

## H1N1 immunisation: too much too soon?

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In April 2009, a new influenza strain – H1N1 'swine flu' – was identified in Mexico with an apparent high case fatality rate (about 5%). As H1N1 spread rapidly throughout the world it caused not only a 'pandemic' but also widespread fear. However, overall, swine flu has been associated with fewer deaths (case fatality rate < 0.01%) than seasonal influenza (case fatality rate < 0.1% approx.),<sup>1</sup> and is of low virulence. While younger people were disproportionately infected by swine flu, it was people aged 50–60 years who had more frequent serious illness in terms of admissions to intensive care units and deaths.<sup>2–4</sup>

In the 2009 Australian winter, swine flu's associated mortality rate was 0.9 per 100 000 people. In those under 40 years with no risk factors, the mortality rate was less than one per million.<sup>3</sup> While there were some differences (for example pregnant women), the overall effects of this virus as judged by absenteeism, hospitalisations and deaths were similar to those of previous seasonal influenza strains.<sup>2–4</sup>

While swine flu is a 'new' virus, it is an H1N1 virus, strains of which have been circulating since 1918. Not surprisingly, many people have pre-existing immunity. Most people over 65 years

appear to be immune, as reflected by their low infection rates.

In an Australian H1N1 vaccine trial of adults (aged 18–65 years), 27% had protective antibody concentrations and 62% had detectable pre-existing antibodies.<sup>5</sup> Most infections in the 2009 winter occurred in children and younger adults.<sup>2–4</sup> It is likely therefore that more than 50% of the Australian population are already immune because of pre-existing immunity or recent infection. In any mass vaccination campaign, those who are already immune are unlikely to get additional benefits from the vaccine, but remain at risk of adverse effects.

The timing of a mass vaccination program is important. In Australia, our mass vaccination program for this virus started in spring 2009. However, it was very unlikely that the swine flu virus would circulate widely in Australia during the summer. The composition of a trivalent vaccine for next winter's seasonal influenza will include a swine flu component. People already vaccinated against swine flu who need protection for seasonal influenza will still need re-vaccination in autumn with the trivalent vaccine as we cannot necessarily predict which influenza strains will be circulating in winter 2010.

The use of multidose vials in the vaccination program was a needless additional risk. In the past, many infections, such as *Staphylococcus aureus*, hepatitis B and HIV, have been caused by vaccination programs using multidose vials.<sup>2</sup> Even a very low individual risk can translate into hundreds of people with cross-infections when multidose vials are used in large populations. Over eight million doses of trivalent seasonal influenza vaccine are given per year in Australia using single-use preloaded syringes. It is difficult to see why this could not have been done for the swine flu vaccine. Also with multidose vials, large amounts of vaccine may be wasted. The advantages of multidose vaccines are small monetary savings in manufacture and the potential for a more rapid roll-out of a vaccine. However, current technology allows single-dose preloaded syringes to be rapidly manufactured.

We need to learn lessons from the past. In the USA in October 1976 there was a mass immunisation campaign for H1N1 swine flu. Unexpectedly, Guillain-Barré syndrome occurred at a rate of about 1 per 100 000 vaccine recipients. The expected swine

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Patients in hospital are at risk of venous thromboembolism, particularly if they have had surgery to their legs. Although heparins have a role in preventing thromboembolism they have to be given by injection. The development of effective oral anticoagulants for prophylaxis is therefore of great interest. Timothy Brighton explains how the new drugs work and Alex Gallus reviews their use in orthopaedic surgery.

Like the control of clotting, the physiology of calcium and phosphate is complicated. Darren Roberts explains how disturbances of this physiology in patients with kidney disease results in bone damage.

flu epidemic did not eventuate. Thus, the complications that occurred were not offset by any meaningful benefits in the general population. It was only after 40 million people had been vaccinated over two and a half months that the association of these rare but serious adverse effects with the vaccine was accepted. The program was stopped in December 1976.<sup>6</sup>

In Australia, we do not have good postmarketing surveillance mechanisms in place and mainly rely on voluntary reporting. This is unlikely to accurately measure the percentage of people who get adverse effects or to identify rare adverse effects in a timely fashion. A more effective way might be to follow a large sample of vaccine recipients for, say, a month. This could be done by practice nurses in a defined number of general practices.

A problem with this vaccine and other influenza vaccines is that there are relatively few well-designed, large randomised studies.<sup>5,7</sup> The efficacy of seasonal inactivated parenteral vaccines in preventing influenza in healthy adults varies from 50% to 80%.<sup>7</sup> The often quoted efficacy for protection from all-cause mortality with seasonal influenza vaccines is around 50%. However, those in vaccinated groups frequently have fewer comorbidities than those in non-vaccinated groups. A recent Californian study looked at over 100 000 deaths over nine years<sup>8</sup> and showed that the decrease in all-cause mortality attributable to seasonal influenza vaccine was 4.6%.

The reason these issues are important is that we do not have robust data on which to make proper decisions on the cost-effectiveness of any mass vaccine programs. In young people without risk factors, the rates of death and complications last winter from swine flu were very low and are similar to the risk of serious vaccine-associated adverse effects such as Guillain-Barré syndrome and anaphylaxis. Around 50% of people who received the H1N1 vaccine in the Australian trial had mild to moderate systemic adverse effects and 1.7% had (solicited) systemic adverse effects recorded as severe.<sup>5</sup> In children, 20% had moderate to severe systemic adverse effects after receiving a single 15 microgram dose of vaccine.<sup>9</sup> It is very important that we make sure we do more good than harm with any vaccine. Thus, we need a large cohort of people (tens of thousands) followed prospectively so that we can accurately know what are the percentages of people with adverse effects in the postmarketing period. We also need a robust system to accurately detect the very rare but serious adverse effects. Otherwise we risk repeating the mistakes made in the 1976 USA swine flu vaccine program.<sup>6</sup>

The disproportionate fear generated by the swine flu virus has caused many decisions to be made that in retrospect were inappropriate. We need to learn from our experiences and more importantly ensure that well-designed, large, prospective long-term studies are done so we can answer basic questions on the true safety and efficacy of influenza

vaccines. This is not only in the elderly but also in groups proposed for routine seasonal influenza campaigns such as children and pregnant women. We need these types of data before embarking on further mass immunisation programs, particularly if done during periods with likely low infection rates (that is, summer) using multidose vials.

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