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Impact of acute respiratory infections on healthcare utilisation in Singapore, 2007 - 2011

Introduction

Singapore experiences influenza all-year round, with influenza seasons occurring bi-annually. The Primary Care Survey conducted by the Ministry of Health (MOH) showed that upper respiratory tract infections (URTI) remained the most common condition (25%) seen in 2005 and 2010 at public polyclinics and private general practitioner (GP) clinics.[1] Majority (87%) of patients with URTI seek care at GP clinics rather than polyclinics.

It is well recognised that influenza pandemics pose challenges to the delivery of healthcare services and resources, especially during the short period in which there are surges in demand. Singapore's control measures to ameliorate the impact of the influenza pandemic are broadly classified into two phases: containment and mitigation.[2] Strategies adopted during the containment phase include triage of febrile patients at frontline healthcare settings, and hospitalisation and isolation of all laboratory confirmed cases.

We assessed the impact of acute respiratory infections (ARI) and pneumonia on healthcare utilisation for primary and tertiary care in Singapore from 2007 to 2011, including the influenza pandemic in 2009 [A(H1N1)pdm09].

Materials and methods

The National Surveillance Programme for Influenza is a sentinel surveillance programme conducted by MOH. Nasopharyngeal, nasal and/or throat swabs are taken from patients with influenza-like illness

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(ILI) at polyclinics and private GP clinics. A number of indicators of influenza activity are also monitored on a weekly basis. We reviewed the weekly trends of various indicators of ARI and pneumonia during the five-year study period.

Results

Table 1 shows the peak in healthcare utilisation for primary and tertiary care due to ARI and pneumonia from 2007 to 2011. During the five-year period, the highest average daily number of polyclinic attendances due to ARI reached an unprecedented height of 4,450 in epidemiological (E)-week 30 (26 July – 1 August) of 2009, which corresponded to the peak in the number of influenza A(H1N1)pdm09 cases in the same week when an estimated 902.2 cases per 100,000 population were seen in polyclinics and private clinics.[3] The highest weekly proportion of total attendances due to ARI at polyclinics ranged from 20% in E-week 7 of 2008 to 28% in E-week 30 of 2009 (*Fig. 1*).

In 2009, the highest weekly number of attendances due to ARI at emergency departments (ED) of acute hospitals in the public sector occurred in E-week 29 (19 – 25 July) and E-week 30 (27 July – 1 August), which was 2.0 to 2.3 times the peaks in 2007 and 2008, and 1.7 to 1.9 times the peaks in 2010 and 2011, respectively (*Table 1* and *Fig. 2*). The highest weekly proportion of ED attendances due to ARI was 26% in E-week 29 of 2009.

There are seasonal trends in the average daily number of polyclinic attendances and weekly number of ED attendances due to ARI, with bimodal pattern of rises in attendances observed in the beginning and also just before the middle of the year. This pattern corresponds to the influenza activity in Singapore which is perennial with two seasonal peaks in a year.

Table 1

Peak in healthcare utilisation for primary and tertiary care due to acute respiratory infections (ARI) and pneumonia, 2007 – 2011

	Year				
	2007	2008	2009	2010	2011
Average daily number of polyclinic attendances due to ARI					
E-week of peak	20	17	30	20	6
Peak	3149	2866	4450	3349	3855
Weekly number of ED attendances due to ARI					
E-week of peak(s)	20	6	29 & 30	21	5
Peak	2444	2196	5005	2576	2932
Weekly number of ED attendances due to pneumonia					
E-week of peak(s)	19	18	30	18	5
Peak	593	543	639	536	525
Weekly number of hospital admissions due to P&I					
E-week of peak	20	18	25	21	19
Peak	317	303	459	326	330

E-week = epidemiological week; ED =emergency department; P&I=pneumonia and influenza

Figure 1
Weekly proportion (%) of total attendances due to acute respiratory infections (ARI) at polyclinics, 2007 – 2011

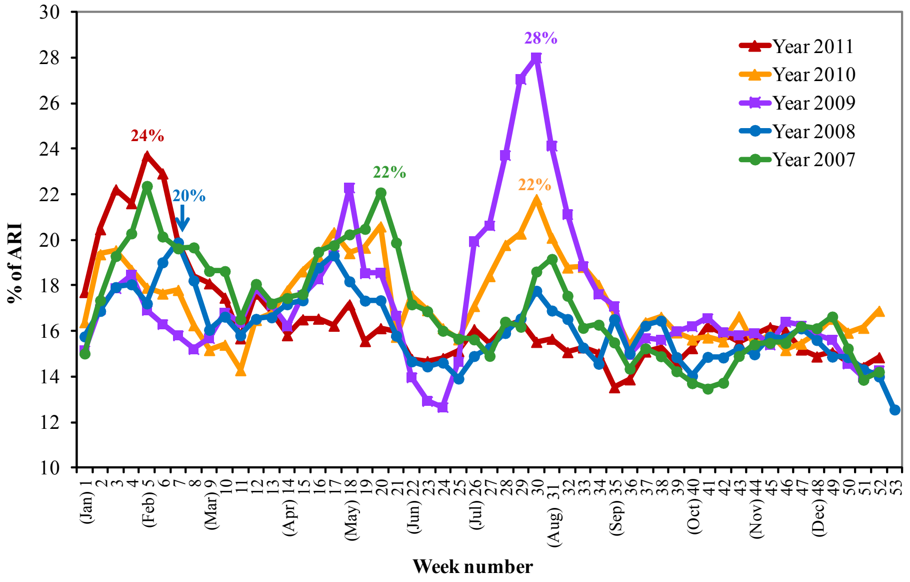
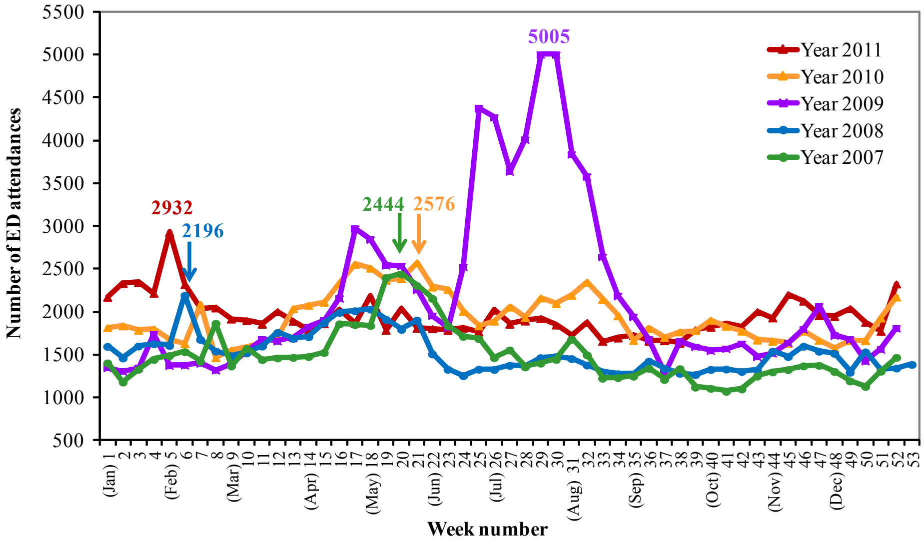


Figure 2
Weekly number of emergency department (ED) attendances due to acute respiratory infections, 2007 – 2011



Singapore typically experiences two periods of higher influenza activity in the beginning and just before the middle of the year, which coincide with the the peaks of influenza activities in winter in countries in the Northern and Southern hemispheres, respectively.

