Possible origin of current influenza A H1N1 viruses

The ongoing outbreak of swine-origin influenza A H1N1 in Mexico, the USA, and 40 other countries reminds us that the risk of an influenza pandemic is high and will persist in the future. The first two cases of H1N1 infection in Southern California, USA, were reported on April 21, 2009.[1] According to WHO's estimation,[2] seasonal influenza epidemics result in about 3 million to 5 million cases of severe illness worldwide, and about 250 000 to 500 000 of the people with severe illness die each year from complications of influenza. In pandemic years, such deaths could easily exceed millions and cost billions of US dollars every year. Compared with avian influenza H5N1 and seasonal influenza epidemics, the 2009 outbreak of H1N1 is relatively mild in terms of mortality rate.

Scientists from the US Centers for Disease Control and Prevention submitted to GenBank (on April 27, 2009) the first set of completed coding sequences for the new influenza A virus, A/California/04/2009 (H1N1),[3] isolated from a 10-year-old boy in California on April 1, 2009.[1] By use of the Basic Local Alignment Search Tool program,[4] we compared the nucleotide sequence of the eight gene segments of this newly isolated virus with hundreds of other available influenza sequences in GenBank and listed the most similar ones in the table. We found that circulating strains of the H1N1 viruses isolated from different countries were essentially identical, and all eight gene segments of the new influenza A virus (A/California/04/2009) possibly originated from swine influenza viruses (table). Sequence analysis also suggests that six gene segments (PB2, PB1, PA, HA, NP, and NS1) of circulating H1N1 viruses probably came from swine influenza H1N2 viruses circulating in the USA from 1999 to 2001 and two gene segments (NA and M1) possibly originated from swine influenza H1N1 viruses circulating in Europe from 1985–98. Important questions are when, where, and how the swine influenza viruses circulating in the USA 8 years ago were mixed with the swine influenza viruses circulating in Europe 11 years ago and mutated to form the current reassortant H1N1 viruses? These events established that the future pandemic influenza could potentially come from reassortant viruses originating from birds, animals, or people in different areas of the world.

	PB2	PB1	PA	HA	NP	NA	M1	NS1
A/California/07/2009 (H1N1)	100	99	100	99	99	100	100	100
A/California/06/2009 (H1N1)	99	99	99	99	99	99	100	99
A/Mexico/InDRE4487/2009(H1N1)	99	99	99	99	100	99	100	100
A/Canada-ON/RV1527/2009(H1N1)	99	99	99	99	99	99	99	99
A/New York/18/2009 (H1N1)	99	99	99	99	99	99	99	99
A/Texas/04/2009 (H1N1)	99	99	99	99	100	99	99	99
A/Swine/Indiana/P12439/00 (H1N2)	96	96	96	95	97	..	88	95
A/Swine/North Carolina/93523/01 (H1N2)	96	96	96	94	96	..	87	96
A/Swine/Illinois/100085A/01 (H1N2)	96	96	96	95	96	..	87	95
A/Swine/Illinois/100084/01 (H1N2)	96	96	96	95	96	..	87	96
A/Swine/Indiana/9K035/99 (H1N2)	96	96	95	95	96	..	88	96
A/Swine/Minnesota/55551/00 (H1N2)	96	96	96	91	96	..	87	96
A/Swine/Ohio/891/01 (H1N2)	96	96	95	95	97	..	87	96
A/Swine/North Carolina/98225/01 (H1N2)	96	96	96	91	95	..	87	96
A/Swine/Minnesota/593/99 (H3N2)	96	96	96	..	96	..	88	96
A/Swine/Iowa/569/99 (H3N2)	96	96	96	..	97	..	88	95
A/Swine/Iowa/533/99 (H3N2)	96	96	96	..	97	..	88	96
A/Swine/Nebraska/209/98 (H3N2)	96	96	96	..	95	..	88	96
A/Swine/Korea/CY05/2007 (H3N2)	96	96	96	..	97	..	88	91
A/Swine/Spain/WVL6/1991 (H1N1)	..	..	..	..	..	94	96	..
A/Swine/England/WVL10/1993 (H1N1)	..	..	..	..	..	94	97	..
A/Swine/England/WVL16/1998 (H1N1)	..	..	..	..	..	93	96	..
A/Swine/Germany/Vi5698/95 (H1N1)	..	..	..	..	..	94	96	..
A/Swine/Belgium/1/1998 (H1N1)	..	..	..	..	..	93	96	..
A/Swine/France/WVL4/1985 (H1N1)	..	..	..	..	..	93	95	..
A/Turkey/France/87075/87 (H1N1)	..	..	..	..	..	92	94	..

Data are sequence similarity (%) with gene segments. ..=no data.

