Swine flu update: bringing home the bacon

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ABSTRACT

- In 6 weeks, swine influenza A(H1N1) virus has spread from 10 to 74 countries.
- Australia has the fifth highest number of cases and the third highest rate of infection among the top five affected nations.
- People who are hospitalised with or die from this novel virus are more likely to have predisposing risk factors.
- There is a predilection for younger age groups and sparing of older age groups. This may be a property of influenza A viruses in general rather than being specific to swine influenza A.
- If unchecked, the sheer number of cases may lead to much higher numbers of deaths and hospitalised patients than would normally be attributed to a standard influenza season.
- Paradoxically, the low case-fatality rate of the virus raises the question of how best to approach management of this outbreak.
- It is uncertain how an expected vaccine against the novel virus will be used.

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It has been 6 weeks since the situation with the H1N1 (swine) influenza A virus was first reported in the *Medical Journal of Australia*.[1] Since then, the infection has relentlessly infiltrated nation after nation, with some countries being disproportionately affected. Even the first case of human-to-swine transmission has been described.[2] At the time of writing the first report, only 10 countries — not including Australia — had confirmed cases. That list has rapidly expanded to include 74 countries, with Australia featuring prominently.[3] The natural history of the illness still appears to be generally mild. The majority of cases appear to involve people aged less than 30 years,[4] supporting a theory that older individuals have cross-reactive antibodies to swine influenza A from previous infection or immunisation. The efforts of Australian health departments to contain the epidemic have not been without controversy.[5] A vaccine directed against this novel virus will supposedly be available in the near future.[6]

International and local situation

There are now more than 29 000 laboratory-confirmed cases of swine influenza A infection worldwide.[3] Among the five countries with the highest total numbers of cases reported to the World Health Organization, Australia has the third-highest rate of infection (Box).

These figures must be interpreted with some caution, as the countries with high numbers of laboratory-confirmed cases are likely to be those with the public health infrastructure to identify cases and test samples en masse. In other words, there is a bias towards developed nations (such as the United States, Canada and Australia). Conversely, developing nations will not be as well resourced to identify cases. This may be why Egypt is the only African nation so far with confirmed cases.[3] This lack of cases in Africa may have been a true reflection of the situation early in the outbreak, when the major risk factor was travel to Mexico, but given the otherwise global spread of the virus, it is hard to imagine that Africa remains almost untouched by the swine influenza A virus. Developing nations, in general, seem particularly vulnerable to the deleterious effects of a pandemic. Very few have national pandemic preparedness plans,[7] and they are unlikely to have the same degree of access to vaccines, antiviral medications and antibiotics as developed nations.

Rate of infection with swine influenza A(H1N1) virus in the five countries with the highest total numbers of laboratory-confirmed cases

	Rate per 100 000 population*	Total laboratory-confirmed cases†
Chile	10.3	1 694
Canada	9.1	2 978
Australia	6.4	1 307
Mexico	5.9	6 241
United States	4.4	13 217

* Source of population figures: World Health Organization. Countries. http://www.who.int/countries/en/. † Reported to WHO by 12 June 2009.[3] ◆

There are few published data on the epidemiology and clinical characteristics of swine influenza A virus infection so far in Australia. Clearly the most extraordinary statistic is the disproportionate number of cases in Victoria, for which there is currently no explanation. Of 1542 confirmed cases nationwide (as of 15 June), 1011 (66%) have been from Victoria.[8,9] This situation has led Singapore to issue a statement specifically advising against travel to Victoria, while some Australian states and territories are barring students from attending school for 7 days after returning from Victoria.[10] The Victorian Premier's unhappiness at having his state singled out during this outbreak evokes memories of Toronto's mayor during the severe acute respiratory syndrome (SARS) epidemic.[11] However, no Australian state or territory has been spared from cases of swine influenza A infection.[8] Authorities have responded to this disparity by placing Victoria in the "Sustain" pandemic phase, while the other states and territories remain in the "Contain" phase.[12,13] This may change in the near future.

