CME Article

Influenza and the pandemic threat

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ABSTRACT

With the increasing concern of an imminent influenza pandemic, Singapore and many other countries have been developing preparedness plans. Influenza affects an estimated 20 percent of the population of Singapore annually, and local outbreaks can last for more than 12 weeks and occur at different periods of the year. The 1968 pandemic in Singapore had a clinical attack rate of about 20 percent and resulted in infections with fever that lasted up to five days. However, absenteeism from work due to seasonal influenza-like illnesses was estimated to be less than one day per person in Singapore. The next pandemic in Singapore is predicted to cause an average of 1,105 deaths and 3,338 hospitalisations, while a severe pandemic will cause more healthcare damage. Preventive strategies include national public health initiatives, vaccination, anti-viral therapy, and hygiene measures. To develop effective preparedness plans, it is important for healthcare workers to understand the disease's epidemiology, outcomes, and treatment and prevention strategies available.

Keywords: epidemiology, infectious disease, influenza, pandemic

Singapore Med J 2006; 47(6):463-470

INTRODUCTION

In Singapore, an estimated 20% of the population is affected by influenza annually, resulting in 500,000 physician visits and 300,000 workdays lost [1]. Apart from the impact of seasonal infection, the current avian influenza outbreak has renewed fears that an influenza pandemic, with severe outcomes, is imminent. The 1918 "Spanish flu" pandemic caused 20 to 40 million deaths worldwide, more than the First World War [2]. Even the less severe 1957 "Asian flu" and 1968 "Hong Kong flu" pandemics resulted in two million and one million deaths, respectively, with countless more infections[3,4]. As such, many countries are implementing pandemic preparedness plans. To prepare healthcare workers, this paper provides a clinical and public health review with the aim of improving understanding about influenza.

VIROLOGY

Influenza are single-stranded RNA viruses of the *Orthomyxoviridae* family. There are three types of influenza, A, B and C, differentiated by antigenic properties of nucleoprotein and matrix proteins. Influenza A and B cause large outbreaks while only influenza A causes pandemics. Influenza A is further differentiated by haemagglutinin (HA) and neuraminidase (NA) surface glycoproteins. The HA protein facilitates host cell binding through sialic acid receptors, while the NA protein cleaves the sialic acid receptors, releasing viral progeny. There are 16 haemagglutinin and nine neuraminidase subtypes[5,6]. All reside in aquatic birds, their natural hosts, and many are found in poultry. Avian and human influenza HA proteins bind to different sialic acid receptors, and avian HA binds poorly to human receptors, preventing effective transmission to humans[7]. At present, only the H1, H2 and H3 haemagglutinin subtypes, and N1 and N2 neuraminidase subtypes are stable in humans[8]. Pigs are alternate hosts and are receptive to all subtypes[9]. The virus also contains two membrane proteins: M1, which allows host cell nucleus entry, and M2, an ion-channel that maintains pH for replication[10].

Influenza A and B cause repeat disease in individuals because of their propensity for mutation, aided by the lack of viral RNA polymerase proofreading during replication. Seasonal influenza (inter-pandemic) epidemics are caused by antigenic drifts that occur by point mutations in HA or NA glycoproteins, producing new strains when adequate mutations occur. These are sufficiently differentiated from previous circulating strains to be poorly recognisable by the host immune system, resulting in epidemics. The amount of differentiation

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determines the epidemic's extent. Pandemics are caused by influenza A through antigenic shifts. This occurs either from direct transmission from another species with frequent exposure leading to adaptation, or from genetic re-assortment. Re-assortment occurs when humans or pigs are co-infected with both avian and human influenza subtypes, giving rise to a novel virus with efficient human-to-human transmission while having avian surface proteins. Few or no humans have immunity against the resultant subtype, facilitating global disease spread with high attack rates. Studies have implicated re-assortment as the cause of the 1957 and 1968 pandemics[11,12], while the 1918 "Spanish flu" strain is postulated to be a direct adaptation of an avian subtype[13].

Three criteria must be fulfilled before a pandemic occurs. These include a novel viral subtype that can infect humans, effective transmission among humans, and a susceptible world population. The current H5N1 influenza lacks only effective transmission among humans but the probability of acquiring such capability is unknown.

