Pandemic Influenza A (H1N1) 2009 in Malaysia - The Next Phase

I-C Sam, MRCPath, Abu Bakar S, PhD

Tropical Infectious Diseases Research and Education Centre, Department of Medical Microbiology, Faculty of Medicine, University Malaya, 50603 Kuala Lumpur, Malaysia

In recent years, zoonotic RNA viruses such as Nipah, SARS coronavirus, avian influenza (H5N1) and Chikungunya have emerged with global impact. The latest has now been designated by World Health Organization (WHO) as pandemic (H1N1) 2009 virus. It was first reported as an outbreak in Mexico in April, and has now caused the first influenza pandemic since 1968. By July 11, 2009, there were 105,304 confirmed cases and 463 deaths in 143 countries, including 627 cases in Malaysia[1]. The rapid spread of the disease has been matched by the speed of dissemination of information and protocols, co-ordinated by WHO. The experiences of SARS and H5N1 have been enormously beneficial in preparing the world for a pandemic.

Influenza A is an enveloped RNA virus containing 8 genomic segments. The haemagglutinin (H) and neuraminidase (N) surface proteins are key virulence determinants and elicit the main host immune response. There are 16 H and 9 N, which determine the influenza subtype. The segmented nature of the genome facilitates swapping of genes between virus strains co-infecting a single host. As influenza is principally an avian virus, this reassortment process mainly involves a vast pool of avian strains, generating countless variants. For unknown reasons, certain avian strains successfully cross species barriers to infect mammals, including humans and pigs. Occasionally, a novel strain with efficient human transmissibility has caused pandemics in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), and now 2009. Since 1977, seasonal H1N1 and H3N2 have been circulating, and constantly mutating, which means the seasonal vaccines need to be changed annually. The current pandemic (H1N1) 2009 is a novel H1N1 strain not previously seen in humans, thus there is widespread susceptibility.

Epidemiological and clinical aspects

Clinically, pandemic (H1N1) 2009 infection resembles seasonal influenza. Most patients have fever, cough, sore throat, headache, dyspnoea, and myalgia, and some have diarrhoea and vomiting[2-4]. Most cases are mild. Deaths occur rarely, mainly due to severe pneumonia. About half involve previously healthy people. The rest have underlying conditions such as lung and cardiovascular disease, diabetes, immunosuppression, pregnancy, and, unexpectedly, obesity[2-5].

The often-quoted case fatality rate (CFR) of 0.4% is an overestimate, as it uses only confirmed cases as the denominator, and excludes mild, undiagnosed cases. Corrected CFR estimates are 0.0004-0.06%, although these estimates will be higher in places with fewer healthcare resources and greater prevalence of HIV and malnutrition[6]. This would certainly include parts of Malaysia. Monitoring the true CFR is critical to detect changes in disease virulence. Also, differences in CFR between countries or populations may indicate local risk factors that require targeting. The task is more difficult as most countries are now screening selected cases rather than all suspect cases. In past pandemics, multiple disease waves of varying severity occurred over a few years[7]. However, the extent of modern global travel and mixing may alter this pattern.

The vast majority of cases have occurred in those <60 years. An increase in pneumonia and shift from older to younger age groups is characteristic of influenza pandemics[7]. This observation is supported by the presence of preexisting immunity to the pandemic (H1N1) 2009 virus in 33% of people >60 years, but rarely in those younger[8]. This may be due to exposure of older people to H1N1 strains which are antigenically more similar to the current pandemic strain than recent seasonal H1N1 strains. The same study also showed that current seasonal influenza vaccines did not protect against the pandemic strain[8].

Origins of the virus

The evolution of the pandemic (H1N1) 2009 virus is complex and fascinating (Table I). It is a reassortant of two distinct swine influenza lineages[9,10]. Six genes originate from a swine virus first isolated in North American pigs in 1998. This was a triple-reassortant containing genes from avian H1N1, seasonal human H3N2, and North American classical swine H1N1[11]. The classical swine H1N1 probably shared a common avian-like ancestor with the human H1N1 causing the 1918 pandemic[12]. The other two genes of the pandemic (H1N1) 2009 virus are from Eurasian "avian-like" swine H1N1 viruses, which arose from the introduction of avian H1N1 into European pigs in 1979[9].

