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Management of novel influenza epidemics in Singapore: consensus recommendations from the Hospital Influenza Workgroup (Singapore)

Hospital Influenza Workgroup (Singapore)

ABSTRACT

The recent emergence and global spread of a novel strain of influenza A (H1N1) virus has resulted in the first influenza pandemic of the 21st century. With its rapid spread to more than 70 countries within three months, governments are faced with the challenge of either containing or mitigating this influenza pandemic. The aim of this paper is to provide evidence-based consensus recommendations in the areas of infection control, antiviral treatment, chemoprophylaxis, antibiotic stockpiling and vaccination to guide decision-making for clinicians and administrators within the Singapore context. As the transmissibility and virulence of this new influenza A (H1N1) virus may evolve over time, we have tailored our recommendations according to several potential scenarios of viral virulence and transmissibility.

Keywords: antibiotic stockpile, chemoprophylaxis, H1N1 virus, infection control, influenza A virus, influenza epidemic, pandemic, vaccination

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INTRODUCTION

The emergence of a novel influenza A (H1N1) virus from Mexico in March 2009 and its rapid dissemination throughout the world has been the first international outbreak of public health concern since the new International Health Regulations came into effect in 2007, prompting the World Health Organisation (WHO) and the international community to escalate their response in anticipation of a pandemic.[1,2] To date, reports have indicated that the severity of illness associated with the new H1N1 virus may be similar to that caused by seasonal influenza,[3] although its transmissibility appears to be higher, consistent with previous pandemic viruses.[4] Uncertainties remain owing to its potential for evolution between seasons – another feature of previous pandemic viruses.[5,6]

Most confirmed cases of the new H1N1 virus infection have thus far been characterised by self-limited uncomplicated febrile respiratory illness with symptoms similar to those of seasonal influenza, although severe illness and death have been reported in adults under 60 years of age, especially those at high risk of complications.[3,7] In the US, approximately 95% of laboratory-confirmed cases have met the case definition of influenza-like illness (ILI) with fever plus cough or sore throat. Additional symptoms described are rhinorrhoea, myalgia, fatigue, headache as well as gastrointestinal symptoms in up to 25% of cases.[7,8] As in seasonal influenza, elderly or immunocompromised patients may not mount a febrile response.

In Singapore, as in other parts of the tropics, influenza is reported year round.[9,10] Infections generally follow two annual incidence peaks during the middle and the end of the year. Influenza A (H1N1) and (H3N2) co-circulate, with H3 subtypes being predominant in recent years. The Department of Laboratory Medicine in Tan Tock Seng Hospital, under the Health Services Development Programme project, has been surveying the incidence of seasonal influenza since January 2008 using respiratory samples submitted within 48 hours of hospital admission. Approximately 40%–50% of samples were positive by polymerase chain reaction for influenza during peak periods and about 5% were positive during non-peak periods. It has been estimated that the local annual excess mortality from influenza is 14.1 per 100,000 per year, a figure that is comparable to temperate, developed countries.[11]

The following recommendations were prepared by the Hospital Influenza Workgroup (Singapore), an informal network of infectious diseases physicians, clinical microbiologists and epidemiologists, formed in the early phase of the 2009 H1N1 outbreak. Contributing authors are listed in the Acknowledgements section. The aim of this paper is to provide evidence-based consensus recommendations in the areas of infection control, antiviral treatment, chemoprophylaxis, antibiotic stockpiling and vaccination that are applicable for the current pandemic, and also potentially for future epidemics

caused by respiratory viruses of differing virulence and transmissibility. The workgroup appreciates that evidence-based recommendations do not directly translate to policy as other factors including resources, public expectation and anecdotes of corporate memory will quite rightly influence this. The devastation of Singapore's health services caused by SARS, rightly or wrongly, is a major influence on the administration and the clinical response at all levels. These recommendations have been reviewed and endorsed by the Society of Infectious Diseases (Singapore) and the Infection Control Association (Singapore).

DEFINITIONS AND PROJECTIONS

Pandemic response measures require calibration based on several important parameters, including the virulence and transmissibility of the outbreak strain as well as the degree of spread within Singapore. Our recommendations are organised according to assumptions about these parameters, to allow for flexible responses should characteristics of the outbreak change for possible subsequent waves. The case-fatality ratio (CFR) is the key indicator of virulence, and is used in determining the pandemic severity index (PSI) that has been used by health systems and governments in pre-pandemic planning (Table I).[12] To place this in context, the 1918 Spanish flu pandemic would be classified as Category 5, as would any potential pandemic caused by the H5N1 avian influenza. The pandemics of 1957 and 1968 were Category 2 events, while the current seasonal influenza is Category 1.

Modelling software, such as FluAid from the United States Centers for Disease Control and Prevention (US CDC), also uses CFR to estimate the impact of a pandemic on deaths, hospitalisations and outpatient visits (http://www.cdc.gov/flu/tools/fluaid/). The software was used by Singapore's Ministry of Health (MOH) to aid in pandemic preparedness. Using FluAid with planning assumptions based on hospitalisation rates in the US during the 1968 pandemic, an average attack rate of 25% and a Singapore population of 4.2 million, the projection indicated potentially1,900 deaths (range 900–3,200) and 11,200 hospitalisations (range 3,100–13,700).[13] Transmissibility of the virus is indicated by attack rates among susceptible individuals, and will greatly impact healthcare facilities in both inpatient and outpatient settings. However, public health interventions could potentially reduce transmissibility through measures such as quarantine, isolation, social distancing and treatment.[12]

The approach to management may be divided into the three phases described below, although the preparedness phase is no longer relevant and will not be discussed:

(1) Preparedness phase: where there are no H1N1 cases in Singapore.
(2) Containment phase: where there are imported cases or small clusters in Singapore with epidemiological links.
(3) Mitigation phase: where there is sustained transmission of the virus in the community.