INFECTIVITY AND SPREAD

Influenza readily spreads through inhalation of virus via droplets (>5 μm) or contact with infected material[14]. Limited airborne transmission of influenza particles (<5 μm) may occur[15]. The incubation period of seasonal influenza lasts one to four days (average two days), while avian influenza in humans has incubation periods ranging from two to eight days[16]. The infectious period (viral detection in respiratory samples) may occur 24 hours before symptom onset, and lasts until five days after[8]. In contrast, children may shed the virus several days before until ten days after, while severely immune-compromised patients may shed for weeks to months[17]. Infected individuals may exhibit subclinical infection without significant symptoms[18], and detection may be difficult.

The clinical attack rate (proportion of the population with clinical infection during an epidemic) is a key factor in assessing the impact of influenza. Clinical attack rates in seasonal epidemics range from 10% to 20%[1,19,20], while pandemics show higher rates due to population susceptibility – being 29% and 24% for the 1918 and 1957 pandemics, respectively[21]. A study at the National University of Singapore during the 1968 pandemic found a clinical attack rate of 19.2%[22].

In temperate countries, seasonal influenza epidemics occur during colder months and remain above baseline levels for six to eight weeks[5]. This may be different in the tropics lacking defined seasons. Seasonal epidemics in Singapore usually occur during the second and fourth quarters of the year. However, the 1957 and 1968 pandemics and the 1977 epidemic (a re-emergence of the H1N1 pandemic strain) occurred at different periods of the year[23]. Singapore surveillance data suggests that influenza outbreaks can persist above baseline levels for more than 12 weeks[23,24]. Combinations of factors including weather, travel and population dynamics, play a part in determining local spread. Singapore, a tropical country at global crossroads, may experience pandemic curves different from temperate countries.

Most severe pandemics exhibited dual wave configurations, with the first wave lasting about six weeks, and a second, more severe wave, occurring three to nine months later[5]. The estimated basic reproductive number (R_0, number of secondary cases produced by a primary case) of seasonal epidemics is below two[25]. Even the 1918 pandemic had an R_0 of less than four[26] - lower than many infectious diseases (measles has a R_0 of ten).

PATHOGENESIS AND CLINICAL FEATURES

Influenza enters the host through inhalation and causes infection by binding to host respiratory columnar epithelial cells, which contain target receptors for HA and other surface proteins. Replication occurs via the host cell's enzymatic processes, and infectious virions are cleaved from the host cell by NA proteins. Influenza causes a range of symptoms including fever, cough, sore throat, myalgia, nasal congestion, weakness, loss of appetite and headache. Respiratory symptoms are caused by local cellular damage and apoptosis, together with inflammation. Other symptoms result from host immune responses[5,9]. Cytokines produced by immune and epithelial cells in response to infection cause fever (by resetting thermoregulatory centres in the brain) and other systemic manifestations. Fever usually resolves after five days but myalgia may last for two weeks[17]. The 1968 pandemic in Singapore had fever lasting four to five days, but exhibited biphasic illness patterns where fatigue and lethargy occurred 24 to 48 hours after the fever settled[22,27]. Children may exhibit lower respiratory symptoms and gastrointestinal complaints, and febrile fits are common[28]. During the 1957 pandemic in Singapore, 40% of children hospitalised for influenza had fits[29].

Occasionally, severe local inflammation results in primary viral pneumonia, and the loss of epithelial and ciliated cells increases the likelihood of secondary bacterial infection. These occur in 0.1% to 1.0% of patients, and are the main causes of influenza

mortality[30]. Certain subtypes, such as H5N1, induce a sharp increase in production of cytokines and other immune mediators (e.g. interleukin, tumour-necrosis factor)[9]. This causes high fever, severe pneumonia leading to acute respiratory distress syndrome (ARDS), multiorgan failure and death[16]. In addition, H5N1 infections also cause gastrointestinal symptoms such as diarrhoea and abdominal pain.