Although the current pandemic strain probably arose in pigs, the only documented swine infections with the pandemic virus to date occurred after the first reported human cases in April 2009, in Canada and Argentina[13]. The pandemic strain probably circulated undetected amongst pigs for some years in countries with no surveillance of swine influenza[9]. Pigs have tracheal cell receptors for influenza viruses which are similar to birds and humans[14]. Thus, pigs can be "mixing vessels" for reassortment of avian, swine and human influenza. However, influenza surveillance in swine has

Corresponding Author: Jamal I-Cheng Sam, Tropical Infectious Diseases Research and Education Centre, Department of Medical Microbiology, Faculty of Medicine, University Malaya, 50603 Kuala Lumpur, Malaysia Emai: wlcsam@doctors.org.uk

lagged behind that of humans and birds, as the disease in swine is mild and has little commercial impact. An opportunity to foresee a potential pandemic strain was missed. With the concurrent risk of a panzootic, or worldwide outbreak amongst swine, surveillance of pigs is now a priority. This is particularly critical, yet difficult, in countries with rudimentary pig farming, where pigs mix freely with birds.

The naming of the virus has been controversial, particularly the media-friendly term "swine flu". This has been rejected by WHO as inaccurate and simplistic. The pandemic (H1N1) 2009 virus contains genes from swine, avian and human influenza sources. Furthermore, previous human infections with true "swine influenza" were rare, and involved direct contact with pigs[15], just as "avian" influenza (H5N1) is acquired from infected birds. Currently, swine play no active role in the ongoing pandemic. Although its recent genetic origin is swine-related, the pandemic (H1N1) 2009 virus is clearly behaving as a human influenza strain, as it transmits easily between humans.

Situation in Malaysia

The first case of pandemic (H1N1) 2009 in Malaysia was reported on May 15. The Ministry of Health (MOH) immediately responded with measures to contain disease spread. Containment focused on active case finding and robust control of contacts. Cases and contacts were placed under home quarantine orders, and given oseltamivir (Tamiflu). In accordance with WHO recommendations, no travel restrictions were made. Instead, travel advisories were issued regarding countries with extensive local spread, including USA and Australia. Some control measures, such as airport screening, have caused debate. They were perceived to incur unsustainable costs and social disruption incommensurate with the mildness of the disease. Also, there is a lack of data on their effectiveness. Nevertheless, it is likely that containment bought some valuable time. By delaying and flattening the inevitable epidemic peak, the nation made preparations such as training staff, and stockpiling antivirals, antibiotics, personal protective equipment, laboratory supplies, and so on.

On June 11, WHO raised the pandemic alert to level 6. At this point, Malaysia had 11 confirmed cases, all imported. Initially, most imported cases were from USA. In recent weeks, most imported cases have been from the Asia-Pacific region, mainly Australia, Indonesia, Thailand and Singapore. The first locally-acquired case was diagnosed on June 17. The incidence of total and locally-transmitted cases continued to rise (Figure 1). The two largest clusters of cases to date started in late June, at a conference in Penang (20 cases), and a school in Cheras, Kuala Lumpur (18 cases). By 9 July, the number of local transmissions had risen to 159 (27.7%) of 574 cases. With sustained community spread, and detection of new cases with no defined links with existing cases, it seemed that the disease could no longer be contained. On the same day, the MOH declared that Malaysia would be moving from containment to a mitigation strategy. Many other countries have also done this, in keeping with international guidance[16,17].

Mitigation focuses primarily on managing disease impact on health and society, rather than containing spread. The aims are to reduce disease-related morbidity and mortality, slow the spread of disease, and ensure running of essential services. Hospital admission, laboratory diagnosis and antivirals will be limited to selected patients with moderate or severe disease, and those at risk of severe disease. Mild cases will be managed at home, to prioritise healthcare resources for severe cases. Individuals will be expected to take responsibility and practise personal measures. These include social distancing (keeping one metre away from others, and avoiding crowds), cough etiquette, frequent handwashing, self-quarantine if ill, and household ventilation. Resource-intensive measures such as screening, tracing and quarantining contacts will be phased out. There will be continued monitoring of unusual clusters or severe cases which may indicate a change in viral virulence or transmissibility.