Table I. Pandemic severity index by case-fatality ratio.

Case-fatality ratio (%)	Pandemic severity index
< 0.1	1
0.1 to < 0.5	2
0.5 to < 1.0	3
1.0 to < 2.0	4
≥ 2.0	5

INFECTION CONTROL

There is currently a paucity of direct data available on the novel H1N1 to guide infection control needs; most recommendations are extrapolated from what is known about seasonal influenza. This section uses current WHO and international guidelines to craft consensus recommendations adapted for healthcare and community settings in Singapore.

Transmission characteristics of influenza A

Much of the understanding has been derived from old studies based on animal models, observational studies or vaccine efficacy trials. In healthy adults, viral shedding can occur 24–48 hours before the onset of illness, but at lower titres.[14] Peak shedding occurs during the first 24–72 hours of illness, declines gradually and should become undetectable by Day 5 of illness.[15] This also occurs in children except that viral shedding may take place for up to 21 days.[16]

Recently, a review of 71 volunteer challenge studies showed that following intranasal inoculation of wild type influenza virus, 90.0% of volunteers shed the virus from Day 1 to Day 7–9 after inoculation. Interestingly, only 35.0% of volunteers had fever > 37.8°C and 58.8% developed upper respiratory illness. This study also showed that the peak and decline of viral shedding coincided with the peak and decline in respiratory symptoms.[17] In a systematic review, the estimated incubation periods of influenza A and B have been estimated at 1.4 days (95% confidence interval [CI] 1.3–1.5) and 0.6 days (95% CI 0.5–0.6), respectively.[18] Infectivity during the incubation period and from asymptomatic infections remains unknown.

It is believed that the main mechanism for transmission

Table II. Groups at high risk of complications of influenza.

- Extremes of age (children < 5 years and adults ≥ 65 years)
- Pregnant women
- Children < 19 years of age on aspirin-containing therapies
- Residents of nursing homes and other chronic care facilities
- Persons with underlying compromised immune systems (such as HIV infection, transplantation, or those on immunosuppressive medications)
- Persons with any of the following underlying comorbidities:
  - Chronic pulmonary disease (including asthma)
  - Haemodynamically significant cardiovascular disease (excluding hypertension)
  - Chronic renal disease
  - Chronic liver disease
  - Haematological disorder
  - Neuromuscular disorder that may compromise the clearance of respiratory secretions
  - Chronic metabolic disorder (including diabetes mellitus but excluding hyperlipidaemia)

in seasonal influenza is by droplet spread. The relative contribution of airborne transmission to influenza spread is uncertain, but can occur under certain conditions, e.g. in shared air spaces with poor air circulation, under conditions of low humidity, and during aerosol-generating procedures. Limited indirect evidence for airborne transmission is outlined in three frequently-cited observational studies: the 1957 influenza outbreak in a Californian veterans hospital for patients with tuberculosis;[19] the influenza outbreak on an Alaskan airline;[20] and the comparison of the proportions of patients affected by influenza infection in a long-term care facility with old and new ventilation systems.[21]

The survival of influenza viruses on surfaces was examined in two studies, although neither investigated infection resulting from contact with contaminated surfaces.[22,23] Influenza A virus concentrations fell by 100- to 1,000-fold within five minutes of transfer to hands and could only be recovered during the first five minutes of contamination.[23] These studies collectively suggest that alternate routes of transmission, albeit minor, do exist. Experimental studies examining the survival of the influenza virus as an aerosol showed that different strains remained viable and retained their infectivity to different host cell types, following artificial aerosolisation from a liquid suspension. In addition, influenza virus was detected in air samples for up to 24 hours at low levels of relative humidity and up to one hour at higher levels of relative humidity.[24]

RECOMMENDATIONS

In deciding on recommendations for personal protective equipment (PPE) for a pandemic, pertinent considerations include: pathogen virulence, major and minor modes of transmission, healthcare settings as potential amplification foci for transmission, maintaining healthcare workers' health and morale, risk of setting and specific occupations, duration of pandemic, availability of PPE supplies, user compliance and comfort. A summary of PPE for different scenarios and settings is found in the supplementary tables (Supplementary Tables I–IV).

Basic infection control measures

Standard precautions, including hand hygiene and cough etiquette, are important and should be practised at all times. Hand hygiene is known to break the cycle of transmission and should additionally be practised after removal of any PPE. It is also good practice to wipe off the stethoscope with 70% alcohol after use. Cough etiquette or "cover your cough" is an effective measure to prevent the transmission of any respiratory illnesses.[25]

For the new H1N1 virus, available data suggests that its mode of transmission is similar to seasonal influenza. Possible modes of transmission are through contact (direct and indirect) or droplets. Droplet precautions are adequate for most respiratory viruses, including seasonal influenza, and will suffice for most areas in the hospitals. However, the inclusion of both airborne and contact precautions represents an additional level of caution: the rationale for this is that a more cautious approach is needed until more is known about the specific transmission characteristics of a new virus. This is applicable for staff entering rooms of probable or suspect cases, or in areas where there is a higher likelihood of encountering cases. We recommend that airborne precautions be applied during aerosol-generating procedures and in certain high-risk areas.

