MedicineToday PEER REVIEWED

Influenza
Time to vaccinate but who and why?

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Influenza vaccination should be recommended not only to all patients who qualify for the government-funded vaccine but also to those shown to be at increased risk of complications in the 2009-10 influenza pandemic, including the clinically obese and tobacco smokers.

MedicineToday 2014; 15(5): 69-72

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THE IMPACT OF INFLUENZA

William Farr, a doctor and statistician in the British Office of the Registrar-General, first described the phenomenon of influenza-associated excess mortality as early as 1847.[1] This excess mortality significantly outweighs that attributed to influenza itself. The true mortality burden of the disease is not obvious, is difficult to tease out, and is still largely unappreciated by the general population and, sometimes, by healthcare workers.

Most influenza-associated mortality occurs in older adults and a significant proportion is recorded as being due to cardiovascular and cerebrovascular events.[2,3] However, such deaths do not only occur in the older adult group, and at least one study found that influenza-related ischaemic heart disease deaths occurred mostly in the 40- to 64-year-old age group.[4] Unfortunately, mortality is only a small part of the overall burden of influenza to the Australian healthcare system.[5]

ANNUAL VACCINATION CAMPAIGNS AND THE NATIONAL INFLUENZA PROGRAM

In recent years there have been annual efforts to encourage those Australians considered to be at greatest risk from the consequences of influenza infection to avail themselves of vaccination. These have resulted in the uptake of influenza vaccination increasing more than 12-fold in the past two decades. Aided by the introduction in 1997 of free vaccine for those aged 65 years and older, vaccination reached approximately 75% in that group in 2009, a little below the peak of 79% in 2004.[6]

In 2010 the Australian National Influenza Program (NIP) was expanded to provide free vaccine for anybody over the age of 6 months with a wide range of conditions associated with increased risk of influenza complications, including pregnancy (see the box).[7,8] Yet, recent surveys suggest that there has been

little change in vaccination rates in these groups, with only 52% of them currently being vaccinated (Influenza Specialist Group Survey; unpublished data). In addition, a recent survey in NSW found that only 27% of pregnant women, rated the highest priority risk group for influenza vaccination by the WHO Strategic Advisory Group of Experts on immunization,[9] were vaccinated.[10]

OTHERS AT RISK

There is nothing like a pandemic to highlight certain risk groups and to reveal other previously unrecognised groups. The H1N1 pandemic of 2009-10 was considered by many to be mild based on a single outcome measure, the number of recorded deaths. Although certainly far less severe, like the 1918 pandemic there was a downward shift in the age of those hospitalised and dying compared with seasonal influenza and this increased the real burden in terms of years of life lost.[11] Evidence was found of pre-existing immunity in many older adults, presumably from experience with antigenically similar viruses circulating in the 1950s and earlier. A similar explanation of prior exposure to related viruses was proposed for the unusual age incidence of mortality in 1918. One interesting feature with influenza is that the infections encountered earliest in life appear to skew subsequent immune responses back to these initial encounters, a phenomenon known as 'original antigenic sin'. Nonetheless, it remains uncertain whether this is the sole reason for the age shift in mortality for the 2009 and some earlier pandemic viruses.

The 2009 pandemic did serve to emphasise that there was a disproportionate impact among the younger and middle-aged adults, particularly pregnant women (Figure) and Indigenous peoples.[12] And although people with the usual recognised risk conditions, together with tobacco smokers, tended to have the more severe outcomes, a substantial percentage of those hospitalised, admitted to the ICU and suffering a fatal outcome had no previously recognised risk condition.[13,14] One early surprising observation was the disproportionate impact of the pandemic virus on clinically obese individuals.[15] Interestingly, a retrospective study in Canada has demonstrated that obese individuals had an increased probability of hospitalisations due to respiratory infection during normal influenza seasons preceding the pandemic.[16]

HOW DOES INFLUENZA CAUSE ITS DAMAGE?