DIAGNOSIS

Influenza infection causes non-specific signs and symptoms which are difficult to differentiate from similar viral respiratory illnesses, labelled as influenza-like illnesses (ILIs). In unvaccinated adolescents and young adults (age<35 years) with ILI, fever alone had a positive predictive value (PPV) for influenza of 76% compared to laboratory-confirmed diagnoses[31]. The two most predictive symptoms are fever and cough (PPV 79%), especially if present for more than 36 hours (PPV 85%). Among older age groups, abrupt onset, fever and cough had a PPV of only 30%[32]. The sensitivities of various definitions of ILIs range from 50% to 93%, with specificities ranging from 20% to 81% when compared with viral culture. No single clinical definition provides a sensitive yet specific identification of infection.

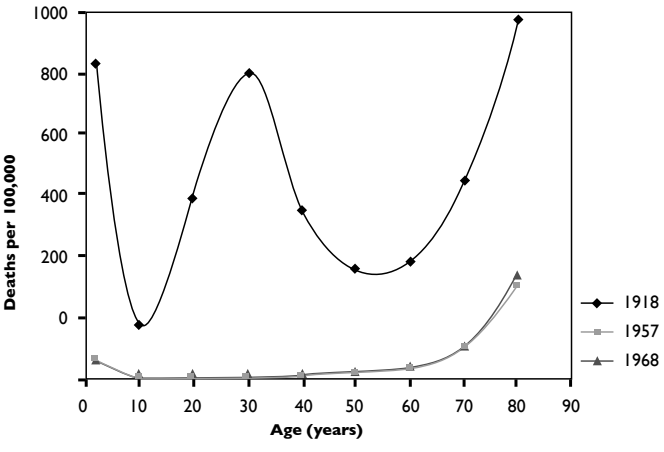
Viral culture of nasopharyngeal and/or throat samples remains the gold standard for diagnosis, but takes three to ten days, limiting its use in prevention strategies. However, viral culture is important to provide information on circulating subtypes for outbreak confirmation and vaccine formulation. Direct immunofluorescent tests offer quicker alternatives but are difficult and labour-intensive, with sensitivities much lower than viral culture. Other tests include reverse-transcriptase polymerase chain reaction, viral serology, and enzyme immunosorbent assays. There are many rapid tests for influenza currently available, providing results in less than 30 minutes, with sensitivities of up to 90%, and specificities that range from 70% to 90%[33]. Disadvantages include high costs, dependency on specimen adequacy and stage of disease, and decreased sensitivity for H5N1 influenza[34], although there are new products being constantly developed.

OUTCOMES FROM INFECTION

ILIs cause loss of productivity, reducing workdays by an average of 2.8 days per episode[35]. A Singaporean study estimated that certified workdays absence per year from ILIs were: 0.76 days, 0.5 days, and 0.11 days for the 20 to 34 year, 35 to 49 year, and 50 to 64 year age groups, respectively[1]. Severe outcomes such as hospitalisations and deaths occur mostly in the elderly, the very young, and individuals with chronic conditions such as respiratory disease, heart disease, and diabetes mellitus. The average length of hospital stay for influenza in Singapore for those below 20 years, 20 to 64 years, and above 65 years was 3.9, 4.6, and 6.2 days, respectively[36].

Multiple factors affect influenza mortality. Mortality from novel subtypes is highest upon first introduction, and subsequent epidemics from similar subtypes have decreasing severity[2]. Seasonal epidemics in Singapore have case-fatality rates of about 0.05%[30], but differ according to risk categories. Those below 65 years with low risk of complications had case-fatality rates of 0.005%, those above 65 years with low risk had rates of 0.34%. For high-risk groups, rates ranged from 0.15% (below 65 years) to 1.7% (above 65 years)[30]. Case-fatality rates are also influenced by geography – rates in Australia, with tropical and sub-tropical climates, is about one-half that of the United States, and one-third of the rates in France[37]. The rates during a pandemic in tropical Singapore will be dependent on these factors.

The feared 1918 pandemic had an average case-fatality rate of 5%, with 99% of excess deaths occurring in those below 65 years of age[2,21]. Peak excess mortality occurred in the 25-34 year age group[38], resulting in the infamous W-shaped mortality curve (Fig. 1). The current H5N1 avian influenza outbreak has high mortality rates[39] and if it acquires effective human-to-human transmission, may result in patterns similar to the 1918 pandemic.



Source : Luk et al[38]

Fig. 1 Age-specific mortality rates during influenza pandemics, United States of America.