Masks

Surgical masks worn effectively will prevent the wearer from being in contact with droplets from an influenza patient. This should be changed when wet or contaminated and discarded after each use. In contrast, the high filtration mask (N95, FFP-2 or equivalent) is worn when there is a risk of inhaling particles < 5 μ in size, especially

Table III. Antiviral drug regimens for therapy and prophylaxis (adapted from the IDSA seasonal influenza guidelines).[27]

Antiviral medication	Treatment dose	Prophylaxis dose
Oseltamivir (neuraminidase inhibitor)	Adults & adolescents aged ≥ 13 years: 75 mg bd.	75 mg capsule om.
	Children aged ≥ 12 months, by weight:	
	≤ 15 kg: 30 mg bd.	30 mg om.
	15–23 kg: 45 mg bd.	45 mg om.
	24–40 kg: 60 mg bd.	60 mg om.
	> 40 kg: 75 mg bd.	75 mg om.
	Children aged 6–11 months: 25 mg bd.	No data.
	Children aged 3–5 months: 20 mg bd.	No data.
	Children aged < 3 months: 12 mg bd.	No data.
Zanamivir (neuraminidase inhibitor)	Adults: 2 × 5 mg inhalations bd for 5 days.	2 × 5 mg inhalations om.
	Children aged > 6 years: same as adult dose.	2 × 5 mg inhalations om (only for > 5 years of age).
Amantadine (adamantanes)	Adults: 200 mg daily in 1–2 doses.	Not applicable.
	Children aged 1–9 years: 5–8 mg/kg daily (maximum 150 mg) in 1–2 doses.	
	Children aged > 9 years: same as adult dose.	

during aerosol-generating procedures e.g. resuscitation, intubation, bronchoscopy, suctioning, etc. A mask fit test is recommended to determine the correct-sized mask to be worn. However, a more important step that should be performed each time high filtration masks are worn is the mask fit check test, which checks that there is no leakage from the sides of the mask at the time of use.

Powered air purifying respirator (PAPR)

PAPR should only be worn by staff that are trained in their use and for specific indications, e.g. aerosol-generating procedures when the user is unable to wear a high filtration mask. This is also an alternative to the N95 mask for those who are not able to wear or fit any N95 mask. There is no need to wear both the N95 mask and PAPR together.

Gown and gloves

These are to be changed after each use per patient so as to prevent transmission of pathogens from one patient to another via direct or indirect contact spread.

Eye protection

This is advised where there is the risk for body fluid splashes as it will protect the eye mucosal surfaces. Goggles or face shields may be worn for this purpose. The goggles are to be carefully disinfected with 70% alcohol after each use, while the face shields are disposable items, i.e. to be discarded after each use.

Environmental infection control

The influenza A virus is able to survive in the environment for up to several hours, depending on factors like temperature, humidity, exposure to sunlight, etc. To prevent spread via indirect contact with contaminated environmental surfaces, it is important to regularly and routinely disinfect potentially contaminated surfaces. Soap and hot water is an effective viral disinfectant and adequate for low-risk areas, e.g. public areas in the community as well as low- and medium-risk areas in the healthcare setting. In the high-risk areas, phenolic or sodium hypochlorite 1,000 ppm (made fresh daily) with a contact time of at least 3–5 minutes may be used.[26] Focus should be placed on high touch areas. Large-surface cleaning methods that produce mists or aerosols or disperse dust in patient-care areas should be avoided.

ANTIVIRAL TREATMENT

Current recommendations by international professional organisations, including the Infectious Diseases Society of America (IDSA), state that persons with influenza who are hospitalised or who are at high risk for complications (Table II) should be offered treatment with antiviral drugs.[27] Antiviral treatment has been shown to improve clinical outcomes as well as reduce misuse of antibiotics.[28-30] Given that the clinical course of the new H1N1 virus currently appears similar to that of seasonal influenza, treatment guidelines may be based on the latter. Furthermore, even in pandemics, other influenza viruses will continue to co-circulate.

Treatment is therefore recommended for all patients with influenza belonging to high-risk groups (Table III). In addition, hospitalised patients with evidence of severe ILI regardless of underlying risk factors should be offered

Table IV. Treatment and chemoprophylaxis recommendations based on virus characteristics and outbreak situation.

