchitis, primary viral or secondary bacterial pneumonia, and death (Taubenberger et al, 2008). Occasionally, fulminant, fatal influenza viral pneumonia can occur leading to dyspnea, cyanosis, hemoptysis, pulmonary edema, and death within 48 hours of the onset of symptoms (Taubenberger et al, 2008). Furthermore, overuse of antiviral drugs can lead to resistance in the majority of influenza virus strains (Noah and Noah, 2013).

Community challenges. Influenza vaccination is associated with several challenges at the community level, such as overloading of the healthcare system,

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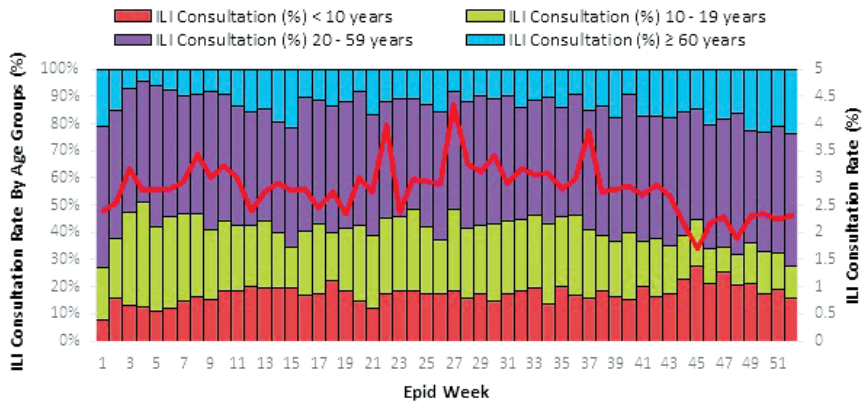


Fig 1-Influenza-like illness (ILI) consultation rate in Malaysia (2016).

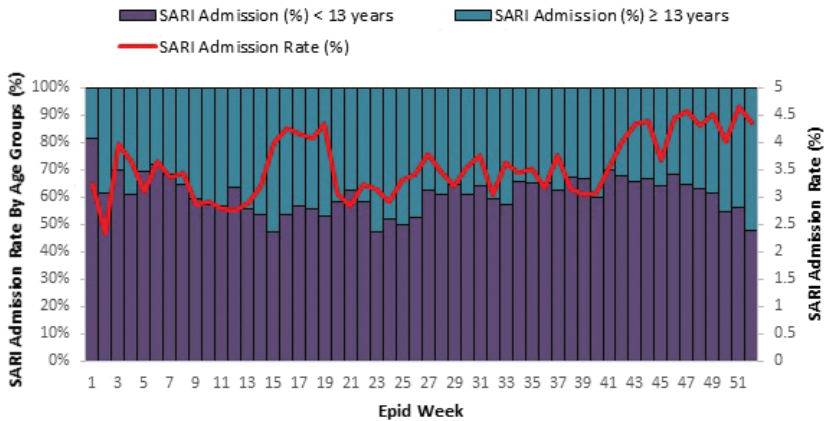


Fig 2-Severe acute respiratory infection (SARI) admission rate in Malaysia (2016).

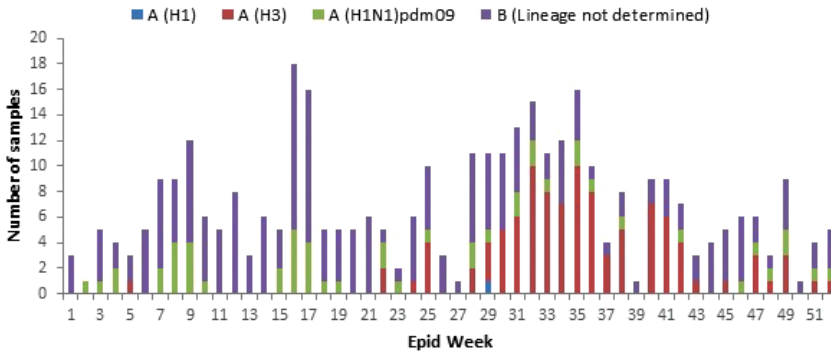


Fig 3-Number of specimens positive for influenza virus according to subtypes, Malaysia (2016).

shortage of medical supplies and disruption of economy and society (Ministry of Health Malaysia, 2006). Rates of infection and illness soar due to minimal or no immunity to a pandemic virus in the majority of population globally. Consequently, a significant percent global population will require medical care. However, most countries are unlikely to have sufficient facilities, equipment, hospital beds, and staff to provide care to patients who suddenly fall ill. The high mortality rates are largely determined by virus virulence, number of people infected, underlying characteristics and vulnerability of affected population, and effectiveness of preventive measures. Vaccines and antiviral drugs usually fall short early during a pandemic that outgrows supply. Manufacturing of influenza vaccines usually requires at least 4-6 months after a pandemic outbreak as global manufacturing capacity is limited. Tough decisions are required in prioritizing use of antiviral drugs and vaccines among the affected population. In addition, influenza can have an impact on the economy of a nation due to a need to impose travel bans; close borders, business and schools; and cancel events. Care for sick family members and fear of exposure to influenza virus may lead to significant worker absenteeism. It is worth noting the belief a healthy person not need vaccination is the most predominant reason for not receiving the influenza vaccination in USA (Johnson *et al*, 2008).