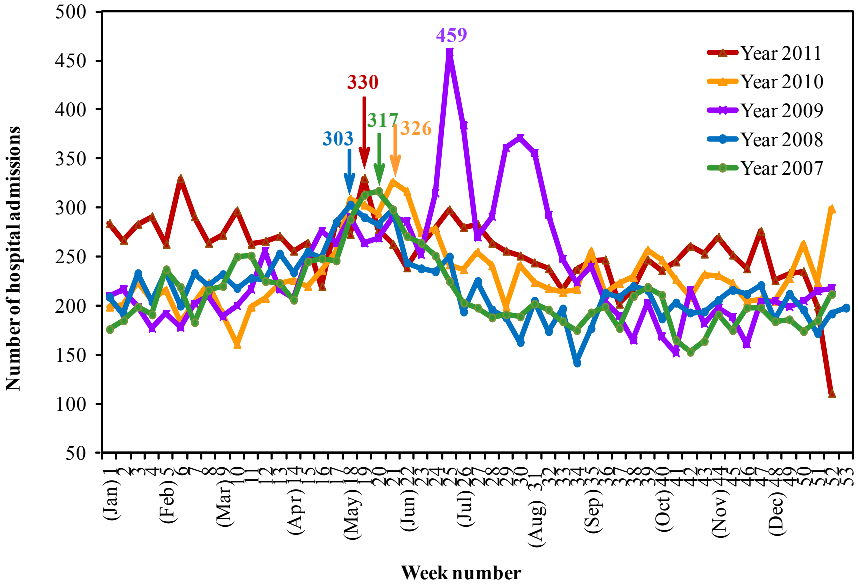
During the five-year period, the highest weekly number of ED attendances due to pneumonia at acute hospitals in the public sector was 639 in E-week 30 of 2009 (*Table* 1). This was 1.1 to 1.2 times the peaks in other years. The highest weekly proportion of ED attendances due to pneumonia was 3.4% in E-week 18 (3 – 9 May) of 2009.

The weekly number of hospital admissions (based on final diagnosis of ICD9 480 – 489) due to pneumonia and influenza (P&I) in both public and private sectors was highest in E-week 25 (21 – 27 June) of 2009, which was 1.4 to 1.5 times the peaks in 2007 and 2008, and 1.4 times the peaks in 2010 and 2011, respectively (*Table* 1 and *Fig. 3*). The average length of stay (LOS) of patients hospitalised due to P&I ranged from 7.6 in 2009 to 8.2 in 2011. Pneumonia has been the fourth most common condition for hospitalisation, and constituted 2.3% to 2.6% of the annual number of total discharges.

Between 15 July and 28 September 2009, a total of 1348 cases of influenza A(H1N1)pdm09 infection were admitted to hospitals.[4] This constituted about 0.6% of the estimated number of influenza A(H1N1) pdm09 cases seen at polyclinics and private GP clinics between E-week 28 and E-week 38 of 2009. Their median LOS was 3 days [interquartile range (IQR), 2 – 5]. Of these patients, 92 (7%) were considered to be severely ill, i.e. admitted to intensive care unit or died after admission. The median LOS of the severely ill patients was 9 days (IQR, 5 – 18). Eighty-eight out of the 92 cases (95.7%) were admitted to ICU, and their median length of ICU stay was 4 days (IQR, 2

Figure 3

Weekly number of hospital admissions due to pneumonia and influenza, 2007 – 2011



– 8). During this period, there were 18 deaths associated with influenza A(H1N1)pdm09 infection with an estimated case fatality rate of 7 deaths per 100,000 infected cases.

Since 2011, public hospitals are required to report all severely ill patients who had been tested positive for any influenza virus type. A total of 89 severely ill patients with influenza were reported by the public hospitals in 2011, giving a hospitalisation rate of 1.7 per 100,000 population. Their median LOS was 11 days (IQR, 5 – 21). Among these patients, 77 (86.5%) were admitted into ICU, and their median duration of ICU stay was 4 days (IQR, 2 – 8). In 2011, 31 severely ill patients (34.8%) died.

Comments

The impact of ARI and pneumonia on healthcare utilisation at primary and tertiary care level is of significance. The National Expert Committee on Immunisation has recommended annual influenza vaccination for elderly Singaporeans and for persons at high risk of having complications from influenza.

The influenza A(H1N1) pandemic resulted in significant increases in attendances due to ARI at polyclinics and ED of acute hospitals, and in hospital admissions due to P&I from mid-June to mid-August in 2009. Our observations also support continued enhancement and strengthening of influenza surveillance in Singapore, so that public health measures can be promptly implemented to mitigate the impact of influenza pandemics and meet the challenges in the provision of healthcare services and resources.

MOH first developed its influenza pandemic preparedness plan in 2004 and 2005 in the aftermath of the severe acute respiratory syndrome (SARS) epidemic in 2003. The national strategy for managing an influenza pandemic has three prongs: (i) establishment of an effective surveillance to detect the importation of a novel influenza virus; (ii) mitigation of the impact; and (iii) rendering the population immune through vaccination when the pandemic vaccine becomes available.[5] It is acknowledged that management of the surges of demand on healthcare services poses the biggest challenge. Hence, a high level of preparedness is required for healthcare services to better cope with the surges. The assumptions which have been made as part of the influenza pandemic preparedness planning include the likely impact of the pandemic in terms of the number of cases who would require outpatient care, the number who would be hospitalised and the number of fatal cases.

The magnitude of the impact of influenza pandemics is highly variable and depends on many factors, including the virulence of the virus, the level of immunity in the community and the control strategies. The anticipated surges in the utilisation of healthcare services and resources have been factored in the planning for a future influenza pandemic in Singapore.

(Reported by Ang LW, Ma S, Cutter JL, James L and Heng D, Public Health Group, Ministry of Health)

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Profile of severely ill patients with influenza in Singapore, 2011

It is estimated that 5–10% of adults and 20–30% of children worldwide are affected by seasonal influenza annually.[1] Severe infections develop in 3-5 million people and 250,000-500,000 deaths occur each year.[2] Singapore is situated in the tropics and experiences influenza all-year round. About 20% of the population is affected by seasonal influenza annually,[3] with an excess mortality rate of 8.3 per 100,000 population estimated between 2004 and 2006.[4]

In 2009, a novel influenza A(H1N1) virus emerged and rapidly caused a pandemic across the globe. The World Health Organization (WHO) announced the novel virus outbreak of H1N1 (previously known as “swine flu”) on 24 April 2009. All hospitals in Singapore were required to report severely ill patients with influenza A(H1N1)pdm09 to the Ministry of Health (MOH) since 28 April 2009. A total of 1348 patients with laboratory-confirmed influenza A(H1N1)pdm09 were hospitlaised between 15 July and 28 September 2009, including 92 severely ill patients.[5] The reporting of severely ill patients in Singapore was terminated after the WHO declared that the pandemic was officially over on 10 August 2010.

Public hospitals were required to report all severely ill patients who had been tested positive for any influenza virus type since end of January 2011 when a spike in influenza activity was observed (*Fig.4)*. We conducted an observational study of severely ill patients with influenza admitted to public hospitals in Singapore during the post-pandemic influenza period of 2011. The aims of our study were to describe the baseline characteristics and outcomes of severely ill patients with influenza admitted to public hospitals in Singapore, and to identify the risk factors associated with mortality.