The restriction of antivirals to selected cases may be difficult for the public to accept. However, indiscriminate use of oseltamivir has led to the first oseltamivir-resistant strains of the pandemic (H1N1) 2009 virus[18]. Up to 64% of seasonal influenza A (H1N1) viruses have a single neuraminidase mutation conferring oseltamivir resistance, including 44% of Malaysian isolates[19]. As resistance is so easily acquired, the effectiveness of oseltamivir in this pandemic may soon be lost. Unfortunately, many countries, including Malaysia, have stockpiled oseltamivir. Pandemic (H1N1) 2009 virus is still susceptible to zanamivir (Relenza), which has the disadvantage that it is inhaled rather than taken orally. The most effective means of control is vaccination. However, an effective vaccine will not be available for several months. There is also insufficient manufacturing capacity for the whole world, and at least the first 600 million doses have been pre-purchased by developed countries[20]. Thus, poorer countries may have limited access to vaccines, even in the medium term.

Some argue that the focus on the pandemic has detracted from other priority diseases such as tuberculosis[21] and dengue. This is a difficult issue. The pandemic has an estimated

Table I: Origins of the pandemic (H1N1) 2009 virus[9,10]

Gene	Recent origin	Historical origin
PB2	North American triple-reassortant swine	avian H1N1
PB1	North American triple-reassortant swine	human H3N2
PA	North American triple-reassortant swine	avian H1N1
H	North American triple-reassortant swine	North American classical swine H1N1
NP	North American triple-reassortant swine	North American classical swine H1N1
N	Eurasian "avian-like" swine H1N1	avian H1N1
M	Eurasian "avian-like" swine H1N1	avian H1N1
NS	North American triple-reassortant swine	North American classical swine H1N1

PB2, polymerase PB2; PB1, polymerase PB1; PA, polymerase PA; H, haemagglutinin; NP, nuclear protein; N, neuraminidase; M, matrix protein; NS, nonstructural proteins.

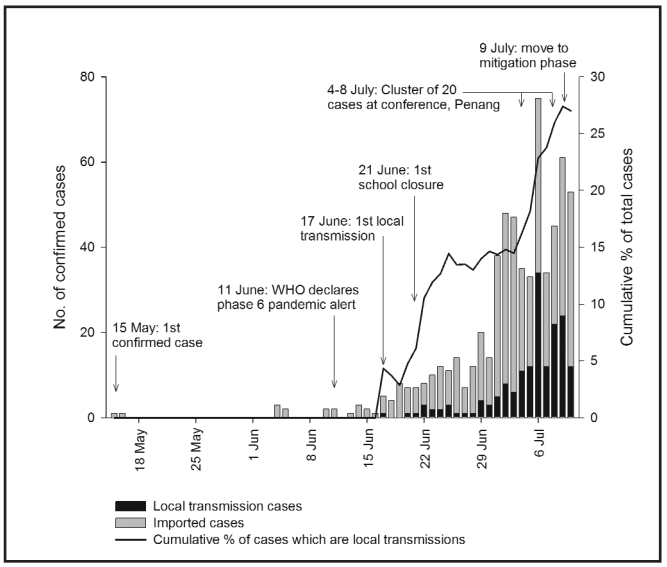

Fig. 1: Confirmed pandemic (H1N1) 2009 cases in Malaysia up to 10 July, 2009, with key events. The rising numbers of local transmission cases are shown. Data was obtained from daily situational updates available at http://h1n1.moh.gov.my/.

reproduction number (R0, the average number of secondary cases arising from each case) of 1.4-1.6, compared to estimates from previous pandemics of 1.4-2.0[22]. This may result in clinical attack rates of at least 25%[23]. The health and socioeconomic impact on Malaysia could be considerable.

Malaysia's move to a mitigation strategy is acknowledgment of the relentless spread of pandemic (H1N1) 2009. Mortality appears low amongst the healthy, so the focus is now on vulnerable at-risk groups. There will be possible shortages in effective antivirals and vaccines, two key components in pandemic control. Effective leadership and communication, particularly in view of rapidly evolving knowledge, will be critical as we face the challenges of this novel virus in the months ahead.

