

Influenza

developments in its prevention and control

Recent efforts to lessen the impact of influenza have followed three approaches:

increased use of existing vaccines, development of new vaccines and specific antiviral therapy. The current status of these efforts is reviewed.



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Influenza continues to be a major public health problem, having its greatest effect on the elderly and on people with underlying medical conditions, including cardiac, respiratory, metabolic and immunosuppressive disorders. The true impact of influenza is often underestimated because much of the morbidity and mortality results from exacerbation of underlying illness.¹ The extent and severity of influenza outbreaks vary from year to year and are generally unpredictable. It was estimated in 1996 that annually in Australia, influenza resulted in an average of 1500 deaths, 20,000 to 40,000 hospitalisations and an overall cost of \$600 million.²

Vaccines prepared from inactivated influenza virus have been available for over half a century, but their use has only become widely accepted during the last 10 to 15 years.³ There is overwhelming evidence that the split product and subunit vaccines that are available in Australia have good safety profiles and greatly reduce the impact of influenza in vaccinated populations.

However, it is recognised that these vaccines are less than ideal.⁴ They need to be administered annually, and they may not match antigenically the strains circulating in the community due to the unpredictable antigenic variability of influenza viruses. In addition, many people for whom vaccination is a priority have a reduced ability to respond to new antigens due to immunosenescence (an age related decline in T cell function).⁵ Consequently, three approaches have been pursued in efforts to improve influenza prevention and control:

- more widespread and effective use of existing vaccines
- increased immunogenicity and effectiveness of vaccines
- development of specific antiviral treatments.

Use of existing vaccines

More effective use of existing vaccines may produce greater benefits and cost effectiveness than developing more efficacious products – especially since

IN SUMMARY

- Influenza continues to be a major public health problem, having its greatest impact on the elderly and on people with underlying medical conditions.
- Vaccines prepared from inactivated influenza virus have been available for more than half a century, but their use has only become widely accepted during the last 10 to 15 years.
- A recent Australian survey found that only 32% of people aged 40 to 64 years who were at risk of complications of influenza were vaccinated annually.
- Clinical diagnosis of influenza is difficult due to the variability of symptoms and clinical similarity of other infections such as that due to respiratory syncytial virus.
- Two new drugs, zanamivir and oseltamivir, have been shown to be beneficial in the treatment of influenza if administered early in the course of the infection.

continued

Table. Influenza vaccination: NHMRC recommendations

Individuals who are at increased risk of influenza-related complications

- All adults >65 years (Aboriginal and Torres Strait Island people >50 years)
- Adults and children (>6 months) with chronic pulmonary or circulatory disorders
- Adults and children (>6 months) with other chronic illnesses requiring regular follow up
- Residents of long term care facilities
- Children and teenagers on long term aspirin therapy

