COMMENTARY

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Swine flu: lessons we need to learn from our global experience

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There are important lessons to be learnt from the recent 'Swine Flu' pandemic. Before we call it a pandemic, we need to have appropriate trigger points that involve not only the spread of the virus but also its level of virulence. This was not done for H1N1 (swine flu). We need to ensure that we improve the techniques used in trying to decrease the spread of infection—both in the community and within our hospitals. This means improved infection control and hygiene, and the use of masks, alcohol hand rubs and so on. We also need to have a different approach to vaccines. Effective vaccines were produced only after the epidemic had passed and therefore had relatively little impact in preventing many infections. Mass population strategies involving vaccines and antivirals also misused large amounts of scarce medical resources.

Keywords: *Influenza*; *H1N1*; *swine flu*; *vaccination*; *anti-viral therapy*; *pandemic response*

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When a new H1N1 strain of influenza was reported in Mexico in April 2009, it appeared to be associated with a high mortality. Media reports helped fuel fears around the world that we might see a recurrence of events associated with the 'Spanish flu' in 1918–1919, when tens of millions of people died. This triggered internationally, pandemic plans—designed to cope with predicted new virulent strains of influenza, such as 'Bird Flu' (H5N1). Governments and their populations asked what would be the effects on themselves and others. Access to antiviral drugs and vaccines and the measures that were needed to prevent the spread of this virus were at the forefront of this discussion.

The virus did indeed spread quickly around the world. However, by May 2009, data from the USA and elsewhere showed that its virulence was considerably less than that initially reported in Mexico (1). The case fatality rate was likely less than 1 in 10,000 people infected (2). However, there remained concerns that enhanced virulence might still be seen during the upcoming winter in the Southern Hemisphere.

Winter arrived and large numbers of cases were reported in southern Australia in June 2009 (1, 3, 4). However, the mortality rate was very low and similar to what had been seen in the USA and Canada during their spring. Data from many countries also showed that the elderly seemed to be relatively protected from getting infected (presumably as a result of previous infections with other influenza viruses and thus acquired immunity). However, certain other groups were more vulnerable (1–6). In general, these were the same groups that were usually more vulnerable during seasonal influenza—those with underlying heart disease, lung disease, and so on. The unexpected, much higher risk group was pregnancy. Women who were pregnant had a hospitalisation and death rate 3–10 times higher compared to other females in the same age group (3, 5, 6). While children and young adults had very high rates of infection, their overall risk of death was low. On a population basis, for those under the age of 30 without risk factors, the chance of dying during the winter epidemic in Australia was less than 1 per million people, even though a large proportion of children worldwide were infected (likely about 50% of children) (6, 7).

The virus was also likely spreading widely and much earlier than initially thought. In Victoria, the spread was likely weeks prior to it being first detected—probably at the same time that the virus was first detected in the USA (8). This was likely to be the case in Mexico as well (with the spread possibly 6 months prior to its initial laboratory diagnosis) (8).

With all the major new 'pandemic' strains of influenza (Asian flu, Hong Kong flu, as well as swine flu) there were delays before it was recognised that we were dealing with new virus strains. This 'late diagnosis' means attempts at containment will always be very difficult or likely impossible. Widespread circulation of the virus occurs for many months before there is recognition that the strain is new. The vast majority of people with a 'new' infection have only very mild disease and thus goes unnoticed until larger than expected numbers of people are admitted to hospital—usually with complications such as bacterial pneumonia. Only then it is recognised that something unusual has happened. It then also takes time before viral isolates are obtained by reference laboratories. Then, sequencing and viral typing finally lead to a realisation that something is 'new'. This makes not only any containment policy very difficult but also means vaccines based on current egg-based technology will never be available in a timely fashion.

Even when attempts were made to contain the virus in areas where it was not circulating, this did not appear to be successful for 'swine flu' anywhere around the world. In Australia, when it became obvious that attempts at containment were unsuccessful, a newly defined 'Protect phase' was developed, which was added to the previous influenza management plans (9). This then appropriately focused our health resources on those who were known to be at a higher risk and thus more vulnerable to complications rather than the entire population. In practice, similar approaches were taken around the world.