It was once assumed that influenza infection simply provided that final stress pushing

SEASONAL INFLUENZA VACCINATION: 2014 RECOMMENDATIONS*[7,8]

Funded under the National Immunisation Program[7]

- All adults aged 65 years and above
- All Aboriginal and Torres Strait Islander people aged 15 years and above
- Pregnant women
- Individuals aged 6 months or over with medical conditions that put them at increased risk of complications from influenza infection as outlined below:
  - Cardiac disease, including cyanotic congenital heart disease, congestive heart failure, coronary artery disease
  - Chronic respiratory conditions, including severe asthma, cystic fibrosis, bronchiectasis, suppurative lung disease, chronic obstructive pulmonary disease, chronic emphysema
  - Chronic neurological conditions, including hereditary and degenerative CNS diseases (e.g. multiple sclerosis), seizure disorders, spinal cord injuries, neuromuscular disorders
  - Immunocompromising conditions, including HIV infection, malignancy, transplantation, chronic steroid use, asplenia or splenic dysfunction
  - Diabetes and other metabolic disorders, including type 1 and type 2 diabetes, chronic metabolic disorders
  - Renal disease, including chronic renal failure
  - Haematological disorders, including haemoglobinopathies
  - Long-term aspirin therapy in children aged 6 months to 10 years

Additional ATAGI recommendations for influenza vaccination (not funded)[8]

- People with Down syndrome
- Obese individuals (defined as a BMI of 30 kg/m^2 or above)
- People with alcoholism
- Children aged 6 months to 5 years of age, particularly Aboriginal and Torres Strait Islander children
- Residents of residential aged care facilities and long-term residential facilities
- Homeless people
- Persons who may transmit influenza to persons at increased risk of complications from influenza infection (e.g. healthcare workers)
- Persons involved in the commercial poultry or pork industry or in culling poultry or pigs during confirmed avian or swine influenza activity
- Persons providing essential community services
- Workers in other industries
- Travellers

ABBREVIATIONS. ATAGI = Australian Technical Advisory Group on Immunisation; BMI = body mass index; CNS = central nervous system; HIV = human immunodeficiency virus.

* Refer to references 7 and 8 for full details on the listed recommendations.

the elderly and infirm over the brink or by predisposing to subsequent bacterial pneumonia.[17] However, we are progressively gaining a better understanding of what happens during influenza infection.

One aspect is the innate inflammatory response that induces molecules such as cytokines, intended to help fight infection but sometimes doing more harm than good. This inflammation may induce a prothrombotic state, atherosclerosis, and trigger plaque rupture, resulting in acute myocardial infarction and stroke;[18] there is growing evidence that influenza vaccination is protective against these outcomes.[19] This inflammatory response may also participate in other outcomes such as organ failure and acute respiratory distress syndrome. It has also been postulated that in extreme infections, such as those experienced in 1918 and recently in human infections with H5N1 avian influenza, a 'cytokine storm' may result, leading to death through multiple organ failure.

In pregnancy, and possibly in obesity, it is likely that a combination of physical and physiological changes that affect breathing, together with immunosuppression, may be the main contributors to the poor outcomes, but the case of obesity does warrant further investigation. In the case of smokers, the main issues are most likely the physical effect of tobacco smoke on the ciliated lining of the respiratory tract combined with local immunosuppression.

WHAT IS COMING OUR WAY THIS YEAR?

As one health official commented recently 'the only predictable thing about influenza is its unpredictability'. Nevertheless, we do review what has happened most recently in other parts of the world; this year the news is not good. In the recent northern hemisphere winter the 2009 pandemic H1N1 virus has predominated in North America and most European countries and, as during the pandemic, it has had a disproportionate impact on younger and middle-aged adults. In the USA, which recorded epidemic influenza and pneumonia excess mortality, approximately 60% of influenza hospitalisations and recorded deaths were in the 18- to 64-year-old age group.

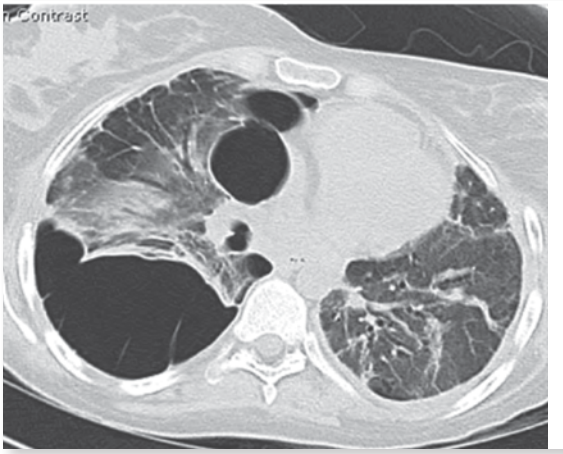

Figure. Consequences of severe pandemic influenza. High-resolution CT scan of chest showing fibrosis and lung cysts in a 26-year-old woman who had contracted severe pandemic influenza nine months previously when she was 30 weeks pregnant. She required intensive care unit support and invasive ventilation for over a week.