Individuals who may transmit influenza to people at increased risk

- Healthcare workers
- Institutional staff
- Family and homecare providers

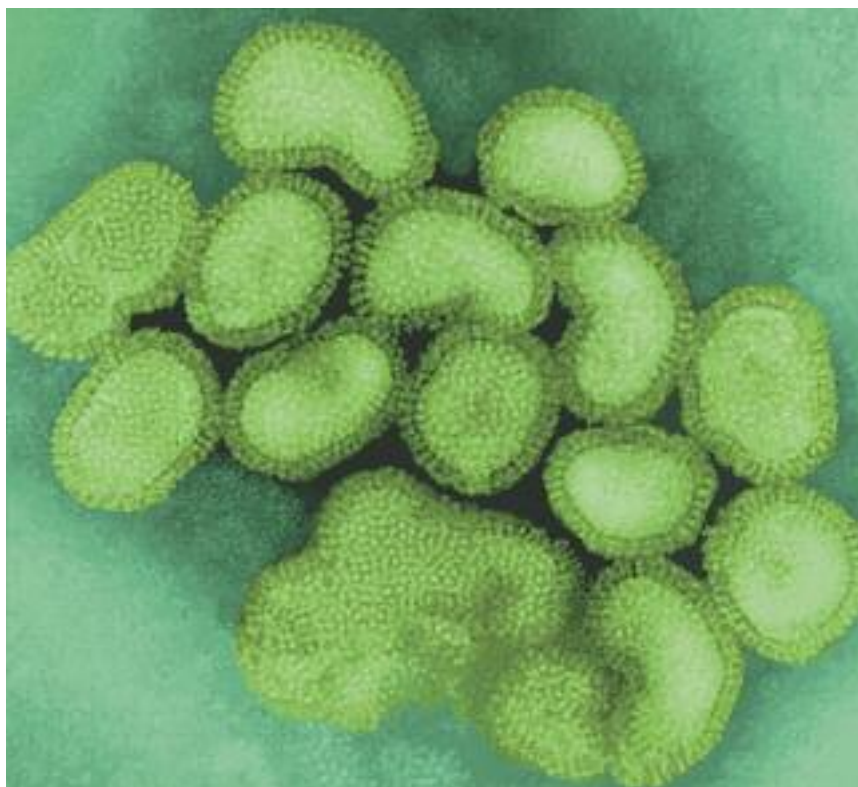
Other indications

- Women who will be in their 2nd or 3rd trimester of pregnancy during the influenza season*
- People infected with HIV
- People wishing to reduce the chance of becoming ill with influenza, including travellers

*Currently available influenza vaccines are inactivated vaccines and are believed safe to administer throughout pregnancy. An extensive study demonstrated no adverse fetal effects associated with influenza vaccines; however, additional data are needed to confirm their safety during pregnancy.⁷ In Australia, the vaccines are categorised as B2 drugs in pregnancy.

improvements in efficacy are likely to be marginal, according to Fedson.⁶ National guidelines for influenza vaccination vary from country to country but usually target adults aged 65 years of age and older, and adults and children with chronic disease or who are immunocompromised. (The NHMRC guidelines are summarised in the Table).

High vaccination rates are often achieved for programs targeting adults over a given age (particularly those



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Figure. Coloured transmission electron micrograph of influenza viruses.

supported by cost reimbursement), but there is generally much less success in vaccinating young people who fall into the at-risk groups. The US 1995 National Health Interview Survey showed that only 38% of individuals aged 50 to 64 years who were at risk of complications of influenza were vaccinated.⁸ Meanwhile, a recent Australian Government survey found that only 32% of at-risk adults aged 40 to 64 years had received annual vaccination.⁹

Attempts to increase rates of vaccination

About 24% of people aged 50 to 64 years in the USA are at risk of severe outcomes from influenza infection.⁴ In an attempt to improve vaccination rates in these individuals the American Committee for Immunization Practices recently lowered the recommended age for universal vaccination to 50 years; however, the

effectiveness of this strategy has not yet been evaluated.

In addition to the risk posed to the individual, influenza outbreaks are often accompanied by dramatic seasonal increases in emergency department attendances. After an epidemic in January 2000, the British government revised its age-based vaccination guidelines to target people aged 65 years and above, replacing the previous age threshold of 75 years. Around the same time, the Victorian Government introduced free vaccination for all high-risk patients hospitalised before the influenza season.

In the winter of 2000 to 2001, the Canadian province of Ontario took a more radical approach and introduced a universal vaccination program for all residents aged 6 months and over in an attempt to lessen the impact of influenza. The program was controversial, and the first season was one of only mild influenza

activity. However, several encouraging outcomes were observed, including proportionally fewer influenza notifications in Ontario compared with Canada as a whole, and substantially fewer institutional influenza outbreaks than in previous years.

Improved vaccines

Efforts to improve the immunogenicity and protective efficacy of inactivated influenza virus vaccines by incorporating adjuvants, liposomes or other formulations have been disappointing. Although such formulations induce greatly improved antibody responses in laboratory animals, this does not reflect their performance in humans. The most probable explanation is that most people have been immunologically 'primed' by exposure to viruses with similar or shared antigens, whereas adjuvants have the greatest effect

in immunologically naive subjects.

Two new vaccines have recently been registered in Europe. One, a liposomal vaccine developed in Switzerland, produced generally better antibody responses than standard vaccines in clinical trials involving children and young and old adults.¹⁰ The vaccine was reported to be well tolerated; however, published data suggest it is associated with more local and systemic reactions than are standard vaccines. The second vaccine has an oil and water emulsion adjuvant (MF59) incorporated with the influenza subunits. It also has been shown to increase the level and duration of antibodies in both young and old adults but is associated with a concomitant increase in injection-site reactions.¹¹ To date there are no data to demonstrate that these increased antibody levels equate to an improvement in protection.

A recent human trial was conducted with vaccines prepared from an H5 influenza virus, a strain closely related to the one that caused the 'chicken influenza' outbreak in Hong Kong in 1997. The standard vaccine induced poor, probably nonprotective, antibody responses whereas an MF59 adjuvanted vaccine produced satisfactory responses. This suggests that vaccines with adjuvants would be of greatest value in an immunologically naive population facing an influenza pandemic.¹²

Live-attenuated vaccines

For many viral diseases, living attenuated vaccines have proven to be safe and highly efficacious. Over 30 years ago, initial work started on the development and evaluation of an influenza vaccine that was attenuated by 'cold-adaption' and could be administered intranasally.