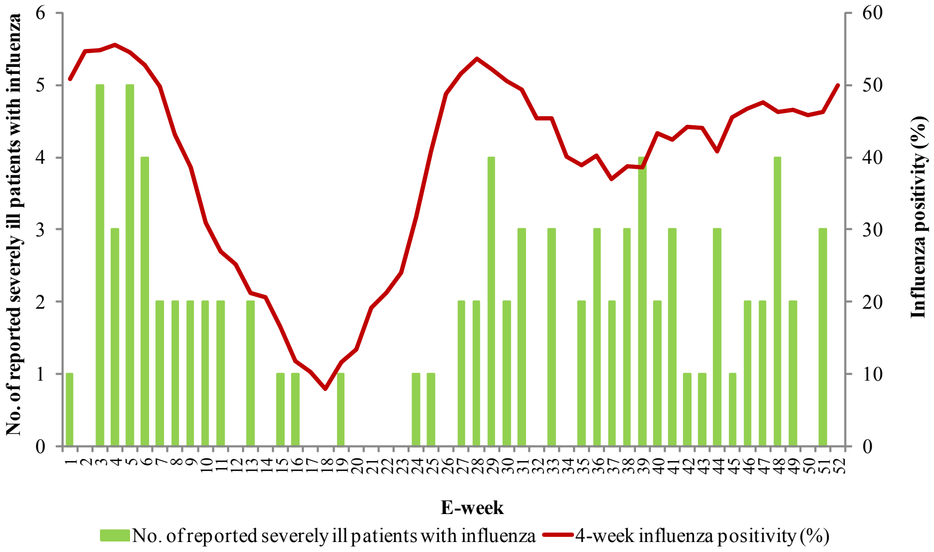
Materials and methods

Data collection

Severely ill patients with influenza were reported from seven public hospitals (Singapore General Hospital, Tan Tock Seng Hospital, Alexandra Hospital, National University Hospital, KK Women’s and Children’s Hospital, Changi General Hospital and Khoo Teck Puat Hospital) in 2011. A severely ill patient was defined as an individual who had been admitted to hospital based on clinical indications and

Figure 4

Weekly number of reported severely ill patients with influenza and 4-week influenza positivity (%), 2011



tested positive for influenza virus of any type and who was subsequently transferred to the intensive care unit (ICU) or died.

Data were collected using a standard template and included demographics such as age, gender and ethnicity of the patients, and medical information such as presence of comorbidities, dates of onset of symptoms, dates of hospital admission and discharge, dates in and out of the intensive care unit (ICU) where applicable, the use of mechanical ventilation, and clinical outcomes.

Laboratory method

Real time reverse transcriptase polymerase chain reaction (RT-PCR) was used by the hospital laboratories for the detection and subtyping of influenza viruses according to their in-house protocols. Appropriate specimens included nasopharyngeal, nasal and/or throat swabs or nasal aspirate. For patients who were intubated, an endotracheal aspirate was also collected. Bronchoalveolar lavage and sputum specimens were also acceptable.

Statistical analysis

Descriptive statistics were presented as counts and percentages for categorical variables, and as medians and interquartile range (IQR) for continuous variables. To assess differences in baseline characteristics between groups or over time periods, the Wilcoxon rank sum test was used for continuous variables, and the Fisher's exact test or Chi-square test was used for categorical variables.

The Kaplan-Meier method was used to estimate the cumulative proportion of severely ill cases surviving until 28 days. Survival time was calculated from the date of hospital admission to the date of outcome, which was either death or discharge from hospital. A p value less than 0.05 was considered to be statistically significant. All analyses were carried out using PASW Statistics software, version 18.0.

Results

In 2011, a total of 89 severely ill patients with influenza were reported by the public hospitals, giving a hospitalisation rate of 1.7 per 100,000 population. The highest age-specific hospitalisation rate was among patients aged 65 years or older (10.5 per 100,000 population). Among these patients, 77 (86.5%) were admitted into ICU and 31 (34.8%) died. Pneumonia (31.5%), sepsis (19.1%) and asthma (7.9%) were the three most common clinical indications for hospitalisation.

The demographics and clinical characteristics of the 89 severely ill patients with influenza were summarised in *Table 2*. The median age was 59 years (IQR, 38 – 76). There were 3 children below 5 years of age (3.4%). About half (50.6%) of the severely ill patients with influenza were females. In terms of ethnicity, Malays appeared to be over-represented among the severely ill patients; of the severely ill patients who were Singapore residents, 20.2% were Malays, compared to 13.4% Malays among Singapore resident population.

Eighty patients (90%) would be considered at increased risk for influenza-related complications either due to age (below 5 years, or 65 years or older) or having an underlying medical condition. More than three-quarters (78.7%) of the severely ill patients reported having at least one underlying medical condition that could predispose them to influenza-associated complications. The three most common underlying medical conditions among the severely ill patients with influenza were cardiovascular disease (27.0%), diabetes mellitus (22.5%) and asthma (19.1%). One pregnant woman who had asthma was admitted to ICU for chest infection.

The median duration from symptom onset to hospital admission was 3 days (IQR, 1 – 5 days) and from hospitalization to ICU admission was within a day (IQR, 0 – 1 day). The median duration of ICU stay was 4 days (IQR, 2 – 8). Among the 77 patients who were admitted to ICU, 62 (80.5%) stayed in ICU for 10 days or less. Two patients stayed in the ICU for more than 28 days; one patient was a 44-year-old woman who was admitted for neuromuscular disease and transferred out of ICU after 38 days, the other patient was a 52-year-old woman with a history of stroke who was admitted for sepsis and died due to pneumonia after staying in ICU for 35 days.

Of the 89 severely ill patients with influenza, 31 died and the main causes of death were pneumonia (48.4%) and influenza (25.8%). The median age of the patients who died was 74 years (IQR, 52 – 84). The median duration from hospital admission to death was 10 days (IQR, 5 – 18). The cumulative proportion of the severely ill cases surviving until 28 days from admission to hospital was 53% (95% confidence interval, 38 – 66%). There were 27 patients (87%) who died within 28 days of admission to hospital. The four patients who died beyond 28 days of admission to hospital were an 88-year-old man whose cause of death was chronic obstructive lung disease, two women aged 46 years and 92 years whose causes of death were pneumonia, and a one-year-old boy whose cause of death was intestinal infection. A total of 12 patients died without prior admission to ICU, and they were significantly older (median age of 85 years; IQR, 75 – 91) than those who died in ICU (median age of 56 years; IQR, 46 – 75) (p=0.002).

Table 2
Demographic and clinical characteristics of severely ill patients with influenza, 2011

Characteristic	All cases (n=89)	Survived (n=58)	Died (n=31)	p-value
Age (in years)				
Below 5 (%)	3 (3.4)	2 (3.4)	1 (3.2)	1.000
65 or older (%)	41 (46.1)	22 (37.9)	19 (61.3)	0.035
Median (IQR)	59 (38 – 76)	55 (34 – 70)	74 (52 – 84)	0.008
Gender (%)				
Female	45 (50.6)	31 (53.4)	14 (45.2)	0.509
Pregnant among the females	1 (2.2)	1 (3.1)	0 (0.0)	1.000
Ethnic group (%)				0.480
Singapore residents				
Chinese	59 (66.3)	39 (67.2)	20 (64.5)	
Malay	18 (20.2)	11 (19.0)	7 (22.6)	
Indian	5 (5.6)	3 (5.2)	2 (6.5)	
Others	3 (3.4)	1 (1.7)	2 (6.5)	
Foreigners	4 (4.5)	4 (6.9)	0 (0.0)	
Existing medical conditions (%)				
Cardiovascular disease	24 (27.0)	14 (24.1)	10 (32.3)	0.411
Diabetes mellitus	20 (22.5)	12 (20.7)	8 (25.8)	0.582
Asthma	17 (19.1)	15 (25.9)	2 (6.5)	0.027
Chronic renal disease	11 (12.4)	6 (10.3)	5 (16.1)	0.505
Chronic obstructive pulmonary disease	8 (9.0)	4 (6.9)	4 (12.9)	0.442
Neuromuscular disease	8 (9.0)	5 (8.6)	3 (9.7)	1.000
Cancer	6 (6.7)	3 (5.2)	3 (9.7)	0.416
Chronic liver disease	1 (1.1)	1 (1.7)	0 (0.0)	1.000
Immuno-compromised	1 (1.1)	0 (0.0)	1 (3.2)	0.348
Obesity	1 (1.1)	1 (1.7)	0 (0.0)	1.000
One or more chronic medical conditions[#]	70 (78.7)	46 (79.3)	24 (77.4)	0.836
Symptom onset to admission (days)[+]				0.289
Median (IQR)	3 (1 – 4.5)	3 (2 – 4)	2 (0 – 7)	
Admission to ICU (days)^				0.158
Median (IQR)	0 (0 – 1)	0 (0 – 3)	0 (0 – 1)	
ICU stay (days)^				0.392
Median (IQR)	4 (2 – 8)	3 (1 – 8)	6 (2 – 10)	
Influenza type/subtype (%)*				0.948
A(H1N1)pdm09	38 (42.7)	26 (45.6)	12 (41.4)	
A(H3N2)	38 (42.7)	24 (42.1)	14 (48.3)	
B	10 (11.2)	7 (12.3)	3 (10.3)	