IMAGE COURTESY OF ASSOCIATE PROFESSOR LOUIS IRVING, MELBOURNE.

In Australia there has been an elevated number of laboratory-diagnosed cases of influenza, with over 1000 reports monthly since the 2013 season peak of 7683 cases in August, which far exceeds normal. The limited data available on the recent Australian virus isolates indicate that at least some of these are of the pandemic H1N1 virus, which is included in our current vaccine as A/California/7/2009. Others are closely related to the two other current vaccine strains: A/Texas/50/2012 (H3N2) and type B/Massachusetts/2/2012, which are both updated strains from the 2013 vaccine.

WILL THE VACCINE WORK AND IS IT SAFE?

The actual effectiveness of influenza vaccines has been a subject of debate recently and there is no doubt that it varies according to the endpoint measured (clinically diagnosed infection, laboratory proven infection, hospitalisation, death, etc.), age and health status of vaccinees and match between vaccine strains and circulating viruses. A recent review of the available information taken from 1967 to 2011, and applying very stringent selection criteria, indicated around 60% protective efficacy from infection;[20] one might expect that some of the earlier trials were with less well-matched vaccines. Individual trials measuring protection against hospitalisation and death even in frail elderly have often demonstrated higher levels of protection (70 to 80%).[21]

Because there is a lead time of five to six months for the manufacture of influenza vaccine there is an opportunity for some further mutation to occur in the circulating viruses. Recently there has been refinement and improved success in the selection of candidate vaccine viruses. This is aided by an extended WHO surveillance program, particularly in the 'hot spots' of Asia and South East Asia, including an expanded role for China in the WHO program. Further comfort can also be taken that the recent WHO vaccine formulation recommendation for the 2014-15 northern hemisphere is unchanged from the current Australian vaccine.

Apart from a recent unfortunate incident with febrile convulsions attributed to one paediatric influenza vaccine in Australia, for which steps have been taken to guard against any future repeat,[22] influenza vaccines have a very good safety record, including in pregnant women. In fact one recent study indicated that vaccinated women were more likely to have improved neonatal outcomes than unvaccinated women.[23]

Despite fears that influenza vaccine may cause Guillain Barré syndrome (GBS), surveillance over recent years has shown that, if this occurs, it is around one case per

million vaccinations and too low to establish a statistically significant association. On the other hand, data are emerging showing a significant risk of acquiring GBS from influenza infection.

The urban myth that influenza vaccines can cause influenza is quite incorrect – all of the vaccines used in Australia consist of inactivated virus that has then been disaggregated into small subunits to reduce reactogenicity to no more than a sore arm or, more rarely, slight malaise that may persist for a few hours.

WHAT SHOULD BE DONE?

Clearly it is important to promote influenza vaccination to patients who qualify for the government-funded vaccine, regardless of age. Older adults have been receptive to annual vaccination; however, this cohort expands each year and the influx of new 65-year-olds need to be recruited. Younger at-risk individuals, including pregnant women, have been relatively resistant to vaccination and, unfortunately, many healthcare workers who may transmit influenza to vulnerable patients still fail to be vaccinated. In a year when the younger cohort may suffer disproportionately, it would be opportune to redouble efforts to convince them.

It is also time to take heed of the known risk among tobacco smokers and the newly discovered risk of clinical obesity – how often do GPs recommend vaccination to these groups? Although people in these groups do not qualify for free vaccine, the small cost is likely to be trivial compared with the cost to themselves and the healthcare system if they become infected. MT

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COMPETING INTERESTS: Dr Hampson is Chairman of the Influenza Specialist Group (ISG), a not-for-profit organisation that receives sponsorship from organisations including pharmaceutical companies. Details of the probity of the ISG's sponsorship and governance are available at: http://www.isg.org.au/index.php/about/. In a private consultant capacity Dr Hampson has in the past five years received: travel and accommodation support from CSL Limited to lecture Communicable Diseases Control students at James Cook University, Townsville and healthcare workers in Brisbane; an educational grant from Sanofi Pasteur to attend the 1st Asia-Pacific Influenza Summit (12-13 June 2012, Bangkok) conducted by the Asia-Pacific Alliance for the Control of Influenza (APACI) and the International Congress on Infectious Diseases (ICID) 13-16 June, 2012, Bangkok; and honoraria from Glaxo Smithkline for a lecture to healthcare workers in Melbourne and a consultation regarding the impact of influenza.