Virus characteristics	Antiviral therapy recommendations		Chemoprophylaxis recommendations	
	Containment phase	Mitigation phase	Containment phase	Mitigation phase
Virus Scenario 1 PSI 1 and low transmissibility (attack rate < 25%)	Limited to persons who are hospitalised with severe ILI or are at risk of complications.	Limited to persons who are hospitalised with severe ILI or are at risk of complications.	• No chemoprophylaxis.	• No chemoprophylaxis.
Virus Scenario 2 (Current new H1N1 influenza virus) PSI 1 and high transmissibility (attack rate ≥ 25%)	Limited to persons who are hospitalised with severe ILI or are at risk of complications.	Limited to persons who are hospitalised with severe ILI or are at risk of complications.	• Consider prophylaxis for close contacts/unprotected HCWs only if they are at high risk of complications from influenza; • Otherwise no prophylaxis for protected or unprotected HCWs or other close contacts who are healthy. • Consider early empiric antiviral therapy for close contacts (including HCWs if in institutional setting) to break transmission chain.	• As per containment phase.
Virus Scenario 3 PSI 2 regardless of transmissibility	Limited to persons who are hospitalised with severe ILI or are at risk of complications.	Limited to persons who are hospitalised with severe ILI or are at risk of complications.	• Chemoprophylaxis of contacts (including unprotected HCWs) to place a "firewall" against transmission. • Early empiric antiviral therapy for close contacts or HCWs if symptoms develop despite prophylaxis.	• Consider prophylaxis for close contacts/ unprotected HCWs only if they are at high risk of complications from influenza; • Otherwise no prophylaxis for protected or unprotected HCWs or other close contacts who are healthy.
Virus Scenario 4 PSI 3–5 but low transmissibility (attack rate < 25%)	All patients with ILI are treated.	All patients with ILI are treated.	• Chemoprophylaxis of all close contacts and unprotected HCWs regardless of risk profile for complications from influenza.	• As per containment phase.
Virus Scenario 5 PSI 3–5 and high transmissibility (attack rate ≥ 25%)	All patients with ILI are treated.	All patients with ILI are treated.	• Chemoprophylaxis of all close contacts and unprotected HCWs regardless of risk profile for complications from influenza. • We should not deny chemoprophylaxis to "protected" HCWs if requested.	• Chemoprophylaxis of contacts (in early stage of epidemic) to place a "firewall" against transmission. • Beyond a certain number of cases (to be determined), it will no longer be cost-effective to try to break the transmission chain via chemoprophylaxis. • Consider long-term chemoprophylaxis of HCWs and other key staff at this point.

PSI: pandemic severity index; ILI: influenza-like illness, HCWs: healthcare workers

treatment. Antiviral treatment is most effective when it is initiated within 48 hours of symptom onset. However it may reduce mortality and should be offered even beyond 48 hours in hospitalised patients with severe ILI.[28]

These antiviral treatment recommendations apply to both containment and mitigation phases of an epidemic or pandemic. In a potential scenario of higher CFR (≥ 0.5%) associated with the new H1N1 virus or another influenza strain, treatment should be expanded to include all with influenza regardless of underlying risk factors (Table IV). Although most healthy adults with influenza recover without the need for specific therapy, in a scenario where the rate of complications, including fatalities, is increased compared to that of seasonal influenza, the benefit of antiviral treatment would theoretically also be greater.

There are two classes of antiviral drugs that may

potentially be used against influenza: the adamantanes (amantadine and rimantadine), which are generally active against influenza A but not B; and the neuraminidase inhibitors (oseltamivir and zanamivir), which have activity against both influenza A and B viruses (Table IV). Since 2007–2008, the majority of seasonal influenza A (H1N1) in Singapore as well as in other parts of the world have become resistant to oseltamivir due to a specific H274Y mutation.[31] It remains susceptible to zanamivir and adamantanes. Seasonal H3N2 is susceptible to both neuraminidase inhibitors but resistant to adamantanes. To date, the new H1N1 virus is identical to the seasonal H3N2 virus with regard to antiviral susceptibility and may be treated with either oseltamivir or zanamivir alone. When subtype information is not available, patients should receive either zanamivir alone or a combination of oseltamivir plus an adamantane drug (only amantadine is registered for use and available in Singapore at present), unless otherwise contraindicated, in order to cover all current circulating influenza viruses. Treatment duration is five days. Testing of respiratory specimens for influenza should be undertaken as soon as possible after symptom onset, if available. Clinicians need to stay informed on local and novel influenza antiviral susceptibility patterns as these may change rapidly.

Antiviral treatment should be used in pregnant women when the potential benefits justify the potential risk to the mother and foetus. Since pregnant women are themselves at high risk for complications of influenza, pregnancy should not be considered a contraindication to treatment. Hospitalisations, miscarriage and one death have already been reported in pregnant women infected with the new H1N1 virus.[32] Oseltamivir and zanamivir are "pregnancy Category C medications" but no adverse effects have been reported in women who have actually received these during pregnancy. In *ex vivo* models, oseltamivir was extensively metabolised by the placenta and undetectable levels were found in the foetus even at doses 5–6 times the peak therapeutic levels.[33] Both amantadine and rimantidine have been demonstrated in animal studies to be teratogenic and embryotoxic and should not be used in pregnant women.

In April 2009, the US Food and Drug Administration issued an Emergency Use Authorization for the use of oseltamivir to treat new H1N1 virus infections in children younger than one year of age. This decision was based on balancing the risk of severe influenza complications in children younger than two years of age and the fact that, although prospective data on safety is lacking in the population of children younger than one year of age, retrospective data does not raise any age-specific safety concerns.[34,35]

CHEMOPROPHYLAXIS

Antiviral chemoprophylaxis has been shown to be effective in preventing influenza in contacts following exposure[36] and has been a cornerstone in the strategy to control seasonal influenza outbreaks in nursing homes and other long-term care facilities.[37] Adapting recommendations from US CDC,[38] and incorporating local epidemiology, sensibilities and resource limitations, the following recommendations for chemoprophylaxis of contacts and healthcare workers (HCWs) are detailed in Table IV. These recommendations are made based on the CFR, transmissibility of the infection and presence of sustained community transmission.