Table: **Nucleotide sequence similarities of A/California/04/2009 (H1N1) to other related influenza A viruses**

The key factor leading to most deaths in the previous three influenza pandemics (the Spanish flu of 1918–19, the Asian flu of 1957–58, and the Hong Kong flu of 1968–69) was the influenza-related secondary bacterial pneumonia caused by common upper respiratory tract bacteria.[5–7] Influenza virus infection and the secondary bacterial pneumonia in animals were summarised in a recent review article.[8] The severity of secondary bacterial pneumonia after influenza virus infection is dependent on viral and bacterial pathogenic factors and their interactions with host immune responses. To reduce the risk of a high mortality rate from potential pandemic influenza, it is important to understand which pathogenic factors (either viral, bacterial, or host) contribute the most to secondary bacterial pneumonia and severe respiratory distress. Therefore, influenza pandemic preparedness should include the development of new drugs and vaccines for efficient control and treatment of the secondary bacterial pneumonia.

Continued circulation of avian and swine influenza viruses in Asia and other areas of the world shows that

a future pandemic from non-human influenza viruses is a real threat. No one can accurately predict the timing and severity of the next influenza pandemic, but severe pandemics in the past have resulted in tens of millions of deaths. The prevention and control of the worldwide spread of pandemic influenza will need improved of animal and human surveillance, early detection and differentiation of causative viruses, identification of new targets for antiviral drugs and control of host immune responses, and the development of universal vaccines for influenza and secondary bacterial pneumonia.

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HZ is an employee of Z-BioMed, a company with products designed for use in influenza research. LC declares no conflicts of interest.

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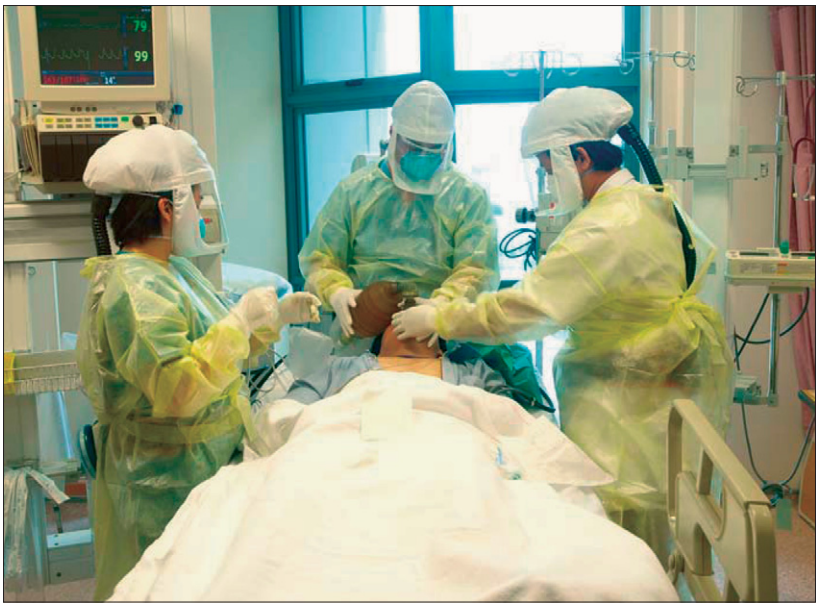
Influenza in the tropics

Compared with temperate countries,[1] data on tropical influenza remain scarce. Russell and colleagues[2] suggest that epidemics of new variants of influenza are seeded into temperate regions from continuously circulating viruses in east and southeast Asia through temporary regionally overlapping epidemics.

Influenza infections happen throughout the year in the tropics; most countries report two peaks in the number of infections associated with rainy seasons.[1,3–6] Clinical data on disease characteristics and impact on heath-care services are lacking. The authors of a study i n Thailand[7] reported that 11% of people hospitalised with pneumonia were influenza-positive, with loss of productivity costing an estimated US$23·4 million to $62·9 million over 12 months. An analysis of influenza in Singapore from 1996 to 2003 concluded that 6·5% of underlying pneumonia and influenza deaths were attributable to influenza,[8] which is a similar proportion to that in the temperate USA and subtropical Hong Kong, with elderly people being most affected. Both studies showed that influenza in Thailand and Singapore were under-recognised.

Lee and colleagues[9] summarised historical records on the three previous influenza pandemics in Singapore. Excess mortality was estimated as 18 of 1000 population in 1918, 0·47 of 1000 population in 1957, and 0·27 of 1000 population in 1968. Influenza pandemic mortality rates in Singapore were similar to those in temperate countries.

A recent laboratory project at Tan Tock Seng Hospital, a 1200-bed general hospital in Singapore, showed that about 10% of respiratory samples from patients admitted within 48 h period were positive for influenza by



Influenza drill in the intensive-care unit of Tan Tock Seng Hospital, Singapore