SOCIOECONOMIC IMPACT OF INFLUENZA

Pandemics cause severe socioeconomic disruption

Table I. Estimated outcomes of pandemic influenza in Singapore.

Scenario	Estimated deaths	Estimated hospitalisations over pandemic's course	Estimated direct economic costs (billion S$)
Pandemic of average severity	1,105	3,338	1.4
Pandemic with 2% case-fatality rate	25,000	160,000	45
Pandemic with 5% case-fatality rate	63,000	330,000	112

Source: Lee, 2006

– a pandemic in the United States could cause up to 207,000 deaths, 734,000 hospitalisations, 42 million physician visits, and cost the economy USD$166 billion[40]. A pandemic of average severity in Singapore would result in 1,105 deaths, 23,000 hospitalisation days, and economic costs of SGD$1.4 billion[30], while a pandemic similar to the 1918 pandemic would cause 63,000 deaths, 1.5 million hospital days, and SGD$112 billion of damage (Table I). Healthcare services will be overwhelmed from patient visits and hospitalisations, in addition to healthcare worker absenteeism from increased risks of influenza infection. Absenteeism may also occur from the need to care for ill relatives, or for children if schools are closed.

PREVENTION STRATEGIES

Prevention and control of influenza can be approached from the pharmaceutical and non-pharmaceutical angles. Due to lack of evidence of pharmaceutical effectiveness during a pandemic, other public health measures, including isolation, quarantine, social distancing, reducing mass gatherings, school closures, and border control, need consideration. The presence of subclinical infections and short incubation periods makes diagnosis, prevention and control difficult[41].

Vaccines, the foundation of annual influenza prevention efforts, offer an effective means to provide individual and herd immunity, and to lessen the pandemic's impact if available. During seasonal epidemics, annual vaccination reduces opportunities for viral re-assortment in humans, and reduces baseline incidence to facilitate surveillance. Vaccines have been modelled to be economically and clinically effective in preventing negative pandemic outcomes[40]. However, with current technology, vaccine development requires up to six months from discovery of a new subtype to mass production[42]. If a future pandemic has two waves, vaccines are unlikely to be available during the first wave but may provide protection against the subsequent wave.

ANTI-VIRAL OPTIONS

Anti-viral drugs are the best pharmaceutical alternative to vaccines. However, its use should be restricted to reduce resistance. Drugs available to treat influenza include adamantanes and neuraminidase inhibitors. Adamantanes, such as rimantadine and amantadine, are effective against influenza A only. They inhibit viral replication by acting on the M2 ion channel protein and interfere with viral uncoating. Adamantine resistance occurs in 12% of circulating human influenza strains[43], and resistance can develop rapidly during treatment[8]. In the current influenza season, the United States Centers for Disease Control and Prevention (CDC) found that 91% of influenza isolates tested had a mutation which confers adamantane resistance[44], and has recommended that rimantadine and amantadine not be used during the 2005 - 2006 season.

Neuraminidase inhibitors disrupt the production of infectious virions, and should be given within 48 hours of illness onset (preferably before 24 hours) for maximal impact in shortening symptoms and reducing complications[45]. They reduce viral shedding and may reduce infectiousness[46]. There are two neuraminidase inhibitors in use, namely: oseltamivir and zanamivir. Oseltamivir is available in capsules or powder (mixed with water to form a suspension) for treatment and prophylaxis of influenza[47], and has a good safety profile with low rates of severe adverse events and drug withdrawal[48]. Resistance has been reported, but previously-resistant strains had poor infectivity[21]. Zanamivir is available as dry powder for inhalation through an inhaler, and is not generally recommended for patients with pre-existing respiratory conditions. It is effective for treatment and prophylaxis, and is well-tolerated[47,49].

Neuraminidase inhibitor treatment reduces severe outcomes in individuals infected with seasonal influenza by up to 90%[50,51]. Prophylaxis reduces infection by 55 to 92%[46]. Although zanamivir has been tested parentally[52], both drugs are not readily available for such use in severely-ill patients. Both drugs are effective against H5N1 in animal models, but oseltamivir treatment in infected humans has so far had equivocal effectiveness[53-57].