"Contacts" are those exposed to confirmed cases, as determined by the diagnostic criteria at that time. "Close contacts" are defined as household contacts, contacts within two metres in an enclosed place including HCWs exposed without appropriate PPE. Drugs recommended for chemoprophylaxis vary according to the susceptibility of the influenza strain. For the new H1N1 virus, recommended chemoprophylaxis is with oseltamivir or zanamivir as listed in Table IV.[27]

For Virus Scenario 1, no chemoprophylaxis is recommended. Assuming an attack rate of 20%, CFR of 0.1% and protective efficacy of 67% against symptomatic infection (extrapolated from seasonal influenza data with oseltamivir),[39] only 20 out of 100 exposed persons would develop infection, but 100 persons would need to receive prophylaxis to prevent 13 infections, and over 7,500 persons would need to receive prophylaxis to prevent one influenza-related death.

For Virus Scenario 2 (this best approximates the new H1N1 virus), we recommend that chemoprophylaxis for close contacts or unprotected HCWs be offered only if they are persons with risk factors of complications from influenza. In an institutional setting such as a nursing home, empiric antiviral therapy can be considered for all close contacts (including all HCWs) that develop ILI symptoms in order to break the transmission chain. These recommendations apply to both containment and mitigation phases of an outbreak.

For Virus Scenario 3, chemoprophylaxis is recommended for all close contacts or unprotected HCWs at risk of complications from influenza, regardless of transmissibility and source of infection. Chemoprophylaxis for unprotected healthy HCWs, without risk of complications from influenza, can also be considered in order to preserve a healthy workforce. For all other close contacts and protected HCWs, chemoprophylaxis is not recommended, but early empiric antiviral therapy should be instituted once influenza-like symptoms appear and

prior to confirmation of diagnosis with laboratory tests.

In the management of an imported case of a highly virulent (CFR > 0.5%) but poorly transmissible (attack rate < 25%) viral influenza (such as the H5N1 avian influenza virus) – Virus Scenario 4, chemoprophylaxis is recommended for all close contacts and unprotected HCWs, regardless of their risk profile. On detection of patients with community acquisition (which suggests viral adaptability), chemoprophylaxis of all contacts (in addition to other measures such as quarantine) is recommended in order to place a "firewall" against future community transmission.

Should a virus with high virulence (CFR > 0.5%) and transmissibility (attack rate ≥ 25%) (c.f. 1918 H1N1 Spanish influenza virus; Virus Scenario 5) be imported, chemoprophylaxis of all close contacts and unprotected HCWs is recommended regardless of their risk profile for complications from influenza. In addition, requests for chemoprophylaxis by other HCWs should not be denied, as it will be important to address the concerns of this group of professionals who face the threat of infection in the course of their work.

In the early stages of community transmission of a highly virulent (CFR > 0.5%) and transmissible (attack rate ≥ 25%) virus, where stockpile and resources allow, we propose chemoprophylaxis of all contacts in order to ring-fence against further transmission. However, it should be noted that safety for antiviral prophylaxis over durations longer than 6–8 weeks is not well studied. Should local transmission progress, it may no longer be sensible to attempt to break the chain of transmission with chemoprophylaxis of contacts. Instead the aim should be to preserve HCWs and other key personnel to maintain essential services in the community during a severe pandemic.

ANTIBIOTIC STOCKPILING

Evidence from epidemiological, clinical and laboratory studies suggests that bacterial pneumonia contributes substantially to the morbidity and mortality that occurs in pandemic and seasonal influenza.[40-43] During a pandemic, the number of patients who need hospitalisation because of complicated respiratory tract infections will increase. Many of them will need to be treated with antibiotics for initial empirical therapy for concurrent bacterial pneumonia, or for subsequent nosocomial pneumonia.

This surge in demand for antibiotics may quickly deplete the existing supply of antibiotics in local hospital pharmacies. Just-in-time supply chains may be insufficient for the purposes of dealing with such a surge, especially if there is a concomitant sharp rise in demand from other countries. Stockpiling of antibiotics is therefore one part of the overall strategy for the middle and the later stages of a pandemic when healthcare resources may be strained.[44] Antibiotic stockpiles are meant for the excess hospitalisations for influenza-related infectious complications only, mainly superimposed bacterial pneumonia. This stockpile is not intended for an increased number of potential nosocomial infections that can be associated with prolonged hospital stay. Although some patients with severe infections will require prolonged hospitalisations and thus may potentially develop nosocomial infections, hospitals should be able to cope with the increased demand for broad-spectrum antibiotics partially due to a projected fall in numbers in other groups of patients (e.g. cancelled surgical electives) who are also at risk for nosocomial infections.

There are two key considerations in preparing an antibiotic stockpile for influenza pandemics: choice of antibiotics and size of stockpile.

Choice of antibiotics

We propose that an antibiotic stockpile should include only essential antibiotics that fulfill the following criteria:

(1) Efficacy. During a pandemic, the availability of diagnostic tests for community-acquired pneumonia may be limited and most patients will have to be treated empirically. It is essential to have antibiotics that are effective against common respiratory pathogens.