REFERENCES

1. World Health Organization. Situation updates - pandemic (H1N1) 2009. [Accessed 8 July 2009]. Available from: http://www.who.int/csr/disease/swineflu/updates/en/index.html
2. Human infection with new influenza A (H1N1) virus: clinical observations from Mexico and other affected countries, May 2009. Wkly Epidemiol Rec 2009; 84: 185-9.
3. Health Protection Agency, Health Protection Scotland, National Public Health Service for Wales, HPA Northern Ireland Swine influenza investigation teams. Epidemiology of new influenza A (H1N1) virus infection, United Kingdom, April – June 2009. Euro Surveill 2009; 14: pii=19232. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19232
4. Chowell G, Bertozzi SM, Colchero MA, *et al.* Severe respiratory disease concurrent with the circulation of H1N1 influenza. N Engl J Med 2009; 361: doi: 10.1056/NEJMoa0904023. Epub 2009 Jun 29.
5. Centers for Disease Control and Prevention. Hospitalized patients with novel influenza A (H1N1) - California, April-May 2009. MMWR Morb Mortal Wkly Rep 2009; 58: 536-41.
6. Wilson N, Baker MG. The emerging influenza pandemic: estimating the case fatality ratio. Euro Surveill 2009; 14: pii=19255. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19255
7. Miller MA, Viboud C, Balinska M, Simonsen L. The signature features of influenza pandemics - implications for policy. N Engl J Med 2009; 360: 2595-8.
8. Centers for Disease Control and Prevention. Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza vaccine. MMWR Morb Mortal Wkly Rep 2009; 58: 521-4.
9. Smith GJ, Vijaykrishna D, Bahl J, *et al.* Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. Nature 2009; 459: 1122-5.
10. Zimmer SM, Burke DS. Historical perspective - emergence of influenza A (H1N1) viruses. N Engl J Med 2009; 361: 279-85.
11. Zhou NN, Senne DA, Landgraf JS, *et al.* Genetic reassortment of avian, swine, and human influenza A viruses in American pigs. J Virol 1999; 73: 8851-6.
12. Gorman OT, Bean WJ, Kawaoka Y, Donatelli I, Guo Y, Webster RG. Evolution of influenza A virus nucleoprotein genes: implications for the origins of H1N1 human and classical swine viruses. J Virol 1991; 65: 3704-14.
13. ProMED-mail. Influenza A (H1N1) - worldwide (80): Argentina, human to pig. ProMED-mail 2009; 1 Jul: 20090701.2376. <http://www.promedmail.org>. Accessed 7 July 2009.
14. Ito T, Couceiro JNSS, Kelm S, *et al.* Molecular basis for the generation in pigs of influenza A viruses with pandemic potential. J Virol 1998; 72: 7367-73.
15. Myers KP, Olsen CW, Gray GC. Cases of swine influenza in humans: a review of the literature. Clin Infect Dis 2007; 44: 1084-8.
16. New influenza A (H1N1) virus: WHO guidance on public health measures, 11 June 2009. Wkly Epidemiol Rec 2009; 84: 261-8.
17. European Centre for Disease Prevention and Control. ECDC interim guidance: Mitigation and delaying (or 'containment') strategies as the new influenza A (H1N1) virus comes into Europe. Stockholm: ECDC, 2009.
18. ProMED-mail. Influenza A (H1N1) - worldwide (84): Tamiflu resistance, China (HK). ProMED-mail 2009; 6 Jul: 20090706.2428. <http://www.promedmail.org>. Accessed 7 July 2009.
19. Hurt AC, Ernest J, Deng YM, *et al.* Emergence and spread of oseltamivir-resistant A (H1N1) influenza viruses in Oceania, South East Asia and South Africa. Antivir Res 2009; 83: 90-3.
20. Collin N, de Radiguès X, Kieny MP, the World Health Organization H1N1 Vaccine Task Force. New influenza A (H1N1) vaccine: how ready are we for large-scale production? Vaccine 2009; doi: 10.1016/j.vaccine.2009.06.034. Epub 2009 Jun 26.
21. Migliori GB, Sotgiu G, Lange C, Macgregor-Skinner G. Defining priorities: swine-origin H1N1 and the MDR-TB epidemic. Lancet 2009; 373: 2108.
22. Fraser C, Donnelly CA, Cauchemex S, *et al.* Pandemic potential of a strain of influenza A (H1N1): early findings. Science 2009; 324: 1557-61.
23. Global Influenza Programme, World Health Organisation. Pandemic influenza preparedness and response: a WHO guidance document. Geneva: WHO Press, 2009.