

While everybody is worrying about when the avian influenza A (H5N1) virus will adapt well enough in human to cause a pandemic, the emergence of a novel swine-origin influenza A (H1N1) virus (S-OIV) has shocked the world. On 29 April 2009, the World Health Organization raised the pandemic alert level from phase 4 to 5. As of 15 May, there have been 7503 laboratory-confirmed cases of S-OIV infections and 65 confirmed deaths globally, with more than 95% of the confirmed cases and all the deaths from the American continent. The S-OIV genome is made up of a unique combination of gene segments that had not been observed in previously known influenza A viruses as a result of genetic reassortment.

The earliest evidence of influenza virus causing acute febrile respiratory illness in pigs can be traced to the 1930s.¹ From the 1930s to the 1990s, classic swine influenza A (H1N1) was the commonest swine influenza virus circulating in the swine population. During these six decades, this virus did not undergo much genetic change. Sporadic cases of human infections due to swine influenza have been reported in the last four decades, of which most were caused by classic swine influenza A (H1N1) virus.²⁻⁶ Occupational exposure to pigs was the most important risk factor for infection.^{7,8} The clinical features of such infections were indistinguishable from those caused by human influenza viruses, although the mortality was higher.⁹ At the end of the last century, multiple subtypes, including H1N1, H1N2 and H3N2, of triple-reassortant swine influenza A viruses emerged on the American continent.^{10,11} The genomes of these triple-reassortant viruses all contained combinations of swine, human and avian influenza virus gene segments. In the past few years of this century, sporadic cases of human infections caused by these triple-reassortant swine influenza A viruses have occurred on the American continent,¹²⁻¹⁵ mainly due to subtype H1N1.¹³ Most patients presented with fever and cough and all recovered, without resulting in efficient, sustained human-to-human transmission.¹²⁻¹⁵

The first report on the clinical features of the 642 confirmed cases of S-OIV infections in the United States showed that most patients presented with upper respiratory and systemic symptoms similar to those of seasonal influenza, the commonest being fever and cough, which were present in over 90% of the patients.¹⁶ The difference from seasonal influenza was that 25% of the patients had vomiting and 25% had diarrhoea.¹⁶ The age predilection reported could be due to outbreaks in schools, instead of inherent properties of the virus.¹⁶ Most infections were self-

limited; 9% of the patients were hospitalised and there were only two deaths.¹⁶ This is in line with an estimated case fatality rate of 0.4% for the epidemic in Mexico, which was calculated using a mathematical model pertaining to data on travellers.¹⁷ It is too early, however, to draw conclusions on the potential virulence of the virus, as the Spanish flu pandemic was also mild initially in the spring of 1918, but the virus became more virulent during the second wave of infection in winter.¹⁸ The present S-OIV differs from the triple-reassortant swine influenza A virus (subtype H1N1) associated with sporadic infections, by virtue of acquiring two gene segments (NA and M) from the Eurasian swine lineage.¹⁶ The other six gene segments (PB2, PB1, PA, HA, NP, and NS) were similar to those of the triple-reassortant swine influenza A virus reported hitherto.¹⁶ The first confirmed case of S-OIV infection in Hong Kong also presented with fever, cough, and myalgia.¹⁹ The diagnosis was confirmed by an ultra-rapid reverse-transcriptase-polymerase-chain-reaction assay, which specifically detects S-OIV but not circulating human influenza H1N1 or H3N2 viruses, with the result available in 50 minutes.¹⁹ This enabled rapid isolation of the patient and quarantine of contacts. The viral load in the nasopharyngeal secretion of the patient was in the range of 10^6 to 10^7 copies per mL during the first 3 days of the illness, but decreased to undetectable level by the sixth day.¹⁹

A major concern is the possibility that S-OIV will acquire resistance to antivirals as the epidemic evolves. The two classes of antiviral agents against influenza viruses are the adamantanes, which include amantadine and rimantadine, and the neuraminidase inhibitors, which include oseltamivir and zanamivir. The M gene encodes the target of the adamantanes. So far, all strains of S-OIV from the current epidemic contain a serine→asparagine mutation at codon 31 of this gene, which confers resistance to both amantadine and rimantadine.¹⁶ This mutation is also highly prevalent among circulating subtypes of European swine influenza A viruses.²⁰ Fortunately, all strains of S-OIV tested so far are susceptible to both oseltamivir and zanamivir, which would be the main stay of treatment for this virus at the moment.¹⁶ This is in contrast to the situation in the 2008-2009 influenza season, in which most circulating influenza A (H1N1) viruses were apparently resistant to oseltamivir though still susceptible to zanamivir.^{21,22} However, massive use of these antiviral agents for treatment and prophylaxis, may lead to development of resistance, which would pose a challenge to the management of patients severely compromised by these infections and result in increased mortality.

It seems that the S-OIV vaccine is the answer to this infection. Nevertheless, there are still many questions to answer and dilemmas to resolve, given that the infection appears mild at the moment. Should companies stop the production of seasonal influenza vaccine and focus on S-OIV vaccine? How can we ensure a fair distribution of the vaccine? Are two shots required for adequate protection against this new virus with antigenic shift? Will S-OIV vaccine be associated with similar profiles of side-effects, in particular, Guillain-Barré syndrome, as seasonal influenza vaccine? These issues have to be addressed before determining the most reasonable vaccine policy.

Patrick CY Woo, MD, FRCPath

E-mail: pcywoo@hkucc.hku.hk

Department of Microbiology

Research Centre of Infection and Immunology

State Key Laboratory of Emerging Infectious Diseases

The University of Hong Kong

Queen Mary Hospital

Hong Kong

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