

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

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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

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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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References

1. Nichol KL. Cost-effectiveness and socio-economic aspects of childhood influenza vaccination. *Vaccine* 2011; 29: 7554–7558.
2. Savidan E, Chevat C and Marsh G. Economic evidence of influenza vaccination in children. *Health Policy* 2008; 86: 142–152.
3. Barr IG, McCauley J, Cox N, *et al.* Epidemiological, antigenic and genetic characteristics of seasonal influenza A(H1N1), A(H3N2) and B influenza viruses: basis for the WHO recommendation on the composition of influenza vaccines for use in the 2009–2010 Northern Hemisphere season. *Vaccine* 2009; 28: 1156–1167.
4. Kelly H and Barr I. Large trials confirm immunogenicity of H1N1 vaccines. *Lancet* 2009; 375: 6–9.
5. Last J and Porta M. *A dictionary of epidemiology*. 5th ed. New York: Oxford University Press, 2008.
6. Valenciano M, Kissling E, Cohen JM, *et al.* Estimates of pandemic influenza vaccine effectiveness in Europe, 2009–2010: results of

- Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case-control study. *PLoS Med* 2010; 8: e1000388.
7. Castilla J, Navascues A, Casado I, *et al.* Interim effectiveness of trivalent influenza vaccine in a season dominated by lineage mismatched influenza B, northern Spain, 2017/18. *Euro Surveill* 2018; 23: 18-00057.
 8. Pebody R, Warburton F, Ellis J, *et al.* End-of-season influenza vaccine effectiveness in adults and children, United Kingdom, 2016/17. *Euro Surveill* 2017; 22: 17-00306.
 9. Flannery B, Chung JR, Belongia EA, *et al.* Interim estimates of 2017–18 seasonal influenza vaccine effectiveness – United States, February 2018. *Am J Transplant* 2018; 18: 1020–1025.
 10. Skowronski DM, Chambers C, De Serres G, *et al.* Early season co-circulation of influenza A(H3N2) and B(Yamagata): interim estimates of 2017/18 vaccine effectiveness, Canada, January 2018. *Euro Surveill* 2018; 23: 18-00035.
 11. Sullivan SG, Chilver MB, Carville KS, *et al.* Low interim influenza vaccine effectiveness, Australia, 1 May to 24 September 2017. *Euro Surveill* 2017; 22: 17-00707.
 12. Baguelin M, Flasche S, Camacho A, *et al.* Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study. *PLoS Med* 2013; 10: e1001527.
 13. Iuliano AD, Roguski KM, Chang HH, *et al.* Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2017; 391: 1285–1300.
 14. Wu P, Goldstein E, Ho LM, *et al.* Excess mortality impact of two epidemics of pandemic influenza A(H1N1pdm09) virus in Hong Kong. *Influenza Other Respir Viruses* 2014; 8: 1–7.
 15. World Health Organization. *International meeting on influenza vaccine effectiveness*, http://www.who.int/immunization/research/meetings_workshops/influenza_vaccine_effectiveness_dec12/en/ (2012, accessed 28 July 2014).
 16. Foppa IM, Cheng PY, Reynolds SB, *et al.* Deaths averted by influenza vaccination in the US during the seasons 2005/06 through 2013/14. *Vaccine* 2015; 33: 3003–3009.
 17. Newall AT, Wood JG and MacIntyre CR. Influenza-related hospitalisation and death in Australians aged 50 years and older. *Vaccine* 2008; 26: 2135–2141.
 18. Mitchell R, Taylor G, McGeer A, *et al.* Understanding the burden of influenza infection among adults in Canadian hospitals: a comparison of the 2009–2010 pandemic season with the prepandemic and postpandemic seasons. *Am J Infect Control* 2013; 41: 1032–1037.
 19. Kuznierz G, Carolina C, Manuel RJ, *et al.* Impact of influenza in the post-pandemic phase: clinical features in hospitalized patients with influenza A (H1N1) pdm09 and H3N2 viruses, during 2013 in Santa Fe, Argentina. *J Med Virol* 2017; 89: 1186–1191.
 20. Wong CM, Yang L, Chan KP, *et al.* Influenza-associated hospitalization in a subtropical city. *PLoS Med* 2006; 3: e121.
 21. Mullooly JP, Bridges CB, Thompson WW, *et al.* Influenza- and RSV-associated hospitalizations among adults. *Vaccine* 2007; 25: 846–855.
 22. European Centre for Disease Prevention and Control. *Risk assessment of seasonal influenza, EU/EEA, 2016–2017 – Update 25 Jan 2017*, <http://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/Risk-assessment-seasonal-influenza-2016-2017-update.pdf> (2017, accessed 16 July 2018).
 23. Muscatello DJ, Bein KJ and Dinh MM. Emergency Department demand associated with seasonal influenza, 2010 through 2014, New South Wales, Australia. *Western Pac Surveill Response J* 2017; 8: 11–20.
 24. McElhaney JE. The unmet need in the elderly: designing new influenza vaccines for older adults. *Vaccine* 2005; 23: S10–S25.
 25. Peasah SK, Azziz-Baumgartner E, Breese J, *et al.* Influenza cost and cost-effectiveness studies globally – a review. *Vaccine* 2013; 31: 5339–5348.
 26. Gozalo PL, Pop-Vicas A, Feng Z, *et al.* Effect of influenza on functional decline. *J Am Geriatr Soc* 2012; 60: 1260–1267.
 27. Booy R, Lindley RI, Dwyer DE, *et al.* Treating and preventing influenza in aged care facilities: a cluster randomised controlled trial. *PLoS One* 2012; 7: e46509.
 28. Gaillat J, Chidiac C, Fagnani F, *et al.* Morbidity and mortality associated with influenza exposure in long-term care facilities for dependent elderly people. *Eur J Clin Microbiol Infect Dis* 2009; 28: 1077–1086.
 29. Utsumi M, Makimoto K, Quroshi N, *et al.* Types of infectious outbreaks and their impact in elderly care facilities: a review of the literature. *Age Ageing* 2010; 39: 299–305.
 30. World Health Organization. *Prevention and control of outbreaks of seasonal influenza in long-term care facilities: a review of the evidence*

