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Authors

Sullivan, Sheena

Price, Olivia

Regan, Annette

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Burden, effectiveness and safety of influenza vaccines in elderly, paediatric and pregnant populations

Sheena G. Sullivan , Olivia H. Price and Annette K. Regan

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Abstract: Vaccination is the most practical means available for preventing influenza. Influenza vaccines require frequent updates to keep pace with antigenic drift of the virus, and the effectiveness, and sometimes the safety, of the vaccine can therefore vary from season to season. Three key populations that the World Health Organization recommends should be prioritized for influenza vaccination are pregnant women, children younger than 5 years of age and the elderly. This review discusses the burden of influenza and the safety and effectiveness profile of influenza vaccines recommended for these groups.

Keywords: influenza, vaccination, child, pregnancy, aged, safety, efficacy, effectiveness, immunogenicity, reactogenicity

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Introduction

Each year, influenza is a significant cause of morbidity and mortality in the community. Prevention by vaccination is a cost-effective and minimally disruptive method of preventing influenza.^{1,2} The influenza vaccine is unique among vaccines in requiring annual readministration and providing brief immunity. Moreover, the composition of the vaccine needs to be frequently updated owing to the continuously changing antigenic structure of the virus. The choice of influenza strains to include in the vaccine is decided once per year for each hemisphere, allowing manufacturers about 6 months to develop, test, license and sell the new vaccine, leaving no time for large randomized controlled trials (RCTs) to test efficacy. Thus, immunogenicity studies are widely accepted as a proxy for efficacy.³ A major limitation of these studies is that they are unable to provide estimates for the number of influenza cases prevented by vaccination and neither immunogenicity studies nor RCTs can estimate vaccine effectiveness (VE) in the community.⁴ Observational studies can provide VE estimates,⁵ and in recent years a number of investigators from Europe,⁶ Spain,⁷ the UK,⁸ the USA,⁹ Canada¹⁰ and Australia,¹¹ have conducted ongoing observational studies to monitor influenza VE.

The World Health Organization (WHO) lists several key populations as target groups for influenza vaccination: pregnant women, children younger than 5 years, the elderly and individuals with underlying health conditions such as HIV/AIDS, asthma or chronic heart or lung diseases that place them at increased risk of a severe outcome. In countries such as Australia, Canada and the UK, influenza vaccine is provided free through government programmes for some or all of those in these target groups. The rationale for vaccination recommendations typically follows one of two approaches: (a) a risk-based approach whereby those most likely to suffer a severe outcome of influenza infection are targeted to reduce the impact of influenza; (b) a transmission-based approach that aims to reduce the spread of the virus by targeting key groups implicated in transmission (e.g. children) to limit spread for other vulnerable groups (e.g. the elderly).¹²

The choice of vaccines to use in these programmes results from a process that balances immunogenicity, efficacy or effectiveness data and safety. For example, while some enhanced vaccines may elicit higher rates of protection, they may also result in higher levels of adverse events following immunization (AEFI). Therefore, vaccine licensing and

Correspondence to:
Sheena G. Sullivan
WHO Collaborating
Centre for Reference and
Research on Influenza,
Peter Doherty Institute for
Infection and Immunity,
792 Elizabeth St,
Melbourne, Victoria 3000,
Australia

School of Population and
Global Health, University
of Melbourne, Australia
Fielding School of Public
Health, University of
California, Los Angeles,
CA, USA

[Sheena.Sullivan@
influenzacentre.org](mailto:Sheena.Sullivan@influenzacentre.org)

Olivia Price
WHO Collaborating
Centre for Reference and
Research on Influenza,
Peter Doherty Institute for
Infection and Immunity,
Melbourne, Victoria,
Australia

Annette K. Regan
School of Public Health,
Texas A&M University,
College Station, TX,
United States; School
of Public Health, Curtin
University, Perth, Western
Australia, Australia, and
Wesfarmers Centre of
Vaccines and Infectious
Diseases, Telethon Kids
Institute, Crawley, Western
Australia, Australia

recommended use may vary among age groups and for specific risk groups. In this review, we discuss the burden, safety and effectiveness of influenza vaccines for three key target groups, that is, the elderly, children, and pregnant women. Table 1 summarizes our key points.