Many countries are stockpiling on neuraminidase inhibitors for treatment or prophylaxis against pandemic influenza. Studies have shown that the benefits of treatment outweigh the costs of providing treatment[30,58]. Prophylaxis may save additional lives over treatment[30], and together with

Table II. Summary of recommendations by the WHO and CDC for influenza prevention and control.

Components	Recommendations	Source
Non-pharmaceutical measures		
Screening	Border entry screening is generally not recommended. Provision of information for international travellers and exit screening is preferred.	WHO[62,63] CDC[64]
Isolation and quarantine	If human-to-human influenza transmission is limited and very localised, aggressive detection, isolation of cases and quarantine of contacts are recommended, together with targeted anti-viral use, to attempt containment.	
	Aggressive isolation and quarantine measures during sustained transmission during a pandemic may be ineffective, and could be socially disruptive. However, ill persons should still be advised to remain at home when symptoms develop.	
Social distancing (e.g. crowded public places, schools)	Impact remains unclear but should be considered depending on the severity of the disease, risk groups affected and epidemiology of transmission.	
Hand washing and respiratory hygiene	To be encouraged in public health messages as routine.	
Wearing of masks	ILI patients should wear surgical masks when in public. Routine public mask use is not required but should be permitted, depending on risk such as exposure frequency and closeness to cases.	
Disinfection of surfaces	Surfaces likely contaminated with infectious secretions may be disinfected, but no evidence for effectiveness is shown.	
Pharmaceutical measures		
Vaccines	Cornerstone of pandemic control.	WHO[65]
	Vaccine production capacity is currently sufficient for average annual demand. However, during a pandemic, timely production of sufficient amounts of vaccine is of concern.	
	As vaccines cannot be stockpiled, priorities for vaccination during a pandemic will have to be developed.	
Antiviral drugs	Neuraminidase inhibitors are the drug of choice for the treatment of pandemic influenza.	
	Pandemic use should be guided by the epidemiology during the pandemic. Similarly, timing of use should be guided by local surveillance data.	
Healthcare infection control		
Patients	Masks should be provided to patients who have respiratory symptoms in healthcare facilities until the patient is isolated or is diagnosed as non-infectious.	CDC[64,66,67]
	Respiratory hygiene should be encouraged, including the use of tissues or masks, hand washing, and encouraging the patient with respiratory symptoms to sit three feet away from others, if possible.	
Healthcare workers	Annual vaccination with the most recent seasonal influenza vaccine should be carried out.	CDC[64,66,67]
	Healthcare personnel in close contact (three feet) with a patient with respiratory symptoms should wear a surgical mask (N-95 for avian influenza) at minimum.	
	Healthcare workers should wear gloves and/or gowns if in contact with respiratory secretions or potentially contaminated surfaces. These must be changed after each patient.	
	Hands must be sufficiently washed before and after each patient contact, irrespective of wearing of gloves.	
	While caring for an influenza patient, healthcare workers should wear at least a surgical mask (N-95 for avian influenza) when entering the patient's room or keep three feet from the patient. Masks must be removed and disposed of when leaving the room.	
	Healthcare personnel infected with influenza should not provide direct patient contact until the infectious period is over.	
	Anti-viral prophylaxis of healthcare workers may be considered.	

treatment, provides respite to healthcare facilities by reducing infections and hospitalisations[59]. In addition, treatment and prophylaxis of healthcare workers may reduce absenteeism at critical moments[60]. However, stockpiling costs are high and the benefits not immediately apparent; hence, these must be weighed against the probability and costs of uncontrolled disease spread. Singapore is stockpiling oseltamivir and zanamivir as part of its pandemic preparedness plans.

NON-PHARMACOLOGICAL AND PUBLIC HEALTH INTERVENTIONS

The World Health Organisation (WHO) has emphasised the need to develop surveillance networks for early detection of a possible pandemic strain, if transmission is limited and highly localised, to attempt containment through isolation, quarantine, and anti-viral therapy[61]. Healthcare workers can contribute through vigilance, detection, and timely reporting of cases. Once the pandemic has spread substantially, measures should focus on delaying the pandemic's impact and spread to allow for vaccine development, anti-viral production, and activation of preparedness plans. Selected recommendations by the WHO and CDC are summarised in Table II.