Challenges in Malaysia. Challenges to influenza management in the primary care setting are: differentiating influenza from other similar illnesses, non-availability of vaccines, lack of time for doctors to explain to their patients of the need for vaccination, and unwillingness of some HCWs to be vaccinated even after the H1N1 epidemic. Physicians are burdened

with a heavy work load as they need to manage more than 60 patients per day (in wards as well as in inpatient and outpatient clinics) (Rampal 2013; Khoo *et al*, 2017). Consequently, it would be near impossible to collect data on influenza or spend time to educate and offer influenza vaccination to patients at risk. The other challenge is the lack of perception by specialty care physicians (*eg* cardiologists, respiratory or geriatric physicians) of offering influenza vaccination as being their responsibility.

Malaysians do not associate influenza with any particular season to become vaccinated owing to the lack of seasonality of influenza in the country. Influenza vaccination is less for Umrah than Hajj owing to a lower number of counseling sessions regarding vaccination for Umrah as compared to Hajj. Patients with several comorbidities belong to a lower socioeconomic group posing affordability issues. Data to advocate influenza vaccination year-on-year is very limited. Questions regarding the desired target population for vaccination and effective methods to sustain the vaccination cost over a long period remain unanswered. It becomes difficult to answer patients' questions regarding criteria for vaccine access and prioritization. Even if vaccination is to be prioritized for geriatric patients, there are issues on affordability and enforcing the need for vaccinations every year. Furthermore, there is lack of understanding on the importance of influenza vaccination among physicians probably due to other health priorities such as dengue. While regular formal physician meetings and discussions are held to discuss such infectious diseases as dengue, this is not the case with influenza, which does not figure as prominently as other infectious diseases when public health resources

are allocated. Annual implementation of influenza vaccination is more difficult as compared to pneumococcal vaccination that is given once in 4-5 years.

According to the panelists, the challenges in managing influenza infection in Malaysia are those pertaining to influenza surveillance and implementation of effective influenza vaccination.

Regarding the former issue, when MISS was initiated, all demographic data were collected, but during the influenza epidemic in 2009, peripheral centers had difficulty in collecting significant amount of data. In order to collect critical data, collection was simplified with a focus on obtaining medical information, with less attention on demographic data. Reporting of influenza is not compulsory in Malaysia, unlike reporting of other infectious diseases, such as HIV/AIDS and pulmonary tuberculosis. Furthermore, there is limited research being conducted

on influenza in Malaysia and, consequently, adequate data on influenza are not collected and/or not available. Challenges facing MISS are: (i) less defined seasonality of influenza, (ii) absence of influenza as a notifiable disease in the Prevention and Control of Infectious Diseases Act 1988 (Act 342), (iii) data collection exclusively from MOH facilities, (iv) lack of data from certain high-risk group (eg pregnant women as they are seen at mother and child health clinics and maternity wards, (v) ILI and SARI data collected only from outpatient's clinics and medical/pediatric wards respectively, and (vi) data collected manually.

Regarding implementation of effective influenza vaccination, the challenges are: (i) less acceptance rate among the junior medical staff compared to senior physicians who along with their family members, (ii) refusal of HCWs to be vaccinated due to attitude and lack of