Elderly

Burden of influenza among the elderly

A recent review identified that influenza disproportionately burdens the elderly, with the risk of death nearly doubled in those aged 75 years or over compared with those aged 65–74 years.¹³ However, in many instances influenza is not recognized as an underlying cause of death. Ecological models have identified influenza-associated excess mortality in elderly persons related to a range of other chronic health conditions, including cardiovascular causes, diabetes, neoplasms and renal disease.^{14–17} These risks extend to increased risk of hospitalization, with elderly adults accounting for more than half of hospital separations in a number of countries,^{17–21} the highest rate of emergency department and intensive care unit (ICU) attendance,^{22,23} and the highest rate of fatal hospitalization cases.²² Secondary bacterial infections post-influenza infection account for 75% of cases that present as severe pneumonia.²⁴ The economic costs for the health system and society for these hospitalizations are significant.²⁵ For the frail elderly who survive an influenza infection, illness can trigger a cascade of health problems, ultimately leading to loss of independence, which imposes further costs on society.²⁶

Influenza outbreaks in aged-care facilities (ACFs) represent an important contributor to the disproportionate hospitalization and mortality burden suffered in this age group. Attack rates of 20–40% have been reported from ACF influenza outbreaks.^{27,28} Moreover, a review of published infectious disease outbreaks in ACFs observed a median case-fatality rate of 6.5% for influenza outbreaks and found influenza to be the most common cause of ACF outbreaks among 37 pathogens studied.²⁹ As the populations in most countries continue to age and demand for ACFs grows, the importance of outbreaks in ACFs will also continue to rise. Surveillance for respiratory infections is recommended by various national and international public health bodies and would inform outbreak management.^{30–34} Similarly,

influenza vaccination policies for residents and staff at ACFs exist in some countries^{31,33,34} and have been endorsed by WHO.^{31,33–35}

Efficacy/effectiveness of influenza vaccines for the elderly

WHO recommends annual influenza vaccination for the prevention of influenza in the elderly aged 65 years and older.³⁶ The immune response to vaccination among elderly persons is reduced compared with younger adults, which can influence the efficacy of vaccines in this population.³⁷ A systematic review of test-negative studies published in 2016 reported lower pooled VE estimates against influenza A viruses for older adults (>60 years) compared with working-age adults (20–64 years), but not for influenza B viruses.³⁸ An updated review published in 2017 confirmed these findings with a pooled VE against any type of influenza of 51% (95% confidence interval [CI]: 45–58) for working-age adults and 37% (95% CI: 30–44) for older adults.³⁹ How well the vaccine protects the elderly is probably associated with antigenic match between the vaccine and circulating viruses. In an earlier 2014 review VE among elderly persons was 41–61% during epidemic periods when the vaccine antigens match circulating viruses, but reduced to an average of 22–48% when the vaccine is not well matched.⁴⁰

There have been a number of issues which may influence VE among the elderly. Recently, identification of a representative A(H3N2) candidate vaccine virus has been hindered by its tendency to acquire adaptations *in ovo* that affect antigenicity,^{41,42} as well as a greater diversity of viruses. This is particularly problematic for the elderly who are more vulnerable to severe consequences of A(H3N2) infection.⁴³ Moreover, there is emerging evidence that repeat annual vaccination may reduce VE, a phenomenon that is most often apparent for the A(H3N2) viruses.⁴⁴ These problems are particularly pertinent to the elderly, who are a highly vaccinated group. Whereas low effectiveness of influenza vaccine among the elderly has commonly been attributed to immunosenescence,⁴⁵ recent evidence suggests it may be associated with immunological responses to repeated vaccination.⁴⁶

Enhanced vaccines for the elderly. Enhanced vaccines, including adjuvanted and high-dose vaccines, may provide better immunogenicity and effectiveness for elderly adults and overcome

Table 1. A summary of the burden, effectiveness and safety of influenza vaccines in different populations.