[#] Comorbid conditions include asthma, chronic obstructive pulmonary disease, diabetes, cardiovascular diseases, cancer, chronic renal diseases, chronic liver diseases, neuromuscular disease (including epilepsy), immune-compromised, obesity and pregnancy.

[+] There was one death with no date of symptom onset.

^ Twelve patients who died without prior admission to ICU were excluded.

* Three patients tested positive for influenza A with no subtyping done were excluded.

percentages may not add up to 100% due to rounding.

There was a significantly higher proportion of elderly aged 65 years or older among the severely ill patients who died than those who survived (61.3% versus 37.9%; p=0.035). The proportion having asthma as an existing chronic medical condition was significantly higher in severely ill patients who survived than those who died (25.9% versus 6.5%; p=0.027). No other significant differences were observed among the severely ill patients who survived compared to those who died.

Comments

This study on severely ill patients with influenza of all virus types was the first to be carried out nationwide after the 2009 influenza A(H1N1) pandemic. We found that the demographics and clinical characteristics of severely ill patients were quite similar to that described in the local study on influenza A(H1N1)pdm09.[5]

The median age of severely ill patients with influenza was 59 years (IQR, 38 – 76), which was significantly older than that of 44 years in the local study done during the pandemic in 2009 (IQR, 23 – 54, p<0.001).[5] This shift to older age may partially account for the higher proportion of fatality in 2011 (34.8%, 31 deaths out of 89 severely ill patients) than that during the influenza A(H1N1) pandemic period in 2009 (19.6%, 18 deaths out of 92 severely ill patients), as older age has been reported to be independently associated with a worse outcome.[6] Our study and the local study in 2009 both showed a J-shaped curve of age-related mortality rate, which was consistent with the patterns observed in the studies in Mexico[7] and South Korea[8] during the pandemic period in 2009.

In our study, more than half (61.0%) of the severely ill patients aged 65 years or older tested positive for influenza A(H3N2), whereas 58.3% of those below 65 years of age tested positive for influenza A(H1N1)pdm09. Similar distributions were observed for the influenza biosurveillance of outpatients with influenza-like illnesss (ILI) in the community; 70.3% aged 65 years or older tested positive for influenza A(H3N2) whilst 44.5% of those below 65 years of age tested positive for influenza A(H1N1)pdm09 in 2011.

There were a significantly higher proportion of severely ill patients having asthma as an existing chronic medical condition who survived compared to those who died in our study. This significant difference was also reported in the local study conducted in 2009 (p=0.02)[5], and in overseas studies including Spain (p<0.001)[9] and Mexico (p<0.05)[10]. A possible explanation for this observation is that patients with asthma seek treatment early in the event of an asthmatic exacerbation based on their past experiences, which may have resulted in more prompt and effective treatment of influenza infection.[5] However, the comparison was not statistically significant in the global pooled study[11] and in the study in Spain.[12, 13]

There are some limitations of our study that should be addressed. As this study focused only on patients with laboratory confirmed influenza, the group may not be representative of hospitalised patients who may not have been tested since diagnostic testing was clinically driven. Although a standardised data collection template was used, information may not be collected for all patients or may be incomplete. Since information on the days that antiviral therapy (if any) had been initiated after onset of illness and status or history of influenza vaccination was not collected in this study, our analysis did not capture the full spectrum of clinical characteristics for comparison with other international studies. In view of the small numbers, studies with longer time series are needed to detect differences among patients with influenza A(H1N1)pdm09 versus those with seasonal influenza, and to identify other risk factors.

The surveillance of severely ill patients should be continued for prompt detection of increased virulence of influenza viruses. As older age was a significant risk factor for mortality, seasonal influenza vaccination of elderly individuals is strongly recommended.

Acknowledgement

We would like to thank the seven public hospitals, Singapore General Hospital, Tan Tock Seng Hospital, Alexandra Hospital, National University Hospital, KK Women's and Children's Hospital, Changi General Hospital and Khoo Teck Puat Hospital, for data collection on the severely ill patients with influenza.

(Reported by Jiang L[1], Ang LW[1], Ma S[1], Lai FY[1], Lim TK[1], James L[1], Cutter JL[2], Epidemiology & Disease Control Division[1], and Communicable Diseases Division[2], Ministry of Health, Singapore)

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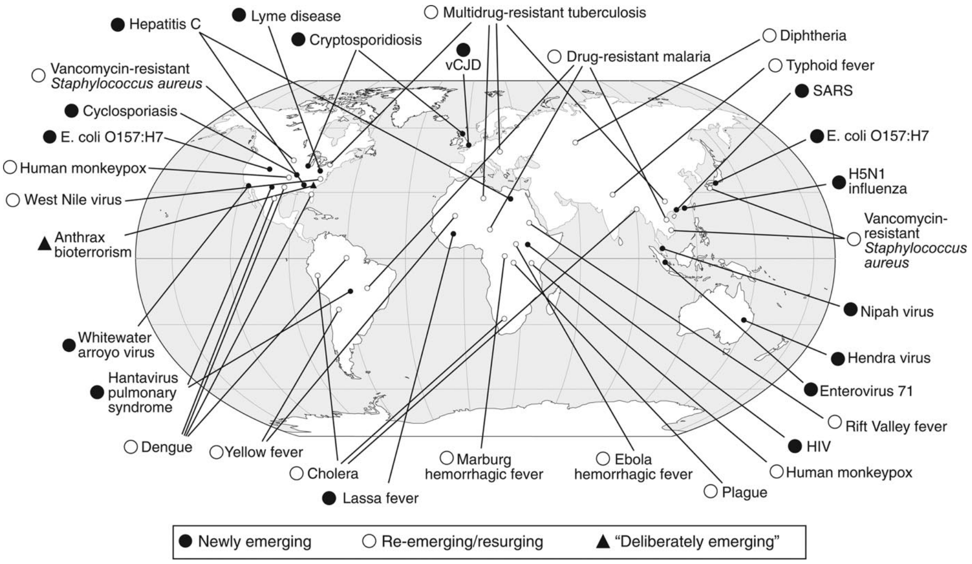
Emerging infectious diseases and its global health impact

Introduction

Emerging infectious diseases (EID) are diseases of infectious origin whose incidence in humans has increased within the recent past or threatens to increase in the near future.[1,2] EID include new or unrecognised infections that appear in the population; or infections that have existed but are rapidly increasing in incidence or spreading to new geographical areas and hosts, as well as those that are re-emerging after a period of quiescence.[1-3]