Clinical features

Recent analysis of a number of confirmed cases has not added much to what was already known about the clinical presentation of swine influenza A. The incubation period is a median of 3–4 days (range, 1–7 days).[4] The virus typically causes an illness characterised by fever, cough, sore throat, malaise and headaches; however, fatal pneumonia or a mild upper respiratory tract illness without fever represent two extremes of multiple possible clinical presentations. Diarrhoea and vomiting were present in more than a third of patients in a US case series,[14] raising the possibility of transmission through vomitus or faeces. It is also worth noting that a lack of

fever has been observed in mild, and even severe, cases.[14] This is important because fever is part of the case definition for identifying and testing a suspected case;[15] therefore, cases in afebrile patients are probably being missed.

Severe cases

Although most cases of swine influenza A virus appear to have been mild, between 2% and 5% of patients in the US and Canada have been hospitalised.[14] In Mexico, a third of hospitalised patients have required mechanical ventilation. Almost half of the individuals hospitalised in the US and half of those who have died in Mexico have had comorbidities such as pregnancy, immunosuppressive therapy, autoimmune disease, chronic lung disease, cardiovascular disease, morbid obesity, and diabetes.[14]

Identification of such risk factors is important: if health services become overwhelmed in the face of rapidly spreading contagion, then diagnostic, therapeutic and prophylactic resources may be preferentially allocated to people with these risk factors, as they will be at highest risk of severe infection.

The median time from illness onset to hospitalisation in Mexico and the US has been 4–6 days (range in Mexico, 1–20 days). The reason for hospitalisation has usually been rapidly progressive respiratory disease, with rapid progression to acute respiratory distress syndrome and renal or multiorgan failure. Interestingly, diarrhoea seems to be uncommon in hospitalised patients. The radiographic appearance has been one of severe pneumonia and multifocal infiltrates with nodular alveolar or basal changes.[14]

Laboratory features in hospitalised patients have included:

- raised lactate dehydrogenase levels (100% of 16 fatal cases in Mexico);
- some degree of renal impairment (in up to 50% of cases — probably multifactorial);
- lymphopenia, leukopenia or leukocytosis; and
- raised creatinine phosphokinase levels (which may contribute to renal impairment through myoglobinuria).[14]

It appears that death from this infection is relatively uncommon so far. On the basis of laboratory-confirmed cases, the global case-fatality rate (CFR) is 0.5% (145/29 669).[3] When Mexican cases are removed from the equation, the CFR drops further to 0.2% (37/23 428). However, even with a CFR of 0.2%–0.5%, given that there have been more than 1000 confirmed cases in Australia already, it would not be surprising if the first death in Australia from this infection occurs soon.

Age and sex

Although not a sexist virus (it affects males and females equally), this emerging influenza infection may be described as ageist, in that it predominantly affects younger age groups with relative sparing of older age groups.[4] As a similar pattern was seen in the 1918–1919 influenza pandemic,[16] one might assume that targeting of the young and sparing of the old is a feature specific to pandemic strains. However, it could be that this is simply the epidemiology of influenza A viruses in general.

One study compared Australian cases of seasonal influenza (from Victoria and Western Australia) in 2007 and 2008 with cases of swine influenza in the US in 2009.[17] The researchers found that the median age for both US swine influenza A cases and Australian cases of seasonal influenza was similar (20 years v 18–23 years, respectively). Similarly, for both groups, there were relatively few cases in those older than 50 years (5% for swine influenza v 4%–12% for seasonal influenza). If there is any difference within the younger age groups, it may be that swine influenza A is more likely than seasonal influenza to affect those aged ⩽ 18 years (60% v 23%–51%, respectively).

One explanation for the difference in age groups affected by swine influenza A is that older people have some degree of immunity to this novel virus. Examination of stored sera samples by the US Centers for Disease Control and Prevention (CDC) supports this explanation. The CDC found that cross-reactive antibodies to swine influenza A were not present in any of the children, but were present in 6%–9% of adults aged 18–64 years and in 33% of those aged over 60 years.[18] This suggests that older people may, in the distant past (rather than the recent past), have encountered a vaccine or circulating influenza virus that was antigenically and genetically related to the new swine influenza A virus. Presumably the antibodies generated to the older virus are now conferring some degree of immunity to the new one.