Population	Burden of influenza	Influenza vaccine effectiveness	Influenza vaccine safety
Elderly	<ul style="list-style-type: none"> • Influenza disproportionately burdens the elderly • The risk of hospitalization and rates of emergency department and intensive care unit attendance and fatal hospitalization cases are highest among the elderly • Influenza outbreaks in aged-care facilities are an important contributor to the increased hospitalization and mortality observed in the elderly 	<ul style="list-style-type: none"> • Vaccine effectiveness is lower in the elderly compared with working-age adults • This reduced effectiveness is often attributed to immunosenescence, however there is increasing evidence to suggest it may be associated with immunological responses to repeated vaccination • To overcome issues of immunogenicity and effectiveness, enhanced vaccines (e.g. adjuvanted and high-dose vaccines) are increasingly being recommended for use in elderly populations 	<ul style="list-style-type: none"> • While influenza vaccines are reactogenic among the elderly, serious adverse events are rare • There is no evidence to suggest an increased risk of adverse events with the use of adjuvanted or high-dose vaccines
Paediatric	<ul style="list-style-type: none"> • Children are believed to have the highest rates of infection and complications arising from influenza • Their increased susceptibility to infection is believed to drive influenza epidemics, so vaccination of children has been proposed as a method of preventing transmission of influenza to other vulnerable groups 	<ul style="list-style-type: none"> • Both IIV and LAIV formulations of influenza vaccine are available for paediatric use • Superior efficacy of LAIV compared with IIV demonstrated in randomized controlled trials led to its preferential recommendation in some countries • However, observational data have provided mixed evidence for the relative effectiveness of LAIV over IIV, so the recommendation for its use continues to be debated • Adjuvanted vaccines may be more effective in very young children 	<ul style="list-style-type: none"> • Both IIV and LAIV vaccines are generally well tolerated in children • IIVs may cause pain, redness and swelling at the injection site, while LAIV is contraindicated in immunosuppressed individuals and their close contacts • Serious adverse events were reported for two vaccines in 2010, highlighting the need for ongoing post-licensure monitoring of vaccine safety
Pregnant	<ul style="list-style-type: none"> • Pregnant women are at higher risk of severe complications following influenza infection • However, there is limited evidence regarding the burden of influenza among pregnant women • The World Health Organization has recommended that pregnant women be made the highest priority group when considering expansion of national influenza vaccination programmes 	<ul style="list-style-type: none"> • Clinical trials and observational studies have demonstrated that IIV is immunogenic and effective in pregnant women • Maternal antibodies elicited by IIV confer clinical protection to the infant against influenza 	<ul style="list-style-type: none"> • Multiple studies have shown that influenza vaccination does not increase risk of pregnancy complications or adverse foetal outcomes • While the evidence is sparser, administration of IIV in early pregnancy is not associated with increased risk of congenital anomalies or spontaneous abortion

(Continued)

IIV, inactivated influenza vaccine; LAIV, live-attenuated influenza vaccine.

some of the limitations of influenza vaccines for this age group. These vaccines are being used increasingly in the elderly populations, although paediatric uses have been considered.⁴⁷ Indeed, at the time of writing, Australia had just replaced standard-dose vaccines with high-dose and adjuvanted formulations for the elderly in their national immunization programme,⁴² and the UK and Canada were investigating the preferential use of enhanced vaccines for the elderly.^{43,44}

Adjuvanted vaccines contain compounds designed to boost the immune response to vaccination. Immunogenicity studies of adjuvanted vaccine indicate higher geometric mean titres (GMTs), seropositivity and seroconversion compared with standard-dose vaccines. However, the evidence for the efficacy and effectiveness of MF59 adjuvanted vaccines is weaker. A 2017 review of these vaccines⁴⁸ identified just one paper that compared the efficacy of adjuvanted vaccine with standard-dose vaccine and reported a relative VE comparing MF59-adjuvanted vaccine with standard trivalent influenza vaccine (TIV) of 63% (95% CI: 4–86%).⁴⁹ While at first this appears promising, this study had several limitations, with few observations, questionable selection criteria and an extraordinarily low standard-dose VE.⁴⁹ A few studies also exist comparing AS03 TIV with standard-dose TIV. In one study⁵⁰ AS03 was found to have a relative efficacy of 29% (95% CI: 7.6–46%) against severe influenza, which is similar to the improvement in VE observed for high-dose vaccines.

High-dose vaccines are named thus because they contain a higher concentration of antigen compared with standard-dose vaccines. For example, while standard-dose vaccines typically contain 15 µg of antigen, the high-dose Sanofi product Fluzone® contains four times this amount of antigen. The immunogenicity of this product in terms of seroconversion,^{51,52} seropositivity^{51,53} and GMTs^{51–56} has been demonstrated to be higher compared with standard-dose vaccines. Its efficacy has also been assessed in a very large RCT, which identified that high-dose vaccine was 24% more effective than standard-dose vaccines.⁵⁷ Observational studies using US Medicare data also suggest that high-dose vaccine may be more effective than standard-dose vaccines for the prevention of hospitalization⁵⁸ and death.⁵⁹ Although these studies used nonspecific outcomes (clinical diagnosis +/- prescription for antiviral medication), their relative VE estimate was similar to the clinical trials, at around