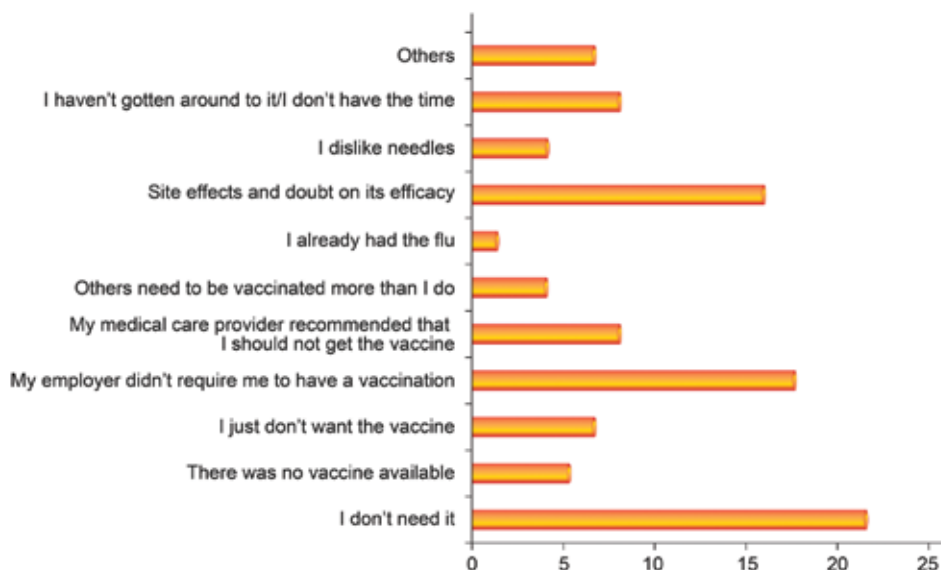


Fig 4-Self-reported reasons for non-vaccination for influenza among healthcare workers in Malaysia (2013).

formal education on the importance of influenza vaccination, vaccine cost, lack of policy to encourage vaccination, concern about possible vaccine side effects, doubts regarding vaccine efficacy, and a non-compulsory employer policy, resulting in 51.4% of HCWs in both government and private hospitals being vaccinated (Fig 4), (iii) knowledge of 41% of HCWs regarding an employer's policy encouraging flu vaccination, highlighting the need for employers to provide subsidized or free influenza vaccination to their HCWs and campaigns to increase HCWs awareness of the health importance of influenza vaccination (Hudu *et al*, 2016), and (iv) reduction in vaccine purchase if the vaccines provided for HCWs in the previous year are not completely used.

Clinical evidences of influenza vaccination benefits in Malaysia

When influenza vaccinations were funded by employers, vaccinated employees demonstrated lower rates of ILI and availed lesser ILI-related sick leaves compared to non-vaccinated colleagues (Samad *et al*, 2006). Employers saved USD53.00 per employee when only labor costs were considered and savings increased up to USD899.70 when operating income of each employee was also taken into consideration, clearly demonstrating workplace vaccination against influenza reduces ILI rates and absenteeism from work and improves productivity, which translates to financial benefits to employer.

Clinical evidences regarding strategies to increase influenza vaccination rates in Malaysia

In order to provide insights on various strategies to enhance influenza vaccination among HCWs in Malaysia, Jalil *et al* (2015) evaluated vaccination

outcome among 1,850 HCWs randomized into six different intervention groups, namely, cohort 1 receiving free vaccine with information provided on posters (control group), cohort 2 receiving free vaccine plus educational lecture, cohort 3 receiving free vaccine plus educational lecture and on-site vaccine accessibility, cohort 4 receiving free vaccine plus educational lecture, on-site vaccine accessibility and declination statement, cohort 5 receiving free vaccine at worksite, and cohort 6 receiving free vaccine at worksite and declination statement. Cohort 5 (free vaccine at worksite provided from 08:00 - 16:30 hour) has a 710 times higher likelihood of vaccination compared to cohort 1 (odds ratio (OR) = 711, 95% confidence interval (CI): 281-1,797, p -value <0.001); cohort 3 has a vaccination rate of 76%, 60 times increase in likelihood compared to cohort 1 (OR = 60, 95% CI: 31-115, p -value <0.001), probably owing to delivery of free vaccine for just an hour post-educational lecture; cohort 4 has 92% vaccination rate (OR = 392, 95% CI: 177-870, p -value <0.00), and cohort 6 has 98% vaccination rate (OR = 761, 95% CI: 301-1,924, p -value <0.001). These findings demonstrated vaccination rates can be improved significantly using intervention strategies containing a combination of incentives, with free vaccination at worksite plus declination statement being the most effective intervention strategy. According to a nationwide cross-sectional survey in England, clear leadership, effective communication on performance and methods utilized to identify and contact eligible patients are independently associated with significantly higher rates of flu vaccination (Dexter *et al*, 2012). In addition, financial targets appear to incentivize harder efforts to maximize seasonal vaccination rate.

Strategies for managing influenza infection in Malaysia

The panelists concluded influenza infection can be managed through specific strategies to increase awareness among target populations, namely, HCWs, elderly patients, patients with underlying medical conditions, and general public.

HCWs. Influenza awareness among HCWs can be increased by generating local prevalence data through a number of ways:

A randomized, placebo-controlled trial can be conducted to determine the effectiveness of influenza vaccine on Hajj pilgrims. If a study is conducted over one year shows beneficial results, influenza vaccination can be proposed as a mandatory requirement for Hajj pilgrims.

A study can be conducted to assess prevalence of influenza or ILI among patients admitted for cardiac care and results can then be propagated as it is observed vaccination rate is high (80%) for the first few years after a published study, but wanes over time. Inputs can be obtained from microbiologists regarding spikes in flu prevalence based on laboratory data.