Virus characteristics

With regard to the ability of this virus to spread, in certain clusters the attack rate has been found to be as high as 33%, with a reproductive number of 1.4–1.6.[4] There has still been no evidence of swine-to-human transmission,[4] although human-to-swine transmission probably occurred in Alberta, Canada, when a sick farm worker infected a herd of pigs.[2]

One major concern is that this novel virus will mutate or reassort into a more virulent form, leading to an increased CFR. Although mutations in the swine influenza A virus have been demonstrated, there have been only five amino acid changes so far, suggesting that the new virus mutates no faster than standard influenza viruses.[4]

Issues for now and the future

Anecdotally, it appears that Australia has diverted significant resources, especially at a public health and laboratory level, into investigating and containing this outbreak. If these resources are not already overwhelmed, one wonders how they will cope if there is a further rise in swine influenza A cases combined with the work generated by Australia's "normal" influenza season.

There has also been some public debate about whether a downgraded response to the outbreak (that would consume fewer resources) would be more appropriate, on the basis that the virus, despite being both novel and infectious, does not seem particularly lethal.[5] This last fact has probably surprised many. Before this outbreak, many experts would have assumed that an influenza virus that crosses the species barrier and is capable of sustained human-to-human transmission would undoubtedly be highly lethal (eg, like avian influenza A[H5N1], with its global CFR of 61% [262/433][19]). Although this is currently not the case, the swine influenza A virus should not be dismissed as unimportant. Assuming a conservative attack rate of 20%, a hospitalisation rate of 2%–5% and a CFR of 0.2%, around 80 000–200 000 people in Australia may ultimately be hospitalised for swine influenza A, with around 8000 deaths. This compares to annual figures of about 18 000 hospitalisations and 3000 deaths directly or indirectly attributable to seasonal influenza.[20,21] In other words, although swine influenza A is currently an imposition mainly on our public health and laboratory infrastructure, it could well

become a burden on our public hospital system — consuming resources, finances and, most importantly, patients. Although these figures suggest that swine influenza A should be taken very seriously, this still does not mean that a downgraded approach would be inappropriate; the arguments for and against this are beyond the scope of this article.

As more neuraminidase inhibitors (oseltamivir, zanamivir) are used worldwide against the swine influenza A virus, monitoring for the emergence of resistance will be important. Many strains of seasonal influenza A virus have already become oseltamivir-resistant.[22]

A vaccine against the swine influenza A virus is expected to be ready in the near future.[6] It is unclear how the vaccine will be used, if at all. Possibilities include a mass vaccination program of the Australian population or a targeted program for the high-risk groups described here. The most recent experience of mass vaccination against swine influenza virus was in the US in 1976 — the program began but was cancelled when concerns were raised about an excess number of cases of Guillain–Barré syndrome in vaccine recipients.[23] However, the circumstances today are different, with sustained human-to-human transmission in multiple countries. Vaccine production is also presumably more advanced than it was 30 years ago; but it is worth keeping the American experience in mind.

Conclusion

The swine influenza A virus has established itself in much of the world, particularly in Australia. Furthermore, the WHO has now officially declared the outbreak to be a pandemic.[24] The virus appears to be targeting younger people who have no cross-reactive antibodies to the virus. The sheer number of cases so far in Australia suggest that there may end up being far more hospitalisations and deaths from this infection than from seasonal influenza. Paradoxically, the low CFR raises the question of whether our response to the virus should be reviewed. The development of a vaccine against the swine influenza A virus may play an important role in controlling its spread, although the possible side effects of a mass vaccination program need to be considered.

Competing interests

None identified.

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References

1 Senanayake SN. A pandemic that's not bird flu? Pigs might fly. *Med J Aust* 2009; 191: 38-40 [Published online ahead of print, 1 May 2009].

2 International Society for Infectious Diseases. ProMED-mail Archive Number 20090502.1653. PRO/AH/EDR> Influenza A (H1N1): animal health (04), infected swine, Canada. 2 May 2009. http://www.promedmail.org/pls/otn/f?p=2400:1001:1598368704429758::::F2400_P1001_BACK_PAGE,F2400_P1001_ARCHIVE_NUMBER,F2400_P1001_USE_ARCHIVE:1001,20090502.1653,Y (accessed Jun 2009).

3 World Health Organization. Epidemic and Pandemic Alert and Response. Influenza A (H1N1) – update 48. 12 Jun 2009. http://www.who.int/csr/don/2009_06_12/en/index.html (accessed Jun 2009).