22–24%. Furthermore, the relative effectiveness is speculated to be better in seasons when A(H3N2) circulates, which is important because this virus subtype is thought to cause the most influenza-associated deaths.⁴³ However, this relative improvement in VE may not necessarily translate to meaningful improvement in disease prevention in years where standard-dose vaccines perform poorly. It remains unclear whether the relative effectiveness of high-dose vaccine remains constant as the standard-dose VE changes. If constant, when the standard-dose vaccine provides VE of 50%, the absolute effectiveness of high-dose vaccine could be expected to be around 62%. However, if the standard-dose estimate was only 10%, which was the interim VE estimate for influenza A(H3N2) for 2017 in Australia,¹¹ VE for high-dose vaccines would only be expected to be around 12%.

Vaccination of ACF staff to protect elderly residents. In addition to immunizing the elderly, immunization of ACF staff is recommended in a number of countries.^{31,33,34} This strategy aims to not only protect staff from infection, but also residents by way of herd immunity. However, no high-quality study has demonstrated that vaccinating staff reduces the risk of laboratory-confirmed influenza infection among residents.⁶⁰ A systematic review of studies that assessed the benefits of staff vaccination for residents of ACFs or patients in hospitals identified eight studies.⁶¹ Four cluster randomized trials conducted in ACFs reported a significant reduced risk of mortality (pooled estimate 42%; 95% CI: 15–41%)^{62–65} and three trials observed reduced risk of acute respiratory infections (pooled estimate 29%; 95% CI: 15–41%)^{62,64,65} among ACF residents. However, the quality of these trials, as assessed by GRADE criteria, was low to moderate.⁶¹ The outcomes were nonspecific (e.g. deaths meant all-cause mortality, not laboratory-confirmed influenza deaths), which has been demonstrated to provide biased VE estimates,⁶⁰ and a later review concluded that the reported estimates were likely to be highly biased.⁶⁶

Safety of influenza vaccines for the elderly

Although influenza vaccines are known to be reactogenic among the elderly, that is, causing localized and mild reactions, severe adverse events are rare. Enhanced vaccines have been associated with increased reactogenicity compared with standard-dose or other types of

vaccines, but not increased risk of serious adverse events. A meta-analysis of 29 studies suggested no significant increased risk of serious adverse events for three classes of adjuvanted vaccine (AS01/AS02, AS03 and MF59) compared with control vaccines.⁶⁷ On the other hand, adjuvanted vaccines were more reactogenic: AS01/AS02-adjuvanted vaccines were associated with more drowsiness, irritability and loss of appetite; AS03-adjuvanted vaccines were associated with more local pain, swelling, fever and irritability; MF59-adjuvanted vaccines were associated with more local pain, redness, fever, irritability and loss of appetite. Fewer publications report on the safety of high-dose vaccines among the elderly. However, a review of seven studies of high-dose vaccines suggested no overall increased risk of serious adverse events associated with high-dose vaccines compared with standard-dose vaccines.⁶⁸

Children

Burden of influenza among children

Children are believed to have the highest rates of infection and complications arising from influenza. A systematic review estimated that in 2008 there were 49–162 million new cases of influenza and 28,000–111,500 influenza-associated deaths in children younger than 5 years of age.⁶⁹ Associated with this are high rates of excess outpatient visits, hospital admissions and antibiotic prescriptions.^{70–74} Bacterial and other complications of influenza are frequent, especially in children less than 3 years of age. The burden of influenza-attributable mortality in young children is being increasingly recognized,^{75–82} and may contribute to sudden infant deaths.^{83,84} This all comes at significant cost to the health system.^{72,76,85–87} This burden is even greater among children with chronic medical conditions, such as asthma, heart disease and other chronic conditions. There are also considerable indirect costs of influenza infection among children, such as productivity losses among parents and caregivers.⁷²

Although vaccination of children to prevent infection is recommended, childhood vaccination has also been proposed as a method of preventing transmission of influenza to other vulnerable groups, such as the elderly.¹² Several studies have suggested that infections among children drive influenza epidemics due to their increased susceptibility to infection and greater contribution to the spread of virus among the population.^{88–90}