Australia was one of the first countries to have a vaccine available for use in the general population. It became available, however, only in early October 2009—months after the epidemic had peaked (Fig. 1) (4). Our current vaccine technology does not have the ability to produce enough vaccine in a timely fashion to protect large proportions of the population when a new form of influenza develops and spreads. We need to develop new influenza vaccines that are safe and effective and that give protection for many years and against multiple strains—including newly emerging ones.

One essential issue, on which we need international consensus, is the trigger point for defining a pandemic. Whenever a 'pandemic' is called, it will have major effects on the way governments and health departments allocate resources. It will also have profound effects in how society functions, particularly if it includes closing schools, workplaces, and so on. The WHO definition of pandemic needs to re-incorporate a component that takes into account severity (2, 10) as, appropriately, does one plan from the USA (11). If we define a pandemic (as was the case for 'swine flu') as merely being the spread of a new influenza virus strain around the world, we will be calling pandemics every few years. Many previous seasonal influenza strains using the current WHO definition could also have been defined as 'pandemic strains'. Unless the severity of the infection is much worse than what we see with seasonal influenza, it is inappropriate to invoke pandemic plans internationally.

'Swine flu' caused major problems for hospitals around the world and their intensive care units. However, one of the major reasons for this difficulty was our chronic lack of spare capacity in hospitals. Overcrowding, bed block, and ambulance bypass occur every winter in Australia and in many other countries (2). In Australia, about 4,900 people with swine flu were admitted to hospital (4). It was mainly short stays of 2 or 3 days or less. Australia, however, has more than 8 million hospital admissions per year (12). It is a concern that an increase in hospital activity of less than 0.1% of yearly admissions and bed

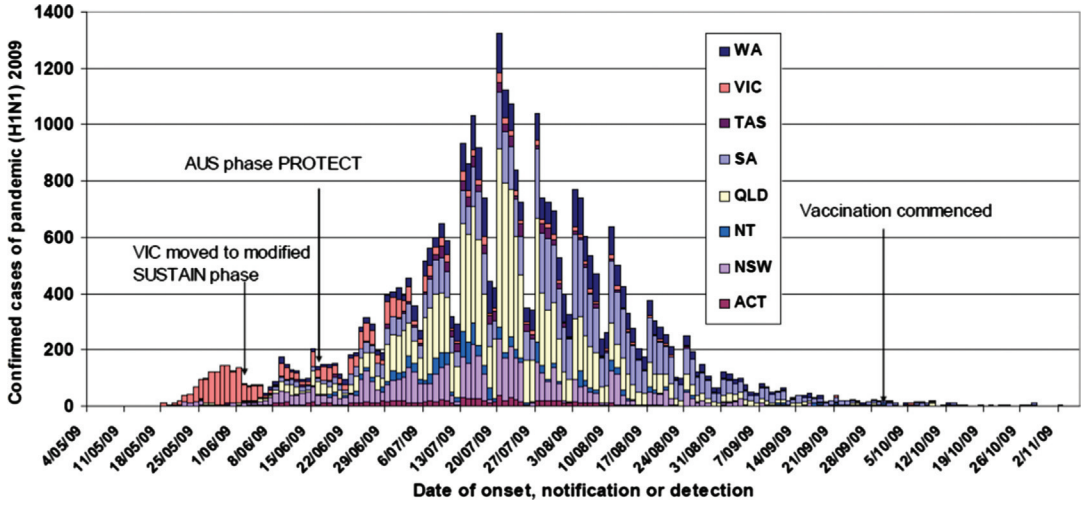

Fig. 1. Laboratory confirmed cases of pandemic (H1N1) 2009 in Australia, up to 6 November 2009 by jurisdiction. Source: Australian influenza surveillance summary report No. 26, 2009, reporting period: 31 October 2009–6 November 2009 (see Ref. 4).

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days managed to severely strain so many health systems around the world. If these systems had more winter capacity (i.e. available staffed beds) particularly in their ICUs, then a lot of strain in our health systems would have been avoided. It also shows that if we ever have a much more virulent virus spreading than swine flu (e.g. involving 25% of the population but with a mortality of 10% instead of the <0.01%), then our hospital systems would not be able to cope with this 1,000-fold higher viral virulence factor and the increased demands on the health system. We will need to find other ways to enable people to care for themselves and their families other than relying on our hospitals.