Infectious diseases are the world's second leading cause of death according to the World Health Organisation (WHO)'s 2004 World Health Report and accounted for about 26% of the 57 million deaths worldwide in 2002 and for nearly 30% of all disability adjusted life years (DALYs).[4] EID can potentially cause severe epidemics or pandemics and result in an upset of the balance in the health care system. Often, EID create major disruptions, economic loss and considerable impact to both the society and the population, hence constituting an important threat to public health. Recent examples of EID (*Fig. 5*) that warrant global attention would be the outbreak of severe acute respiratory syndrome (SARS) in 2003 and the H1N1 influenza pandemic that occurred in 2009.[5]

Figure 5
Examples of emerging and re-emerging infectious diseases in the world



Source: Morens DM et al. The challenge of emerging and re-emerging infectious diseases. Nature 2004; 430: 242-9

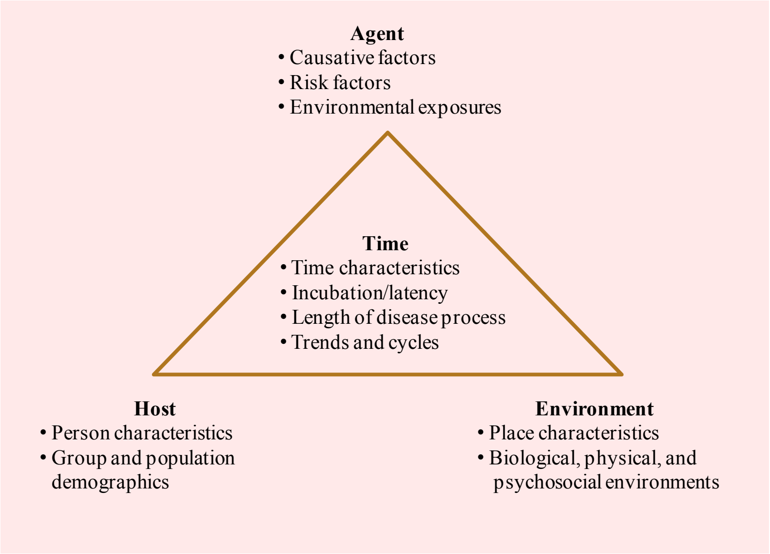
Factors that drive the development of EID

In the recent decades, EID that result from novel emerging pathogens have significantly increased, possibly a result of interaction between the epidemiological triad of host, agent, and environment (*Fig 6*); or alterations in various human demographics and behaviour, environmental, biological, socioeconomic, and political factors as well as trends in globalisation such as the expansion in international travel and trade which have extended the reach and increased the pace at which infectious diseases spread.[5] The main factors that contribute and drive the development of EID are broadly categorised as: (1) human demographics and behaviour changes; (2) ecological changes and agricultural development; (3) socioeconomic influences; (4) international travel and commerce; (5) technological advances; (6) microbial adaptation and change; and (7) inadequate public health infrastructure and measures (*Table 3*).[1,6-8]

I. Human demographics and behavior changes

The size of the human population and density of habitation; movements or upheavals in the population caused by migration, wars, or major catastrophes as well as the influence of human behaviour are often important factors attributing to disease emergence.[6] Rapid population growth could result in a high population density that carries increased potential for person-to-person transmission of infectious diseases such as tuberculosis among crowded living settings.[6] Increase in migration from rural areas to cities may allow infections that once remained obscure and localised in the rural areas to reach larger populations in the cities.[6] Once in the city, the newly introduced infection would have the opportunity to spread locally among

Figure 6
The epidemiologic triad of agent, host and environmental factors



Source: Miller RE. Epidemiology for health promotion and disease prevention professionals. New York. The Haworth Press. 2002; p.63, Figure 3.1

Table 3
Factors contributing to the emergence of infectious diseases

Factor	**Examples of specific factors**	**Examples of diseases**
Human demographics and behaviour changes	Societal events: population growth and migration (movement from rural areas to cities); war or civil conflict; urban decay; sexual behaviour; intravenous drug use; use of high-density facilities	Introduction of HIV; spread of dengue, HIV and other sexually transmitted diseases
Ecological changes and agricultural development	Agriculture; dams, changes in water ecosystems; deforestation/reforestation; flood or drought; famine; climate changes	Schistosomiasis (dams); Rift Valley fever (dams, irrigation); Argentine haemorrhagic fever (agriculture); Hantaan (Korean haemorrhagic fever)(agriculture); hantavirus pulmonary syndrome, southwestern US, 1993 (weather anomalies)
Socioeconomic influences	Poverty, low income, low socioeconomic status, poor housing and living conditions; poor water and sanitation; poor access to healthcare facilities and treatment	Water and vector-borne diseases: cholera, malaria and hepatitis E in India
International travel and commerce	Worldwide movement of goods and people; air travel	"Airport malaria"; dissemination of mosquito vectors; rat-borne hantavirus; introduction of cholera into South America; dissemination of O139 *V. cholerae*
Technology advances	Globalisation of food supplies; changes in food processing and packaging; organ or tissue transplantation; drugs causing immunosuppression; widespread use of antibiotics	Haemolytic uremic syndrome (*E.coli* contamination of hamburger meat), bovine spongiform encephalopathy; transfusion-associated hepatitis (hepatitis B, C), opportunistic infections in immunosuppressed patients, Creutzfeldt-Jakob disease from contaminated batches of human growth hormone (medical technology)
Microbial adaptation and change	Microbial evolution, response to selection in environment	Antibiotic-resistant bacteria, "antigenic drift" in influenza virus
Inadequate public health infrastructure and measures	Curtailment or reduction in prevention programmes; inadequate sanitation and vector control measures	Resurgence of tuberculosis in the United States; cholera in refugee camps in Africa; resurgence of diphtheria in the former Soviet Union

Source: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis 1995;1: 7-15.

the population and along inter-urban transport routes and airplanes.[6] The influence of human behaviour is also an important determinant for contributing to EID. In regions such as sub-Saharan Africa, unprotected sex or intravenous drug use have contributed to the rapid dissemination of sexually transmitted diseases and the emergence of human immunodeficiency virus (HIV) infection.[6,9] Other factors that are responsible for disease emergence are influenced by a variety of human actions which include motivating appropriate individual behaviour and constructive action for control of emerging infections.[6]

II. Ecological changes and agricultural development

Ecological changes which include agricultural and economic development are most frequently identified as factors that result in outbreaks of previously unrecognised diseases with high case fatality rates.[6] Zoonotic infections are often associated with ecological changes. Ecological factors precipitate disease emergence by placing people in contact with a natural reservoir or host for a zoonotic or arthropod-borne infection, either through increasing proximity or by changing conditions to favour an increased population of the microbe or its natural host.[1,6] An example would be the emergence of Lyme disease in the United States and Europe due to reforestation, which increased the population of deer and the deer tick, the vector of Lyme disease.[6] The movement of people into these areas placed a larger population in close proximity to the vector. Other changes to the agriculture, dams, water ecosystems, deforestation, flood or drought, famine, as well as climate changes could upset the natural habitat and ecosystem, thus leading to the emergence of diseases such as the swine or H1N1 influenza pandemic in 2009. The 2009 H1N1 pandemic is caused by a new influenza A virus subtype that originates from the triple-reassortant swine influenza A (H1) virus circulating in North American pigs.[10-13] In Malaysia, a new disease called the Nipah virus encephalitis where fruit bats were the original reservoirs, has recently emerged.[14] The Nipah virus could likely be transmitted to the pigs from the bats as a result of deforestation which causes the bats to flee to agricultural lands or pig farms. In turn, abattoir workers who were exposed to the infected pigs, contracted the Nipah virus and suffered from encephalitis. Other water-borne diseases such as *Vibrio cholerae O159* has also occurred in countries that suffer from massive floods or climate changes.[15] Climate changes such as global warming will likely change the distribution of vectors and enable them to increase and thrive in warmer habitats.[1] There will be an increase in the incidence of malaria and dengue fever as parasites develop more rapidly in mosquitoes at warmer temperatures.[1]