Efficacy and effectiveness of influenza vaccines for children

In most countries, paediatric formulations of inactivated influenza vaccine (IIV), which have reduced concentration of each antigen, are available for use among children aged at least 6 months. Both inactivated and live-attenuated formulations of influenza vaccines (LAIVs) are available, although the use of these vaccines varies by country. For children receiving their first dose of influenza vaccine, two doses are recommended at least 1 month apart in order to ensure adequate protection. The first dose primes the immune system and the second dose ensures protection through the influenza season. Children who are ‘partially’ vaccinated because they have received only one dose, may not be protected against influenza.^{91,92}

A recent update to a Cochrane systematic review confirmed that IIVs had 59% efficacy in preventing laboratory-confirmed influenza (95% CI: 41–71%) and 36% effectiveness in preventing influenza-like illness (95% CI: 24–46%) in healthy children aged 2–16 years.⁹³ This review found a lack of data about efficacy and effectiveness in children less than 2 years of age. However, this review did not consider the evidence from observational studies, which in recent years has drastically increased due to the widespread use of the test-negative design.⁹⁴ Both test-negative studies^{95–97} and traditional observational study designs^{98,99} have generally reported positive VE point estimates for IIVs for children younger than 2 years of age, but these studies have often been based on few cases and present wide CIs. For children less than 5 years of age, the evidence from observational studies is stronger, with reported estimates as high as 86% (95% CI: 29–97%).¹⁰⁰ It is unclear whether VE is likely to be better for older (2–5 years) or younger (<2 years) children.^{95,96,98,100–102} In studies where VE is reported for both children and adults, however, the estimates for children are often higher.¹⁰³ The differences in VE among children and adults is likely to be affected by immune system responses associated with prior exposure to the vaccine and virus, which is currently poorly understood in children.^{99–101}

For children aged at least 2 years, LAIVs are available in some countries and are administered by nasal spray. Unlike the IIVs, LAIVs are able to stimulate innate immunity,^{104,105} but do not stimulate a strong antibody response.¹⁰⁶ Although they are licensed for persons up to age 50 years in

the USA, their effectiveness is believed to be inferior in older age groups.¹⁰⁷ Several RCTs have demonstrated superior efficacy of the LAIV compared with IIV among children.¹⁰⁸ Observational data have provided mixed evidence for the relative effectiveness of LAIVs over IIVs, particularly in recent years.^{109–114,115}

LAIV was preferentially recommended for children by the US Advisory Committee on Immunization Practices (ACIP).¹¹⁴ However, data from the 2015–2016 influenza season, which reported very poor VE for children, prompted the removal of this preferential recommendation. Although the initial ACIP recommendation was based on a comprehensive review of existing evidence,¹¹⁶ all available estimates were based on trivalent formulations. Since 2014, LAIV has had a quadrivalent formulation and competition among the influenza B lineages has been postulated to have reduced subsequent VE.¹¹⁶ Moreover, the VE for the A(H1N1)pdm09 component has been poor for several years and might be explained by reduced replicative fitness of the A(H1N1)pdm09 strains included in the vaccine, which may in turn have resulted in viral interference. In addition, some have queried whether repeated vaccination may have contributed to the attenuated effectiveness seen in the recent US studies, since attenuated effectiveness has not been seen in Europe, where LAIV has been available for fewer years.^{117,118} However, preliminary studies in Finland¹¹¹ and the USA¹¹⁹ reported no statistically significant association between repeated vaccination and LAIV VE, although both studies were limited by low case numbers.¹¹⁹

In 2018, the ACIP re-reviewed available evidence for LAIV and found it to be similar in effectiveness to IIV against A(H3N2) viruses and generally effective against influenza B viruses, but limited in effectiveness against A(H1N1)pdm09-like viruses.¹²⁰ Since this review, the A(H1N1)pdm09 vaccine component has been updated to A/Slovenia/2903/2015. Data provided by the manufacturer suggest it elicits significantly higher antibody titres than the previous A(H1N1)pdm09 component and comparable seroconversion rates to A(H1N1) seasonal strains that were considered effective.¹²¹ However, there are currently no effectiveness estimates available for the newly formulated vaccine. This reformulation led to the ACIP reinstating its recommendation for LAIV use for the 2018–2019 influenza season, although with no preference over IIV.¹²¹

Adjuvanted formulations have also been developed for children. The rationale is that children respond poorly to standard influenza vaccines while adjuvants may elicit a more robust and persistent response.⁴⁷ Therefore, adjuvants will probably be most useful in very young children who are both vaccine and infection naïve. Studies have shown that MF59 vaccines may be more immunogenic and efficacious than standard vaccines, particularly in very young children aged 6–24 months; however, the benefits are inconsistent across subtypes and lineages.^{122–124} Few data on effectiveness exist, except from the 2009 A(H1N1)pdm09 pandemic, which suggested low VE.^{125,126} In contrast, the AS03 monovalent A(H1N1)pdm09 vaccine was observed to have good VE for children that was superior to standard vaccines.^{47,127} However, these benefits were overshadowed by safety concerns (see next section).