For many people admitted to ICU, there were considerable delays in both diagnosing their infection and receiving appropriate therapy. The value of drugs such as oseltamivir is still controversial (13). However, if anyone infected is likely to obtain major benefits from its use, it is those with underlying risk factors. However, there were often delays—in pregnant women a median of 9 days (5)—before those with recognised risk factors received therapy after the onset of their symptoms.

The widespread media coverage as well as government press releases induced panic and undue fear in the population. This resulted in Emergency Departments and doctor surgeries being overwhelmed with requests, initially for antivirals and then for vaccination. The effect of this was those who were much more likely to be at risk for this infection were often not able to access drugs. The vast majority of people who do not have risk factors just needed to stay at home and get better by themselves (usually within 2 or 3 days) and seek medical help only if they developed symptoms to suggest that they developed a secondary complication such as bacterial pneumonia.

Given the inevitable delays in producing influenza vaccines, we need to re-examine how effective mass vaccination is ever likely to be (14), as well as its cost benefits. In the UK, 'swine flu' vaccines had very poor cost benefits (15). This was mainly because the vaccine was only available after the epidemic had peaked. The other problem with mass population vaccination programmes was that the majority of those with risk factors were the elderly, and they were already immune (and was evident early during the epidemic, as they were not getting infected). Vaccine and other studies also suggested that at least a third of those between the ages of 18 and 65 years had protective levels of antibodies and that 70% had detectable antibodies (7, 14–16). It was only in children where there was a large proportion of individuals who were not already immune prior to the 2009 winter. However, given the widespread infection rate in children (with most asymptomatic), a large proportion of children are now also immune (3, 7, 14). Thus, rolling out a vaccine campaign to a population after the epidemic has peaked and where the majority are already immune is unlikely to ever have a very favourable cost–benefit ratio. One viewpoint suggested in the UK, where more than £1billion was spent on vaccines, was that it was likely that the vaccines prevented only 26 deaths in the 2009/2010 winter (17). There may have been some added small benefits for the subsequent 2010/2011 winter, but if a large proportion of population were already immune by early 2010 (7, 14) it is hard to see how the vaccination programme had a very favourable cost benefit.

By October 2010 and at the start of most seasonal flu vaccination campaigns, in the northern hemisphere and elsewhere, there had been no predicted catastrophic 'second wave' with swine flu. The subsequent winter (2010/2011) also followed the same pattern as what had occurred in the Southern Hemisphere (18). While H1N1 was the prominent virus that spread, because of widespread immunity (mainly from previous infections), the number of people infected and admitted to hospital was considerably less than in the previous winter. Following initial widespread infections, high levels of subsequent immunity seem to be what occurred also after previous 'pandemics' in the past 120 years (7).

We need systems in place that can show us on an ongoing manner that we are not seeing unusual side-effect profiles from vaccines that have changed their composition from the previous season. Passive surveillance is usually the only way that influenza vaccines are monitored for safety in a population after their release and a change in formulation. Passive surveillance, however, frequently greatly underreports the number of adverse events that may have occurred (19). A lack of active surveillance resulted in slow recognition of the problem with the swine flu vaccine in the USA in the 1970s, when a much higher risk of Guillain Barré syndrome occurred (20). This was also the case in Australia with febrile seizures. Even though 9 in 1,000 young children developed febrile seizures after receiving a CSL Biotherapies trivalent seasonal vaccine containing a swine flu antigen, there was a delay in recognising the problem and actions to stop further vaccinations (21–23). We need active prospective surveillance done through general practices and/or vaccine clinics to detect any untoward side effects occurring in, say, the first 3,000–4,000 adults and children vaccinated with any vaccine, where the composition has been changed from what was used previously.

Before we roll out any vaccine to the entire population, we need to ensure that it is both effective and safe and not just rely on surrogate markers. Antibody levels often correlate poorly with immunity and protection (7). We need good active surveillance systems in place to detect

side effects and/or poor efficacy, particularly because we can detect those side effects that are unexpected (21–25).