III. Socioeconomic influences

Socioeconomic factors such as poverty, low income, low socioeconomic status are often associated with poor housing and living conditions, poor water and sanitation and poor access to healthcare facilities and treatment.[1] As a result, these lead to ill health among the poor or low income groups. These groups who are frequently exposed to disease threats, tend to be more vulnerable to water and vector-borne diseases such as cholera and malaria as well as outbreaks of hepatitis E in India which have been traced to sewage-contaminated piped water.[1]

IV. International travel and commerce

New or localised infections that occur in a geographically isolated area could be introduced or brought to a new place through travel, commerce or war.[6,16] Air travel and international commerce have allowed the movement of goods and people across different continents and facilitated the rapid dissemination of new bacterial and viral strains to distant places through different means and modes of transport and along routes of trade and travel.[6] Some well-identified examples would be SARS, 2009 H1N1 influenza pandemic, as well as imported cases of "airport malaria" in non-endemic areas and the introduction of the Asian tiger mosquito to the United States, Brazil and parts of Africa in shipments of used tires from Asia and has resulted in the development of locally acquired encephalomyelitis.[6]

V. Technological advances

Rapid advancements in technology and high volume industry movements to reduce costs and increase efficiency in food production, processing and packaging, have increased the risks of accidental food contamination.[6] The effects of such contamination are often amplified with the globalisation of food supplies.[6] Some examples would be the contamination of hamburger meat by *Escherichia coli* (*E. coli*) bacterial strains causing haemolytic uraemic syndrome (HUS), a medical emergency that requires urgent treatment in the United States as well as the recent outbreak of the *E. coli* strain *O104:H4* in Germany in May 2011.[6,17]

With the advent of medical procedures such as blood transfusion, organ and tissue transplantations, blood-borne infections such as HIV, hepatitis B and C could occur through unprotected or accidental contact with infected blood and tissue products or contaminated apparatus. Nosocomial or hospital-acquired infections such as pneumonia are also commonly found in health care settings, often a result of poor hand hygiene among healthcare workers which is further compounded by the reduced resistance of individual patients especially those who are on immunosuppressants or develop drug-resistant bacterial strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) as a result of widespread use of antibiotics in the health care settings.[6]

VI. Microbial adaptation and change

Microbes are constantly evolving with changes that arise in response to natural selection for adaptation to the environment.[6] Antibiotic-resistant bacteria and drug-resistant parasites have emerged as a result of wide and inappropriate use of anti-microbial drugs in a variety of applications.[18-20] Pathogens can also acquire new antibiotic resistance genes from other, often non-pathogenic species in the environment, selected or driven by the selection pressure of antibiotics.[6]

Some viruses have also shown a high mutation rate and can rapidly evolve to yield new variants such as the influenza viral strains that result from either antigenic drifts or shifts in the haemagglutinin protein.[6] The new variant strains could reinfect persons who were previously infected because the altered antigen could not be immediately recognised by the immune system of the body and these subsequently could result in a pandemic if infection control policies and measures are not in place.

VII. Inadequate public health infrastructure and measures

The presence of adequate public health infrastructure and policy measures can prevent the development of many infections, especially those that are food-borne or water-borne.[1] Good water and sanitation measures for example, could minimise the potential spread and human exposure to water-borne pathogens such as cholera. Immunisation programmes could help prevent the outbreak of influenza pandemics and having a comprehensive vector control programme could also reduce the spread of arthropod-borne diseases such as dengue fever. An efficient public health system detects and responds quickly to an epidemic during its initial phase and is also sensitive to spot a new or previously unidentified infection. Hence, when the public health infrastructure and control measures or programmes are deficient in a health system, endemic diseases may re-emerge and/or new infections may occur, resulting in massive epidemics.

International collaboration to combat EID

EID are a global phenomenon that needs to be understood in a global context and managed with a global strategy, given its complexity.[8] EID can affect global employment, the economy and global trade.[2]

They also cause an impact on transport, travel, tourism, social gatherings or events and the delivery of health care.[2] These are discussed in details below:

I. Impact on employment

Industries, companies or workplaces may experience reduced attendance due to infection, fear of infection, or absenteeism of workers to take care of their families.[2] The reduction in workforce or manpower could also initiate an economic downturn and hence results in further unemployment or high attrition rates.[2] This could take place in the global context as well.

II. Impact on economy and global trade

EID can affect the economy and global trade when disease outbreaks occur among livestock. Food supplies, food production and their prices are often reduced as a result of decrease in demand and consumption of the affected products among consumers for fear of food contamination with pathogens. Further losses can result from culling of infected livestock, reduced animal value due to control measures such as mandatory vaccination and business interruption costs etc.[2] The impact on trade could be more severe for areas that had an important and established export market before the outbreak.[2] The possible loss of access to both regional and international markets would result in greater economic implications than local production losses alone.[2]

III. Impact on transport, travel, tourism, and social events

News of a localised outbreak in a country or region could potentially spread across the global continents through media communications. This in turn will affect travellers and their decisions in visiting a country with a recent disease outbreak. Their plans for travel may be altered in consideration of personal safety and wellness. Air travel, tourism and transport trades are affected when travellers cancel trips or depart from the affected country. Social gatherings or events such as symposiums or conventions may also be cancelled for public health interests.[2]

IV. Impact on delivery of health care

Pandemics or epidemics such as SARS would have an enormous and incapacitating impact on the health care industry across the globe.[2] Health care providers and workers are affected during the pandemic preparedness planning, mitigation phases as well as response plans that are put in place for control of pandemics. The quality of care could well be compromised as frontline healthcare workers (HCWs) often have to deal with large numbers of patients and uninfected persons who seek medical reassurance.[2] The HCWs also have to bear societal and family responsibilities as well as the mental burden of the risk they may pose in spreading the disease to their families. Such fears and anxiety could drive health care professionals, staff, and elective patients away from health care facilities, particularly those from the private or for-profit sectors. This in turn results in pressure to sustain these operations.

Given the epidemiological complexity of EID and the impacts on social, economic, political and environmental aspects across continents, a comprehensive global strategy needs to be employed with strong international collaboration and much concerted efforts taken to combat EID. International collaboration between various stakeholders is important for effective governance and control of the threat from EID. It is necessary not simply because of the multiple and interacting factors of disease emergence but also because economic interests such as tourism, food, trade and pharmaceuticals are often at stake.[8] Geo-political interests of different nations may not align, even if the economic and national interests of institutional and political actors were perfectly aligned with population health needs, the task of coordination across the vast array of national, international and transnational entities that are relevant to detecting and coping with emerging infections would be intimidating.[8] Hence, a global strategy that involves the collaboration of actors at the national level (nation states), international agencies (United Nations, World Health Organisation) and transnational entities (multi-national corporations and global non-government organisations) and provides capacity for communication, coordinated decision-making could eventually be scaled up and implemented with sufficient speed to combat EID. Global surveillance could also be carried out through reference laboratories and collaborating centres around the globe for early detection and control of EID.[8]

Past examples of global efforts against SARs have demonstrated that EID require a similar joint response for rapid containment.[1] Global networks of laboratories, epidemiologists and clinicians were quickly identified by WHO and concerted efforts yielded commendable results.[1] In 2000, WHO also launched the Global Outbreak Alert and Response Network (GOARN) which links more than 100 networks, institutes and experts to provide support to countries on behalf of the international community in responding to disease outbreaks.[1] The revised International Health Regulations (IHR) was also implemented in 2007 to facilitate containment of the international spread of EID with minimal disruption in the trade and human activities across borders.[1] These examples of global cooperation demonstrated the importance of international collaboration to combat outbreaks when national capacities fall short to contain the same.