Safety of influenza vaccines for children

In general, studies indicate that influenza vaccines are well tolerated by children. For example, in a large population-based study of children aged 6–23 months the risk of medically attended AEFI was not statistically significant.¹²⁸ Active vaccine safety surveillance in Australia has shown that less than 5% of children experience a febrile adverse event following IIV immunization, and events requiring medical attention are uncommon.¹²⁹ IIVs may be more likely to cause pain, redness and swelling at the injection site, which are not a concern for LAIVs,¹³⁰ while LAIV is contraindicated in immunosuppressed individuals and their close contacts. Although adjuvanted vaccines are not widely available for children, safety data from clinical trials of adjuvanted influenza vaccines suggest no apparent safety concerns.¹³¹

While influenza vaccines are generally well tolerated in children, in 2010, two vaccines were associated with increased risk of severe adverse events. In Finland, AS03 adjuvanted A(H1N1)pdm09 Pandemrix® vaccine was found to contribute to the onset of narcolepsy in children aged 4–19 years,¹³² an observation that was later reported elsewhere in Europe.^{133–135} It was hypothesized that it resulted from differences in antibody binding that were associated with particular genetic signatures common among northern Europeans and identified in affected children.^{136,137} The event resulted in delicensing of AS03 for children younger than 20 years in Europe. In Australia, vaccination of children less

than 5 years of age was suspended after an increase in emergency department presentations for febrile convulsions after vaccination.¹³⁸ It was thought to be associated with manufacturing processes that enhanced immune responses to vaccination and may have been peculiar to the new viral strains included in that year's vaccine.^{139,140} The event resulted in the removal of BioCSL's licence to use Fluvax® in children aged less than 5 years.¹⁴¹ These two incidents highlight the limitations of clinical trials, which are typically underpowered to detect infrequent (1 per million) events, and the crucial role of implementing appropriate post-marketing surveillance of vaccine safety.¹⁴²

Pregnant women

Burden

Pregnant women are considered to be at higher risk of severe complications following influenza infection.¹⁴³ Based on evidence documenting this increased risk of severe disease among pregnant women,¹⁴³ the safety of vaccination during pregnancy,¹⁴⁴ and the effectiveness in preventing disease in pregnant women and their infants in the first 6 months,¹⁴⁵ the WHO Strategic Advisory Group of Experts has recommended that pregnant women be the highest priority group for countries initiating or expanding seasonal influenza vaccination programmes.¹⁴⁶ More than 44% of WHO member states have policies which recommend routine administration of IIV for pregnant women.¹⁴⁷ However, the recommended gestational timing of vaccination varies by country, and in some nations influenza vaccine continues to be listed as a contraindicated medication for pregnant women.

Few studies have comprehensively documented the burden of seasonal influenza among pregnant women, particularly in low- and middle-income countries.^{148,149} However, existing epidemiological studies have consistently shown the risk of severe infection is greater among pregnant women compared with nonpregnant women.^{143,150,151} Several studies have shown mortality associated with seasonal influenza may be greater during pregnancy¹⁵² and increased maternal and foetal mortality was documented during the 2009 H1N1 pandemic.^{153–155} Although it is well accepted that pregnancy is associated with increased risk of hospitalization with influenza, results from studies describing the risk of mortality and ICU admission due to influenza among

pregnant women are highly heterogeneous, and the potential risk of these outcomes among pregnant women remains uncertain.¹⁴³

Efficacy/effectiveness of influenza vaccines for pregnant women

In many countries, IIV is recommended for women who will be pregnant during the influenza season. LAIVs, as well as other live-attenuated vaccines, are contraindicated during pregnancy due to the hypothetical risk of transmission to the foetus. More recently, ACIP expanded their recommendation for influenza vaccines for adults to include recombinant influenza vaccines, which may be administered during pregnancy.¹⁵⁶