(2) Ease of administration. During a pandemic, it is likely that the healthcare manpower resources may be stretched. Antibiotics administered several times a day may not be practical. In isolation wards, the first priority is to provide the best possible care to patients while maximising the safety of HCWs. Once daily administration will minimise exposure of HCWs to infectious patients, while conserving PPE supplies required for bedside care. In addition, antibiotics with high oral bioavailability can allow early discharge and shorten hospitalisation.

(3) Cost. It is difficult to predict the timing of the next influenza pandemic and antibiotic stockpiles may expire before it happens. Although these antibiotics can be rotated into daily usage and replaced through fresh procurement, we recommend that more cost-effective options should be selected wherever possible without sacrificing on efficacy.

Size of stockpile

The uncertainty surrounding a pandemic requires some assumptions that are based on evidence from past experiences and mathematical modelling (see "Definitions and Projections" above). These assumptions include: (1)

transmissibility and attack rate of pandemic influenza; (2) severity of disease caused by the virus; and (3) incidence of bacterial pneumonia. These assumptions allow an estimate of the number of persons seeking care and requiring hospitalisation and antibiotic therapy, to be made.

The antibiotics recommended for stockpiling and the reasons for their choice are given below:

(1) Amoxicillin/clavulanate: Very good activity against common respiratory pathogens, oral form available, good safety profile, affordable.

(2) Ceftriaxone: Although available in parenteral form only, it is effective, safe, affordable and administered once daily. It can also be used as an intramuscular injection in patients with difficult intravenous access.

(3) Clarithromycin: Good activity against both common respiratory pathogens as well as atypical bacteria (*Mycoplasma, Chlamydia and Legionella* spp.), oral form available, good safety profile, affordable.

(4) Respiratory fluoroquinolones: These currently include levofloxacin and moxifloxacin. Very good activity against common respiratory pathogens, oral form available, good safety profile and can be administered once daily. It is relatively expensive but provides an alternative for patients with beta-lactam allergy and allows the duration of therapy to be shortened to five days.

(5) Cefazolin: Reliable activity against methicillin-sensitive *Staphylococcus aureus* (MSSA). MSSA is known to cause a significant proportion of secondary bacterial pneumonias during previous influenza pandemics.[40,42]

(6) Vancomycin: This antibiotic was added to the stockpile only because of the concern of the increased incidence of respiratory infections caused by community-associated methicillin-resistant *Staphylococcus aureus*.

VACCINATION

There is currently no vaccine available against the new H1N1 virus. In a pandemic situation, vaccination will be an important strategy to control the spread of influenza and protect a susceptible population. Once the pandemic vaccine becomes available, there will be several issues in terms of priority of vaccination and monitoring for potential adverse reactions associated with vaccines for novel influenza strains of swine origin.

Meanwhile, the use of seasonal influenza vaccination will reduce mortality and morbidity from seasonal influenza, reduce the strain on hospital beds, reduce oseltamivir use (thus saving it for the novel influenza infections) and possibly even reduce the potential for re-assortment should a pandemic result from the current outbreak. An additional measure would be the use of pneumococcal vaccination.

Seasonal influenza vaccination

Influenza viruses can cause disease among persons in any age group resulting in serious illness and death, especially among persons aged more than 65 years, children aged younger than five years, and persons of any age who have comorbidities that place them at an increased risk for complications from influenza.[37] In Singapore, a recent study revealed that persons older than 65 years of age had influenza-associated deaths 11.3 times higher than the general population.[11]

Annual influenza vaccination is effective for preventing influenza virus infection and its complications. The trivalent inactivated influenza vaccine is effective for any person aged > six months, including those with high-risk conditions.[37] The Advisory Committee on Immunization Practices of the United States, consisting of experts in fields associated with immunisation selected by US Department of Health and Human Services, suggests that annual vaccination for all persons, including school-aged children, who want to reduce the risk of becoming ill with influenza is appropriate.[37]

Singapore's MOH recommends seasonal influenza vaccination for elderly persons aged 65 years or above, young children aged six months to five years, those with chronic heart and lung diseases and persons with diabetes mellitus or renal diseases, who are at a higher risk of developing complications from influenza, to undergo routine annual flu vaccination. The workgroup supports MOH's recommendations. Women in the second or third trimester of pregnancy and HCWs should also be encouraged to be vaccinated. However, the coverage of seasonal influenza vaccination in Singapore remains low. Employers may wish to consider offering workplace influenza vaccination. A recent study has shown benefits in the reduction of morbidity with influenza vaccination of HCWs in Singapore.[45]

In the case of pandemic vaccine, it is likely that supply will be limited, especially in the early stages, thus priority for vaccination is necessary. Vaccination should first be given to individuals at the highest risk of complications of influenza (Table II) and to those who are most at risk of transmitting the infection through their occupations. It has been shown that in the United States, one third of individuals over the age of 60 years have immunity to the novel swine origin H1N1-2009 influenza A virus.[46] Although data is absent from Singapore, it is plausible that a similar situation exists. It is recommended that priority in

vaccination with a novel pandemic vaccine should be given to children under the age of five years and to those with underlying medical conditions, including diabetes mellitus, cardiac and respiratory illnesses. In addition, priority should be given to HCWs, schoolteachers and those involved in the provision of essential services including the military, police and civil defence. As the 1976 swine flu vaccination was associated with severe unusual neurological consequences in a significant number of individuals, it is recommended that careful post-vaccination surveillance be considered to monitor for such sequelae.