Conclusion

Emerging infections have significantly increased over the past two decades, posing a potential threat to public health. The main key drivers that contribute to the development of EID involve the interaction between the epidemiological triad of host, agent and environment or simply the interaction between human behaviours, cultural and social practices with the natural environment. Many of the more specific contributing factors encompass reasons associated with human demographics and behaviour changes; ecological changes and agricultural development; socioeconomic influences; international travel and commerce; technology advances; microbial adaptation and changes as well as inadequate public health infrastructure and measures in place.

A global systems perspective needs to be adopted to better understand the global impact caused by EID on employment, economy, trade, transport, travel and health care delivery and to develop an effective global strategy that emphasises on the international collaboration between different countries for effective governance and control of EID, and more importantly, for promotion of global health across continents.

(Contributed by Tiong WW, Communicable Diseases Division, Ministry of Health)

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Influenza outbreak in a nursing home

Influenza is an acute viral infection of the respiratory tract. It is caused by the influenza virus and can easily be transmitted from person to person through contact with respiratory droplets and nasal secretions of an infected person.[1,2] The mean incubation period is two days, with a range from one to four days. Influenza illness is characterized by fever and one or more symptoms of cough, sore throat, headache, myalgia, prostration and coryza.[1] Although the illness is generally mild and resolves in five to seven days, it could cause severe illness in the elderly, immunocompromised persons and persons living in confined settings.[1,3,4]

The vulnerability of nursing homes residents to influenza infections has long been recognized.[3-7] Influenza-related morbidity and mortality rates are higher in the elderly, especially those with underlying medical conditions.[1,3,4,8] The closed environment of the nursing homes facilitates the rapid transmission of the infection within the home.[4,8] Influenza virus introduced to these closed environments could spread rapidly and cause outbreaks.[8]

On 16 July 2012, the Ministry of Health was notified of a cluster of cases with fever and respiratory symptoms amongst residents and staff of a private nursing home in Singapore. We report herein the findings of an epidemiological investigation into this outbreak.

Epidemiological investigation

Outbreak setting

The private nursing home had a total of 137 residents who were mainly elderly persons or persons with mental illness requiring moderate to full assistance in daily activities. The median age of the residents was 85 years and ranged from 42 years to 98 years. The majority (90%) of the residents were either bed-ridden or wheelchair bound. There were a total of 79 staff in the home, comprising 64 staff who had regular contact with the residents and 15 office staff who had no contact with the residents. None of the staff stayed in the premises of the home.

The home was a four-storey building consisting of single, double and four-bedded rooms. The only air-conditioned premises were two two-bedded rooms and the office. Electrical fans were installed in all rooms and activity areas to keep the premises cool and to facilitate ventilation.

Data collection and case definition

Active case detection was conducted from 17 July to 7 Aug 2012 with thrice daily fever surveillance and assessment for respiratory symptoms among the residents and staff. Those with fever and/or respiratory symptoms were cohort isolated in the home's isolation facilities, advised to rest at home or admitted to hospital. These cases were attended to by a family doctor who visited the home every other day or more frequently, if necessary. Cases who required further clinical investigations and treatment were hospitalized.

All the cases in the isolation facilities were tested for influenza virus infections from 24 to 30 July 2012. In addition, 154 asymptomatic (or absence of acute fever or respiratory symptoms for those with known chronic cough) residents and staff of the home were screened for influenza viruses on 27 July 2012.

Throat swabs were collected using flocked swabs and universal transport medium as recommended by the World Health Organization.[9] Nucleic acid was extracted followed by real-time PCRs of influenza A and H3 subtyping according to in-house protocols. Primers and probes of influenza A and H3 protocols were adopted from Spackman et al 2002 and the protocol of the Centre for Health Protection, Hong Kong SAR, China (unpublished in-house protocol), respectively.[10]

Sequencing of hemagglutinin (HA) and neuraminidase (NA) genes was carried out as described by Ghedin, et al. 2005. [11] The HA and NA sequences obtained were compared with sequences of local isolates and available sequence data from Global Initiative on Sharing All Influenza Data (GISAID). Nucleotide sequences were aligned using ClustalW. Phlyogenetic analyses were conducted in Mega 4 software. Neighbour-joining consensus trees were constructed from 1000 bootstrap replicates using the Maximum Composite Likelihood method.

The cases were categorized as either clinically diagnosed or laboratory confirmed. A clinical case was defined as one with an acute onset of fever and respiratory symptoms and epidemiologically linked to a known laboratory-confirmed case. A person with compatible clinical signs and symptoms and whose respiratory sample tested positive for influenza virus was considered a laboratory confirmed case.

Findings

A total of 72 cases were found to be infected with the influenza virus. 40 of them were laboratory-confirmed while the remaining 32 were clinically diagnosed (*Table 4*). Of the 40 laboratory confirmed cases, 12 (30%) did not display the typical symptoms of influenza-like illness (ILI) (fever of 37.8°C or higher and cough and/or sore throat) as defined by the US Centers for Disease Control and Prevention.[12] These 12 cases had only fever or respiratory symptoms and were detected through the influenza screening exercise on 27 July 2012.

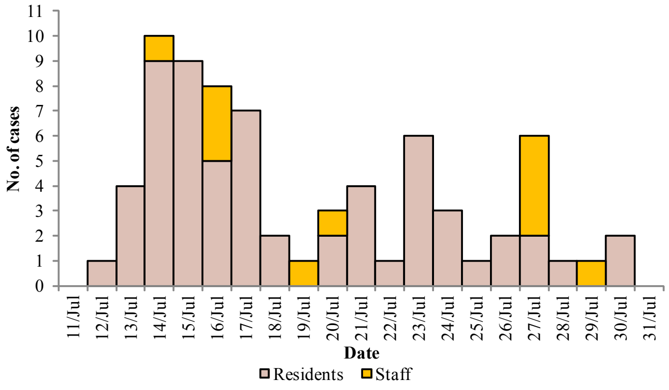
Table 4
Classification of 72 reported cases of influenza in a nursing home

Classification	No. of cases	% of cases
Laboratory-confirmed	40	56
Clinically diagnosed	32	44
Total	72	100

The onset of illness was from 12 to 30 July 2012 (*Fig. 7*). The overall attack rate was 33%. The resident-specific attack rate was 45% while the staff-specific attack rate was 14%.

The majority (78%) of the cases were aged 65 years and above and ranged from 23 to 95 years. The median age of cases among the residents was 91 years (range 42 to 95 years) while the mean age among

Figure 7
Time distribution of 72 reported influenza cases in a nursing home based on the date of onset of illness



the staff was 29 year (range 23 and 38 years). There was almost equal number of male (46%) and female (54%) cases. The ethnic-specific attack rates of the residents were 60% among the Indians, 45% among the Chinese and 33% among the Malays. Most of the cases were residents on level three of the home. The attack rate was 62% for residents at level 3, 45% at level 2 and 35% at levels 1 and 4.

None of the cases had recently travelled out of Singapore. All had contact with persons with coughs. About half of the residents had chronic coughs or self-resolving mild coughs on any given day. None had received influenza vaccination in the past 12 months. Among the 11 hospitalized cases, one died of pneumonia and the rest recovered.

All 40 laboratory-confirmed cases were tested positive for influenza A. Of these, 38 had the seasonal H3N2 subtype and 2 were undetermined due to low viral titre. Among the 38 samples positive for influenza A/H3N2, 28 were genetically sequenced. The 24 full-length HA gene sequences and 20 full length NA gene sequences were obtained. All HA and all NA sequences were 100% identical, in terms of nucleic acid, except that there were single point mutation in two HA genes and four NA genes, which suggested that the viruses of this outbreak could origin from a single source.