4 World Health Organization. Considerations for assessing the severity of an influenza pandemic. *Wkly Epidemiol Rec* 2009; 84: 197-202.

5 Allen P. Swine flu: pandemic or panic? *ABC Radio Australia News* 2009; 10 Jun. http://www.radioaustralianews.net.au/stories/200906/2594199.htm (accessed Jun 2009).

6 ABC News. Swine flu vaccine ready for trial: manufacturer. 13 Jun 2009. http://www.abc.net.au/news/stories/2009/06/12/2597233.htm (accessed Jun 2009).

7 World Health Organization. Epidemic and Pandemic Alert and Response. National influenza pandemic plans. http://www.who.int/csr/disease/influenza/nationalpandemic/en/ (accessed 14 Jun 2009).

8 Australian Government Department of Health and Ageing. Health Emergency. H1N1 09 Outbreak. National case update. 15 Jun 2009. http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/health-swine_influenza-index.htm#june155am (accessed Jun 2009).

9 Grayson ML, Johnson PDR. Australia's influenza containment plan and the swine flu epidemic in Victoria [editorial]. *Med J Aust* 2009; 191: 150 [Published online ahead of print, 17 Jun 2009].

10 Miletic D, Gregory P. Victoria on swine flu alarm list. *The Age* (Melbourne) 2009; 6 Jun. http://www.theage.com.au/national/victoria-on-swine-flu-alarm-list-20090605-bylc.html (accessed Jun 2009).

11 CTV.ca News. WHO travel advisory met with anger, disbelief. 23 Apr 2003. http://www.ctv.ca/servlet/ArticleNews/story/CTVNews/1051101880715_222/ (accessed Jun 2009).

12 Australian Government Department of Health and Ageing. Health Emergency. H1N1 09 Outbreak. Increased public health response in Victoria. 3 Jun 2009. http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/health-swine_influenza-index.htm#3junehv (accessed Jun 2009).

13 Cheng AC, Dwyer DE, Kotsimbos ATC, et al. ASID/TSANZ guidelines: treatment and prevention of H1N1 influenza 09 (human swine influenza) with antiviral agents. [Published online ahead of print, *Med J Aust* 18 Jun 2009].

14 World Health Organization. Human infection with new influenza A (H1N1) virus: clinical observations from Mexico and other affected countries, May 2009. *Wkly Epidemiol Rec* 2009; 84: 185-189.

15 Australian Government Department of Health and Ageing. Health Emergency. Clinical information. Case management. 3 Jun 2009. http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/healthprof#clinical (accessed Jun 2009).

16 Brundage JF. Cases and deaths during influenza pandemics in the United States. *Am J Prev Med* 2006; 31: 252-256.

17 Kelly H, Grant K, Williams S, Smith D. H1N1 swine origin influenza infection in the United States and Europe in 2009 may be similar to H1N1 seasonal influenza infection in two Australian states in 2007 and 2008. [Published online ahead of print, *Influenza Other Respi Viruses* 7 Jun 2009]. http://www3.interscience.wiley.com/cgi-bin/fulltext/122443393/HTMLSTART (accessed Jun 2009). DOI: 10.1111/j.1750-2659.2009.00088.x

18 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: 521-524.

19 World Health Organization. Epidemic and Pandemic Alert and Response. Cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to WHO. 2 Jun 2009. http://www.who.int/csr/disease/avian_influenza/country/cases_table_2009_06_02/en/index.html (accessed Jun 2009).

20 Newall AT, Scuffham PA. Influenza-related disease: the cost to the Australian healthcare system. *Vaccine* 2008; 26: 6818-6823.

21 Owen R, Barr IG, Pengilley A, et al. Annual report of the National Influenza Surveillance Scheme, 2007. *Commun Dis Intell* 2008; 32: 208-226.

22 Moscona A. Global transmission of oseltamivir-resistant influenza. *N Engl J Med* 2009; 360: 953-956.

23 Sencer DJ, Millar JD. Reflections on the 1976 swine flu vaccination program. *Emerg Infect Dis* 2006; 12: 29-33.

24 World Health Organization. World now at the start of 2009 influenza pandemic. Statement to the press by WHO Director-General Dr Margaret Chan. 11 Jun 2009. http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html (accessed Jun 2009).

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