Although vaccines of this type have been used in Russia for several years, US requirements are more stringent. The process of refining the vaccine, establishing its safety and efficacy, and overcoming technical problems associated with a relatively labile virus have progressed slowly.

There are several potential advantages in the use of living attenuated intranasal influenza vaccine over the nonliving parenteral products. These include the production of local respiratory tract immunity, greater patient acceptability and, based on recent trial data, improved capacity to cope with antigenic changes in the circulating viruses.¹³

Recently, the US FDA evaluated a cold-adapted attenuated vaccine (Flu-Mist) and determined that although there were adequate data to support its effectiveness in healthy children and adults aged 1 to 64 years, further data were needed to establish its safety. It is likely that this data will be available shortly.

If registered and widely available, the intranasal vaccine could reduce the influenza burden (particularly otitis media) in children, as there may be a reticence by healthcare providers to use parenteral products in this age group. Since there is evidence that children have a major role in the spread of infection, vaccinating them may also have an impact on the overall burden of influenza in the community. Based on studies to date, the living vaccine shows no advantage over existing parenteral products in older adults and is unlikely to replace standard vaccines in this group.

Treatment of influenza

Until recently amantadine (Symmetrel) was the only drug with anti-influenza activity available in Australia. However, it has several disadvantages, including side effects, a complete lack of activity against influenza B viruses and an association with rapid development of drug resistance by influenza A viruses. Amantadine (and a closely related compound

rimantadine, which is not registered in Australia) has been used in North America, particularly for outbreak control in long-term care facilities, but has found little application in Australia.

Two new drugs, zanamivir (Relenza) and oseltamivir (Tamiflu), are now available that act on influenza virus neuraminidase and inhibit the release of virus from infected cells. They have been shown to be beneficial in the treatment of influenza if administered early in the course of infection and to be effective for short-term prophylaxis.¹⁴ Both are registered for the treatment of influenza, and zanamivir has a limited indication for prophylactic use. Early and accurate diagnosis is essential to obtain a benefit from anti-influenza drugs because they are quite specific and of benefit only if administered within 48 hours of symptom onset, with greater benefit resulting from earlier administration.

Diagnosing influenza

Clinical diagnosis of influenza is difficult due to variability of symptoms and the clinical similarity of other infections, such as that resulting from respiratory syncytial virus. Currently, despite extensive development programs, there are no point-of-care diagnostic tests for influenza with sufficient sensitivity and specificity for routine use.

A working party recently reviewed literature reports of symptoms in confirmed influenza cases.¹⁵ It concluded that, in healthy adults, sudden onset of fever or feverishness together with cough, myalgia or malaise were important diagnostic criteria. Moreover, the predictive value of these symptoms was strengthened by knowledge of laboratory-confirmed influenza in the community. Yet, even with well-defined criteria the accuracy of clinical diagnosis for influenza is no better than 63 to 75% and is often lower.¹⁵

Conclusion

There is little doubt that a substantial decrease in the annual impact of influenza

could be achieved by improved use of the currently available vaccines in the recommended target groups. Whether there are significant public health benefits from more widespread use of these vaccines in the general population should soon become evident from the results of the universal vaccination program in Ontario, Canada.

Despite extensive research, improvements to the nonliving influenza vaccines have been modest and seem unlikely to have a major impact on improved control. Living attenuated vaccine, while not of special benefit to the older adult, shows considerable promise for protection of younger individuals and may offer benefits by reducing community spread of infection.

The available antivirals, both old and new, have the potential to further limit the impact of influenza, particularly in individuals who fail to respond adequately to vaccination. However, the difficulties in accurately diagnosing the disease are likely to impose limitations on their effective use. MT

References

The list of references is available on request to the editorial office.

For historical reasons the WHO Collaborating Centre for Reference and Research on Influenza is located on the campus of CSL Limited and, under a WHO-sanctioned agreement with the Commonwealth Government, receives infrastructural support from CSL. I and my staff are employed specifically to carry out work on influenza surveillance and related matters as prescribed in the Terms of Reference of the Centre's WHO designation and the agreement with the Commonwealth. We are not involved in commercial programs other than the provision of relevant expert advice on matters relating to influenza when consulted by government, industry or other interested groups.

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