Pneumococcal vaccination

The role of bacterial secondary infections in influenza pandemics is well recognised.[40-43] During an influenza pandemic, cases of pneumonia both from influenza and from secondary bacterial pneumonia may be expected to increase, adding to the high burden of pneumonia already seen in community settings. In Singapore, there have been recent reports of pneumococcal disease complicating acute influenza infections in migrant workers living in dormitories.[47] An enhanced pneumococcal vaccination strategy may potentially have public health benefits. However, we recognise that few specific data exist on the effectiveness of such vaccination for reducing pneumococcal pneumonia-associated illness and death after infection with influenza A virus. Furthermore, the 23-valent pneumococcal polysaccharide vaccine (23PPV) in current use, while shown to be protective against invasive pneumococcal disease, has not been shown to be protective against pneumococcal pneumonia in the absence of bacteraemia.[48] Nevertheless, as the current take-up rate for this vaccine in the targeted group is low, it is recommended that 23PPV vaccination should be encouraged for those at risk, which is for persons > 65 years of age and for high-risk groups of all ages. This is in keeping with the practice in most developed countries.

For children, there is a heptavalent conjugate vaccine available (Prevnar). Since its introduction in the US in 2000, a decline in invasive pneumococcal disease in children has been seen. Furthermore, a reduction of 32% for those aged 20–39 years and 18% for those aged > 65 years were documented.[49] This vaccine is currently adopted in many countries for children but does carry a cost. The benefits of routine use of this vaccine in children may result in a change in herd immunity, which is beneficial. The degree to which adults may remain at risk for vaccine-preventable disease may change but issues like the serotype replacement phenomenon, in which decreases in disease due to vaccine-type *Streptococcus pneumoniae* are counterbalanced by increases in disease due to non-vaccine serotypes, may also limit the impact of these vaccines.[50] Furthermore, there is no existing data with regard to the efficacy of such vaccination policies in a pandemic setting. On balance, however, we consider the use of heptavalent conjugate vaccines in children and 23PPV in adults an appropriate part of a pandemic strategy in Singapore.

CONCLUSION

The preceding recommendations are based on current existing evidence and placed in the context of Singapore. We have tried as far as possible to create a degree of flexibility in order to account for a variety of different scenarios based on changing viral virulence and transmissibility as well as potential evolving outbreak situations in Singapore. Many of these recommendations are provided for the hospital setting and presuppose that supplies (such as antiviral drugs and PPE) —although finite—will not be exhausted. We are aware that the situation remains fluid and these recommendations will be reviewed and refined as more evidence and/or new data emerges.

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Supplementary Table I. Use of personal protective equipment (PPE) in hospitals in the event of an influenza pandemic of pandemic severity index 2 or lower.

Phase	Location	Staff	Patients	Visitors
Containment	• High-risk areas 1. Emergency Medicine designated fever screening area and fever area	N95 mask	Surgical mask	Surgical mask
	2. Isolation wards	N95 mask, gown, gloves and eye protection when attending to suspect/confirmed patients		
		N95 mask and face shield when performing aerosol-generating procedures		
	• Medium-risk areas Fever screening counters	Surgical mask for screeners	Respiratory hygiene/cough etiquette	Respiratory hygiene/cough etiquette
	Staff Clinic fever area	N95 mask	Surgical mask for febrile staff	Nil
	Other clinical areas, e.g. general wards, outpatient clinics, therapy areas, etc.	Standard precautions	Nil	Nil
		Surgical mask and eye protection for aerosol-generating procedures		
	• Low-risk areas Offices and other non-clinical areas	Nil	N.A.	Nil
Mitigation	• High-risk areas 1. Emergency Medicine designated fever screening area and fever area	N95 mask	Surgical mask	Surgical mask
	2. Isolation wards	N95 mask, gown, gloves and eye protection when attending to suspect/confirmed patients and/or when performing aerosol-generating procedures		
	• Medium-risk areas Fever screening counters	N95 mask	Surgical mask	Surgical mask
	Staff Clinic fever area	Surgical mask	Surgical mask	Surgical mask
	Other clinical areas, e.g. general wards, outpatient clinics, therapy areas, etc	Surgical mask	Surgical mask for outpatients	Surgical mask
		N95 mask and eye protection when performing aerosol-generating procedures		
	• Low-risk areas Offices and other non-clinical areas	Surgical mask	N.A.	Surgical mask

Within various locations, whether high, moderate, or low risk, the levels of PPE should be appropriate for the activity in question as well as for the exposures that staff are likely to face.

Supplementary Table II. Use of personal protective equipment (PPE) in hospitals in the event of an influenza pandemic of pandemic severity index 3 or higher.