A range of clinical trials and observational studies have shown IIV is immunogenic in pregnant women.^{157,158} Two clinical trials observed a 6–10-fold increase in GMTs among mothers who received IIVs, and more than 72% seroconversion was observed.¹⁵⁸ However, these trials also found that certain factors, such as immune impairment with HIV, may impede the maternal response to vaccination.¹⁵⁸ Although GMTs were lower, the estimated efficacy of IIV in these trials was similar for HIV-infected and uninfected women. Several additional clinical trials in low- and middle-income countries have suggested the efficacy of IIV is 50–70% in preventing laboratory-confirmed influenza in pregnant women.¹⁵⁹ Observational studies have similarly estimated that IIV is 44–65% effective against influenza among pregnant women.^{160,161} There is, however, limited evidence demonstrating the effectiveness of influenza vaccine against severe influenza (i.e. infection requiring hospitalization) among pregnant women. This is likely due to the low incidence of influenza infection and small numbers of hospitalized women within each influenza season, making it difficult to estimate reliably IIV effectiveness against hospitalized disease among pregnant women.

Maternal antibodies produced in response to IIV cross the placenta and can offer protection to the infant through to 6 months of age; since infants less than 6 months of age cannot receive IIV, vaccination during pregnancy offers the best method of protection.¹⁵⁹ Although antibody transfer occurs most efficiently in the third trimester of pregnancy,¹⁶² a recent clinical trial in Nepal showed there was no difference in maternal seroconversion or infant:mother ratio of antibodies based on gestational timing of vaccination.¹⁶³

Maternal antibodies have been shown to confer clinical protection against laboratory-confirmed influenza in infants. Three recent clinical trials in Nepal, Mali and South Africa documented 30–63% efficacy in preventing laboratory-confirmed influenza in infants less than 6 months of age.¹⁵⁹ In high-income countries, a number of observational studies have been used to estimate VE. A UK study in 2013–2014 suggested that IIV in pregnancy was 71% effective (95% CI: 24–89%) in preventing influenza infection and 64% effective (95% CI: 6–86%) in preventing influenza hospitalization.¹⁶⁴ A US case-control study suggested IIV in pregnancy was 91% effective (95% CI: 62–98%) in preventing influenza hospitalization; however, the selection of controls in this study may have inflated this estimate.¹⁶⁵

Safety of influenza vaccines for pregnant women

A large number of post-licensure vaccine safety studies have demonstrated that influenza immunization during pregnancy is safe for both mother and infant. Studies over the past decade have shown that there is no increase in the risk of pregnancy complications, including pre-eclampsia and chorioamnionitis,^{144,166,167} or adverse foetal outcomes, including stillbirth, preterm birth and foetal growth restriction.^{144,168,169} However, the majority of these studies have been restricted to cohorts of pregnant women immunized in the second or third trimester. Although less frequently investigated, several studies have shown that administration of IIV in early pregnancy is not associated with an increased risk of congenital anomalies or spontaneous abortion.¹⁴⁴ However, one recent case-control study reported an increase in the risk of spontaneous abortion associated with IIV,¹⁷⁰ and although this study had methodological shortcomings,^{171–173} it has stimulated additional review of the safety of IIV administration in early pregnancy.

Several studies, including recent clinical trials, have suggested IIV during pregnancy may be associated with improved health at birth.¹⁷⁴ For example, clinical trials in Bangladesh and Nepal showed that influenza immunization during pregnancy reduced the occurrence of low birthweight births.¹⁷⁵ However, results in this area have been extremely heterogeneous,¹⁷⁶ and several methodological issues in assessing potential foetal benefits of influenza vaccination during pregnancy have been raised in these findings.¹⁷⁷

Conclusion

Key populations targeted by vaccination programmes in many countries include elderly adults, children and pregnant women. While evidence exists to support these policies, ongoing surveillance and evaluation of influenza vaccines are necessary, both because changes to the vaccine formulation can shift the safety and effectiveness profile, and to increase the wealth of evidence. In particular, studies among children and pregnant women currently suffer from small sample problems and will benefit from the pooling of data across studies, for example through meta-analysis, to generate summary estimates and to better understand sources of heterogeneity.

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Conflict of interest statement

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ORCID iD

Sheena G. Sullivan  <https://orcid.org/0000-0002-0856-0294>

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