By including the sequences of other influenza viruses circulating in Singapore and worldwide during the same period, the phylogenetic analyses of HA and NA genes showed that the viruses of this outbreak were similar to other circulating strains isolated during Jan to Jun 2012 (*Fig. 8, A* and *B*). Although no hemagglutination- inhibition (HI) assay was conducted for the isolates from this outbreak, sequencing results suggested that the viruses were similar to H3N2-FEB-NPHL12-KK110 (♦ in *Fig. 8A*) which was a vaccine-like strain (A/Victoria/361/2011) identified by the WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia.

Discussion

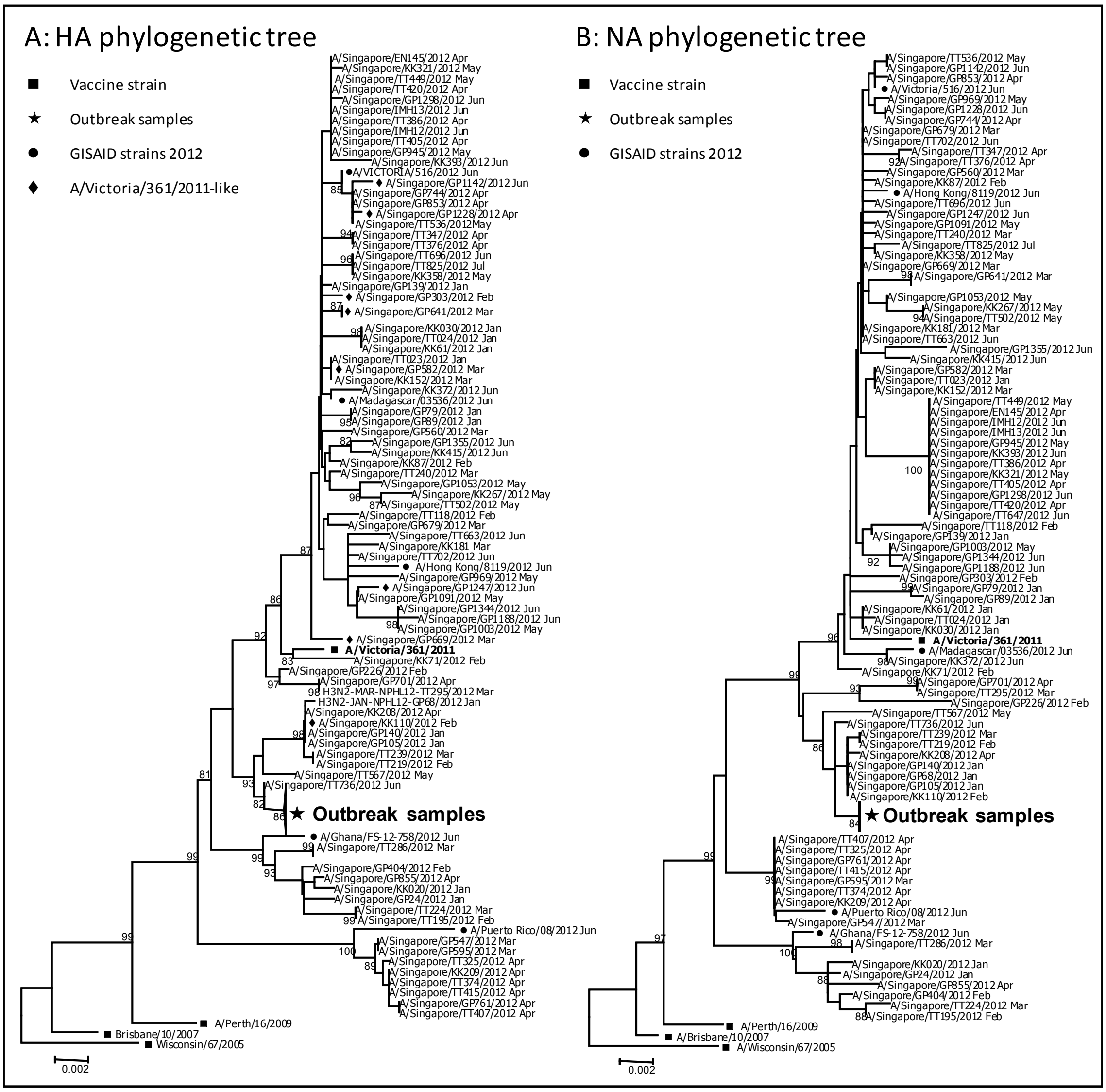
This report describes an outbreak of influenza A/H3N2 virus infection in a nursing home over a period of 19 days. Epidemiological links and genetic sequencing showed that it was a common source outbreak which propagated within the nursing home. The source of the infection and how the virus was introduced into the nursing home was not known.

Early diagnosis of influenza is difficult without the support of laboratory tests as influenza may be clinically indistinguishable from other respiratory diseases such as respiratory syncytial virus and rhinovirus infections.[1] Studies have shown that 50% or more of adults with influenza infections might not show ILI symptoms. [1, 6, 13-15] Atypical presentations of influenza infections, such as non-specific symptoms and exacerbation of underlying medical conditions, are common in elderly persons.[1, 6, 13-15] The high baseline rate of residents with chronic chough or mild self-resolving coughs had made the early diagnosis of influenza even more challenging in this outbreak.

It is hypothesized that the influenza infection was introduced into the nursing home by an infected person who did not have the typical ILI symptoms. It could be a staff, a visitor or a volunteer with mild respiratory symptom(s) who came into contact with the residents during group activities in the home. The bed-ridden residents could be infected by the staff who moved from level to level during a typical shift.

Figure 8

Phylogenetic analysis of the influenza A/H3N2 HA and NA sequences of the outbreak samples and reference sequences



It could also be introduced by a resident who might have contracted the infection during a regular follow-up visit to the clinics but went undetected as he/she did not display the typical ILI symptoms.

Influenza can be prevented by routine vaccination.[3,4,6,8] Increasing the herd immunity among persons in closed settings such as the nursing homes and intermediate and long-term care (ILTC) facilities is effective in reducing the risk of influenza outbreaks when the vaccine and epidemic strains are well-matched.[16,17] This outbreak may have been prevented had the residents and staff been routinely vaccinated as the outbreak causing strain of the influenza virus matched the prevailing influenza vaccine strain at that time.

In the tropical city of Singapore, influenza is reported throughout the year and the local surveillance of influenza showed that the seasonal human influenza subtypes are detected throughout the year.[2] Outbreaks of influenza in ILTC facilities have been reported locally and during summers in temperate countries.[5,8,18]

The routine influenza vaccination for residents and staff in nursing homes and ILTC facilities have been strongly recommended in countries such as Australia and the United States of America to prevent outbreaks in these facilities and to reduce the health impact of influenza on the healthcare system.[3,19]

Conclusion

This outbreak illustrated the vulnerability of elderly persons staying in an institution to infections that are easily spread by respiratory droplets, such as influenza. It has also highlighted the importance of routine influenza vaccination in the prevention of influenza outbreaks in a population who may not display typical ILI symptoms.

The inclusion of influenza vaccination as standard requirements for residents and staff in local ILTC facilities can be considered to prevent future influenza outbreaks and to reduce the incidence of influenza-related complications in the vulnerable groups. More local studies are needed to determine the impact of influenza vaccination in ILTC facilities and on the healthcare system to facilitate better public interventions in the prevention of infectious diseases in Singapore.

(Contributed by Chua A[1], Tow C[1], Phuah SP[2], Quek D[2], Cui L[2], Hishamuddin P[1] and Tay J[1], Surveillance & Response Branch[1], and National Public Health Laboratory[2], Communicable Diseases Division, Ministry of Health)

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