We also need better and timelier data on vaccine efficacy. The Canadians have done a commendable job in setting up such surveillance and this has also been done in Victoria (24, 25). The Canadian data, however, unexpectedly showed that for those vaccinated in 2008 with their seasonal influenza vaccine, there was a twofold increased risk of becoming infected with swine flu compared to those not vaccinated.

Another important issue to consider is 'original antigenic sin' (26). This means that if the first exposure to a virus is through a vaccine strain, an individual may have less long-term and cross-protection against new strains of influenza than if they acquired immunity via a natural infection. This raises questions as to whether the routine immunisation of children with seasonal influenza vaccines might increase their subsequent risk if a new pandemic strain spreads.

We need to learn lessons from the past. In 1918/1919, the majority of deaths in that pandemic were from secondary bacterial infections—usually pneumonia (2, 27). Even in more recent times, bacterial infections play a major part. In the USA, a large proportion of those after influenza infections have bacteria isolated from sterile sites (28). When one considers that it is relatively uncommon in pneumonia to culture bacteria from sterile sites such as blood, this implies that bacteria are still playing a major part in the majority of deaths following influenza infections—just as they were in the past (2, 27). The reason this is important is that by mainly focusing just on the virus through antivirals and influenza vaccines, we may be not targeting the best interventions that will prevent deaths. More effective may be identifying that small number of people who develop more serious bacterial complications following influenza and then make sure that not only we give them promptly antivirals but also antibiotics, as our ability to discriminate a viral from bacterial infections in those with more severe lung involvement is relatively poor (29).

This pandemic and other reviews show the importance of infection control and hygiene. We tend to have an undue focus on medical interventions such as drugs and influenza vaccines. Overall, oseltamivir may have caused more harm than good, as well as being an inappropriate waste of money for the vast majority of people who took them, especially otherwise healthy children (2, 13). The widespread use of oseltamivir had no obvious effect on the epidemic curve in any country compared to previous influenza seasons. Its use was however associated with widespread nausea and vomiting, especially in children in whom the morbidity and mortality of influenza was very low. Infection control is relatively inexpensive and likely more effective in stopping the spread of viruses. A recent Cochrane review suggests that if masks, alcohol hand hygiene and other approaches were used, these give good protection (30). In Hong Kong during the SARS epidemic, the widespread use of masks and hand hygiene by the population resulted in marked reduction in all respiratory illnesses (31). All these suggest that there may be a lot more diseases transmitted through hands than we have previously recognised. The value of masks may be more to stop a person touching one's own nose and mouth rather than decreasing the inhalation of any respiratory aerosols or droplets. This has had some significance as there was a lot of controversy as to what type of masks needed to be used, for example, surgical masks or N95 masks (30). The available evidence suggests that using masks is protective compared to not using them. However, there is no great difference in regard to which type of mask is used.

In summary, there are important lessons for us to learn from the recent swine flu pandemic. First, before we pull an international trigger to call a pandemic, we need to have appropriate trigger points that involve not only the spread of the virus but also its level of virulence. This was not done for swine flu in 2009. We need to ensure that we improve techniques to decrease the spread of infection both in the community and within our hospitals. This essentially means improved infection control and hygiene and the use of masks, alcohol hand rubs, and so on. We need to have a different approach to vaccines. The vaccines were produced only after the epidemic had passed and so have had and will have little efficacy in preventing many infections. Mass population strategies also misused large amounts of scarce medical resources. The large-scale uses of antivirals such as oseltamivir also appear to have been ineffective and very poor value for money on a population level.

Overall, our response to swine flu shows that we need to rethink how we declare and respond to pandemics. Even though, around the world, huge efforts were made to try and contain the spread of swine flu virus, these were unsuccessful. Overall, they appear to have had little influence on the spread of the virus, despite vast amounts of resources and effort expended. The virus in the vast majority of people infected caused only a mild illness and from which people made a full and rapid recovery and then developed immunity. Maybe it is time for a different approach. Australia changed to a newly defined 'Protect phase' when it realised that the pandemic could not be controlled. Then, they focused on those who were known to be at high risk and thus more vulnerable to complications. This may be a better international

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approach rather than trying to look at a whole population approach using vaccines and antivirals.

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