The importance of influenza vaccination should be highlighted not only in influenza disease-related conferences, but also in other related specialty conferences, such as (for example) obstetrics, cardiology, endocrinology, and nephrology. The importance of influenza vaccination can also be discussed and promoted in various specialty symposia, such as cardiology, respiratory, geriatrics, endocrinology, and primary care.

Given that pregnant women have the highest risk of influenza morbidity, vaccination of pregnant women will protect young infants <6 months of age.

HCWs in Malaysia should document prevalence and burden of influenza, especially in elderly population and those with multiple comorbidities.

In the Second National Health and Morbidity Survey in Malaysia, 35.8% of children <5 years of age have an upper respiratory tract infection (URTI) episode in the preceding 2 weeks and 75% of these children have sought treatment from doctors (Ng *et al*, 2008). Partly because of parental demand and uncertainty of diagnosis as to whether URTI is due to a bacterial or viral infection, many of these children receive unnecessary antibiotics. Teng *et al* (2006) reported prescription of antibiotics for children with URTI is seven times higher in private general practice clinics compared to public primary care clinics, and 1.6 times higher than that in university-based primary care clinics. Use of antibiotics by healthcare givers could be reduced if URTI due to influenza is prevented by vaccination, reducing both visits to clinics and use of unnecessary antibiotics.

Elderly patients and patients with underlying medical conditions. Elderly patients and patients with underlying medical conditions should be educated regarding the importance of influenza vaccination not just to prevent influenza but also to prevent a flare-up of underlying disease conditions, such as pneumonia, heart failure and chronic obstructive pulmonary disease (COPD). Boards/charts can be displayed in waiting areas of clinics to educate patients on flu, need for influenza vaccination and benefits of influenza vaccination in preventing heart attack and stroke. In addition, it is important to ensure such educational boards/charts are appropriately positioned and visible to the patients. A printed vaccination schedule for adults,

similar to that of pediatric schedules, may serve as a reminder to maintain vaccination compliance.

General population. People can be educated regarding influenza vaccination during events such as Hajj and Umrah-related pilgrimages.

Promotion of influenza vaccination among target populations in Malaysia

HCWs. The panelists concluded promoting influenza vaccination among HCWs provides protection not only to HCWs but the spill-over effect also protects their patients. While influenza vaccination is available free of cost for staff of Kementerian Kesihatan Malaysia, HCWs do not volunteer to be vaccinated. In the private sector, ensuring that 80% of the HCWs receive influenza vaccination will boost patient confidence. Delivery system should be made available at the location of the target population, e.g. at staff clinics for HCWs. Vaccination centers should be set up in all hospitals, which can serve as one-stop centers providing all necessary vaccinations and help keep track of frequency and timing of vaccination. Information on the arrival of influenza vaccines can be displayed on laptops of HCWs along with suggestions for vaccination regimen.

General population. Geriatric patients can be provided with vaccination cards which can serve as reference documents to increase compliance. Messages to remind flu vaccinations can be sent through handphones. HCWs and the general public can be mobilized for vaccination by organizing talks sponsored by pharmaceutical companies. Such a strategy has been noted to be associated with improved vaccination rates. Organizing campaigns among school children can provide good learning to implement

influenza vaccination. Introducing an “Influenza Day” nationwide when a maximum number of target population is vaccinated on the same day may reduce the apprehension of injections.

Pilgrims. Liaising with websites of travel agencies such as Bumitra and others (which handles the majority of Umrah packages) to educate pilgrims about influenza and recommend vaccination can help to promote influenza vaccination.

Overall. Implementation of a consistent policy and free supply of influenza vaccine will help mobilize patients to be vaccinated regularly. ILI data generated every month can be a useful source of information to support the necessity and health benefit of influenza vaccination.

Prioritization of influenza vaccination among target populations of Malaysia

The panelists concluded administration of influenza vaccine to target populations should be prioritized as resources are always short. Although it may be difficult or next to impossible to vaccinate the whole population, it would be prudent to ensure regular immunization of critical risk populations. Hence, influenza vaccination should be provided on a priority basis to individuals >50 years of age with underlying medical conditions. MSIDC guidelines for immunization in adults identified persons 50-59 years of age as a target group because approximately 33% have high-risk medical conditions and age-based recommendations are more successful than medical-based recommendations in raising vaccination rates (MSIDC, 2014).

CONCLUSION

Mortality and morbidity of influenza infection are generally not evident to the general public and HCWs due

to prevalence of other more serious infectious diseases. However, the threat is perceivable in children, patients ≥ 65 years of age and in those with underlying medical conditions. Compounding factors for influenza in Malaysia are lack of seasonality of the infection, frequent mass travel of the general population in pilgrimages such as Hajj and Umrah, and expectation of government funding of vaccination. The consensus strategies documented here provide practical insights for better management of influenza infection at a community level in the Malaysian context.

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