The CDC recommends that individuals with ILIs during periods of increased influenza activity should wear surgical masks in public[64]. In the healthcare setting, respiratory hygiene, standard and droplet precautions should be observed. For avian influenza, the CDC suggests implementing precautions similar to SARS – healthcare workers in contact with suspected patients should adopt contact, airborne (including using N-95 masks), and eye precautions, in addition to standard precautions[67]. These measures will reduce spread among healthcare workers, from patients to healthcare workers, and vice versa[68]. Healthcare facilities should also consider stockpiling protective equipment, as these are likely to be in short supply.

Preparedness plans must also include education to allay public fear as misconceptions undermine preparedness efforts, through personal anti-viral stockpiling and indiscriminate anti-viral use, which promotes resistance. Education must include basic hygiene measures such as washing of hands and staying away from public places if unwell, and should be practised as a daily routine rather than emphasised only during a pandemic.

CONCLUSION

Healthcare workers play an important role in influenza preparedness, and should be familiar with national preparations, keep abreast with global developments, and educate patients to deal with the effects of a pandemic. Only by combining resources will we be able to reduce the impact of the next pandemic.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME
Multiple Choice Questions (Code SMJ 200606B)

	True	False
Question 1: The following statements about influenza virology are true:		
(a) Influenza C causes pandemics.	❑	❑
(b) Haemagglutinin surface glycoproteins facilitate viral binding to the host cell.	❑	❑
(c) Antigenic drifts lead to pandemics.	❑	❑
(d) There are four criteria that must be met before a pandemic occurs.	❑	❑
Question 2: The following statements about influenza infectivity and spread are true:		
(a) Influenza spreads through droplets and contact with infected material.	❑	❑
(b) Seasonal influenza has an incubation period lasting one to four days.	❑	❑
(c) Children and immune-compromised patients shed the virus for a shorter duration compared to normal adult individuals.	❑	❑
(d) Influenza may manifest as a sub-clinical infection.	❑	❑
Question 3: Influenza causes the following clinical features and outcomes:		
(a) Influenza-like illness (ILI) describes viral illnesses that have similar signs and symptoms to influenza infection.	❑	❑
(b) Children may exhibit gastrointestinal symptoms or febrile fits.	❑	❑
(c) Dehydration is the main cause of death in influenza infections.	❑	❑
(d) Fever and cough and the most predictive symptoms of influenza.	❑	❑
Question 4: Regarding pharmacological interventions against influenza:		
(a) Seasonal vaccination is useful for pandemic preparedness	❑	❑
(b) Adamantanes (amantadine and rimantadine) are the drugs of choice for influenza treatment.	❑	❑
(c) Oseltamivir is used in the treatment and prophylaxis of influenza.	❑	❑
(d) Oseltamivir and zanamivir are readily available for parenteral use.	❑	❑
Question 5: The following non-pharmacological measures are recommended:		
(a) Isolation of influenza cases and quarantine of contacts should be rigorously enforced throughout an influenza pandemic.	❑	❑
(b) ILI patients should wear surgical masks when appearing in public.	❑	❑
(c) Healthcare personnel in close contact with patients with respiratory symptoms should wear surgical masks.	❑	❑
(d) Public education on influenza and hygiene should be emphasised as routine and not only during a pandemic.	❑	❑

Doctor's particulars:

Name in full:_____

MCR number:_____ Specialty:_____

Email address:_____

Submission instructions:

A. Using this answer form

1. Photocopy this answer form.
2. Indicate your responses by marking the "True" or "False" box ☑
3. Fill in your professional particulars.
4. Post the answer form to the SMJ at 2 College Road, Singapore 169850.

B. Electronic submission

1. Log on at the SMJ website: URL <http://www.sma.org.sg/cme/smj> and select the appropriate set of questions.
2. Select your answers and provide your name, email address and MCR number. Click on "Submit answers" to submit.

Deadline for submission: (June 2006 SMJ 3B CME programme): 12 noon, 25 July 2006

Results:

1. Answers will be published in the SMJ August 2006 issue.
2. The MCR numbers of successful candidates will be posted online at http://www.sma.org.sg/cme/smj by 15 August 2006.
3. All online submissions will receive an automatic email acknowledgment.
4. Passing mark is 60%. No mark will be deducted for incorrect answers.
5. The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.