Phase	Location	Staff	Patients	Visitors
Containment	• High-risk areas 1. Emergency Medicine designated fever screening area and fever area	N95 mask	Surgical mask	Surgical mask
	2. Isolation wards	N95 mask, gown, gloves and eye protection when attending to suspect/confirmed patients		
		N95 mask and face shield when performing aerosol-generating procedures		
	• Medium-risk areas Fever screening counters	Surgical mask for screeners	Surgical mask	Surgical mask
	Staff Clinic fever area	N95 mask	Surgical mask	N.A.
	Other clinical areas, e.g. general wards, outpatient clinics, therapy areas, etc	Surgical mask	Surgical mask for outpatients	Surgical mask
		N95 mask and eye protection for aerosol-generating procedures		
	• Low-risk areas Offices and other non-clinical areas	Surgical mask	N.A.	Surgical mask
Mitigation	• High-risk areas 1. Emergency Medicine designated fever screening area and fever area	N95 mask	Surgical mask	Surgical mask
	2. Isolation wards	N95 mask, gown, gloves and eye protection when attending to suspect/confirmed patients and/or when performing aerosol-generating procedures		
	• Medium-risk areas Fever screening counters	N95 mask	Surgical mask	Surgical mask
	Staff Clinic fever area	N95 mask	Surgical mask	Surgical mask
	Other clinical areas, e.g. general wards, outpatient clinics, therapy areas, etc	N95 mask	Surgical mask for outpatients	Surgical mask
		N95 mask and eye protection when performing aerosol-generating procedures		
	• Low-risk areas Offices and other non-clinical areas	Surgical mask	N.A.	Surgical mask

Within various locations, whether high, moderate, or low risk, the levels of PPE should be appropriate for the activity in question as well as for the exposures that staff are likely to face.

Supplementary Table III. Use of personal protective equipment (PPE) in the community in the event of an influenza pandemic of pandemic severity index 2 or lower.

Phase	Location/occupation	Staff	Patients	Public / visitors
Containment	• High-risk areas Ambulances Quarantine officers Quarantine cleaners	N95 mask	Suspect cases are to wear surgical mask	Accompanying person to wear surgical mask
	General practitioners and outpatient services	Standard precautions: - hand hygiene - cough etiquette - surgical mask and eye protection when performing aerosol-generating procedures	Respiratory hygiene/cough etiquette	Respiratory hygiene/cough etiquette.
	• Medium-risk areas Aircraft/airport cleaners Immigration	Standard precautions: - hand hygiene - cough etiquette	N.A.	Cough etiquette
	Fever screeners	Surgical mask	N.A.	N.A.
	School sick bay	Standard precautions: - hand hygiene - cough etiquette	Respiratory hygiene/cough etiquette	Respiratory hygiene/cough etiquette
	Dialysis Long-term care facility	Standard precautions	Respiratory hygiene/etiqutte	Respiratory hygiene/cough etiquette
	Temperature screeners	Surgical mask	N.A.	N.A.
	• Low-risk areas Public places Work places Shopping malls	Nil	Nil	Nil
Mitigation	• High-risk areas Ambulances Quarantine officers Quarantine cleaners	N95 mask	Suspect cases are to wear surgical mask	Surgical mask
	General practitioners and outpatient services	N95 mask	Suspect cases are to wear surgical mask	Surgical mask
		N95 mask, gown, gloves and eye protection when attending to suspect patients and/or when performing aerosol-generating procedures		
	• Medium-risk areas Aircraft / airport cleaners Immigration	Surgical mask	Suspect cases are to wear surgical mask	Surgical mask
	Fever screeners	Surgical mask	Suspect cases are to wear surgical mask	Surgical mask
	School sick bay	Surgical mask	Suspect cases are to wear surgical mask	Surgical mask
	Dialysis Long-term care facility	Surgical mask	Surgical mask	Surgical mask
	Temperature screeners	Surgical mask	Surgical mask	Surgical mask
	• Low-risk areas Public places Work places Shopping malls	Surgical mask	N.A.	Surgical mask

Supplementary Table IV. Use of Personal Protective Equipment (PPE) in the community in the event of an influenza pandemic of pandemic severity index 3 or higher.

Phase	Location/occupation	Staff	Patients	Public / visitors
Containment	• High-risk areas Ambulances Quarantine officers Quarantine cleaners	N95 mask	Suspect cases are to wear surgical mask	Accompanying person to wear surgical mask
	General practitioners and outpatient services	Surgical mask	Surgical mask	Surgical mask
		N95 mask and eye protection for aerosol-generating procedures		
	• Medium-risk areas Aircraft/airport cleaners Immigration	Surgical mask	Suspect cases are to wear surgical mask	Surgical mask
	Fever screeners	Surgical mask	N.A.	N.A.
	School sick bay	Surgical mask	Surgical mask	Surgical mask
	Dialysis Long-term care facility	Surgical mask	Surgical mask	Surgical mask
	Temperature screeners	Surgical mask	Surgical mask	Surgical mask
	• Low-risk areas Public places Work places Shopping malls	Surgical mask	N.A.	Surgical mask
Mitigation	• High-risk areas Ambulances Quarantine officers Quarantine cleaners	N95 mask	Suspect cases are to wear surgical mask	Surgical mask
	General practitioners and outpatient services	N95 mask	Suspect cases are to wear surgical mask	Surgical mask
		N95 mask, gown, gloves and eye protection when attending to suspect patients and/or when performing aerosol-generating procedures		
	• Medium-risk areas Aircraft/airport cleaners Immigration	N95 mask	Suspect cases are to wear surgical mask	Surgical mask
	Fever screeners	N95 mask	Suspect cases are to wear surgical mask	Surgical mask
	School sick bay	N95 mask	Suspect cases are to wear surgical mask	Surgical mask
	Dialysis Long-term care facility	N95 mask	Surgical mask	Surgical mask
	Temperature screeners	N95 mask	Surgical mask	Surgical mask
	• Low-risk areas Public places Work places Shopping malls	Surgical mask	N.A.	Surgical mask