- and best-practice guidance. Copenhagen: WHO Regional Office for Europe, 2017.
31. Centers for Disease Control and Prevention. *Interim guidance for influenza outbreak management in long-term care facilities*. Atlanta: Centers for Disease Control and Prevention, 2011.
 32. Public Health England. *PHE guidelines on the management of outbreaks of influenza-like illness (ILI) in care homes*, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/747543/Influenza-like_illness_in_care_home_2018_FINAL.pdf (2017, accessed 17 July 2018).
 33. Communicable Diseases Network Australia. *Guidelines for the prevention, control and public health management of influenza outbreaks in residential care facilities in Australia*, [https://www.health.gov.au/internet/main/publishing.nsf/Content/27BE697A7F5AB5CA257BF0001D3AC8/\\$File/RCF_Guidelines.pdf](https://www.health.gov.au/internet/main/publishing.nsf/Content/27BE697A7F5AB5CA257BF0001D3AC8/$File/RCF_Guidelines.pdf), 2017.
 34. Public Health Agency of Canada. *Guidance: infection prevention and control measures for healthcare workers in acute care and long-term care settings: seasonal influenza*, <https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/noisinp/guide/pdf/ac-sa-eng.pdf> (2010, accessed 17 July 2018).
 35. World Health Organization. *Strategy and action plan for healthy ageing in Europe, 2012–2020*. Copenhagen: WHO Regional Office for Europe, 2012.
 36. Vaccines against influenza WHO position paper – November 2012. *Wkly Epidemiol Rec* 2012; 87: 461–476.
 37. Demicheli V, Jefferson T, Di Pietrantonj C, *et al*. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2018; 2: CD004876.
 38. Belongia EA, Simpson MD, King JP, *et al*. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis* 2016; 16: 942–951.
 39. Rondy M, El Omeiri N, Thompson MG, *et al*. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: a systematic review and meta-analysis of test-negative design case-control studies. *J Infect* 2017; 75: 381–394.
 40. Darvishian M, Bijlsma MJ, Hak E, *et al*. Effectiveness of seasonal influenza vaccine in community-dwelling elderly people: a meta-analysis of test-negative design case-control studies. *Lancet Infect Dis* 2014; 14: 1228–1239.
 41. Zost SJ, Parkhouse K, Gumina ME, *et al*. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. *Proc Natl Acad Sci U S A* 2017; 114: 12578–12583.
 42. Skowronski DM, Janjua NZ, De Serres G, *et al*. Low 2012–13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses. *PLoS One* 2014; 9: e92153.
 43. Vestergaard LS, Nielsen J, Krause TG, *et al*. Excess all-cause and influenza-attributable mortality in Europe, December 2016 to February 2017. *Euro Surveill* 2017; 22: 30506.
 44. Belongia EA, Skowronski DM, McLean HQ, *et al*. Repeated annual influenza vaccination and vaccine effectiveness: review of evidence. *Expert Rev Vaccines* 2017; 16: 1–14.
 45. Targonski PV, Jacobson RM and Poland GA. Immunosenescence: role and measurement in influenza vaccine response among the elderly. *Vaccine* 2007; 25: 3066–3069.
 46. Mosterin Hopping A, McElhaney J, Fonville JM, *et al*. The confounded effects of age and exposure history in response to influenza vaccination. *Vaccine* 2016; 34: 540–546.
 47. Wilkins AL, Kazmin D, Napolitani G, *et al*. AS03- and MF59-adjuvanted influenza vaccines in children. *Front Immunol* 2017; 8: 1760.
 48. Domnich A, Arata L, Amicizia D, *et al*. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: a systematic review and meta-analysis. *Vaccine* 2017; 35: 513–520.
 49. Van Buynder PG, Konrad S, Van Buynder JL, *et al*. The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. *Vaccine* 2013; 31: 6122–6128.
 50. van Essen GA, Beran J, Devaster JM, *et al*. Influenza symptoms and their impact on elderly adults: randomised trial of AS03-adjuvanted or non-adjuvanted inactivated trivalent seasonal influenza vaccines. *Influenza Other Respir Viruses* 2014; 8: 452–462.
 51. Falsey AR, Treanor JJ, Tornieporth N, *et al*. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis* 2009; 200: 172–180.
 52. Couch RB, Winokur P, Brady R, *et al*. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine* 2007; 25: 7656–7663.
 53. DiazGranados CA, Dunning AJ, Kimmel M, *et al*. Efficacy of high-dose versus standard-dose

- influenza vaccine in older adults. *N Engl J Med* 2014; 371: 635–645.
54. DiazGranados CA, Dunning AJ, Jordanov E, *et al.* High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009–2010 season. *Vaccine* 2013; 31: 861–866.
 55. Keitel WA, Atmar RL, Cate TR, *et al.* Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Arch Intern Med* 2006; 166: 1121–1127.
 56. Tsang P, Gorse GJ, Strout CB, *et al.* Immunogenicity and safety of Fluzone® intradermal and high-dose influenza vaccines in older adults \geq 65 years of age: a randomized, controlled, phase II trial. *Vaccine* 2014; 32: 2507–2517.
 57. DiazGranados CA, Dunning AJ, Kimmel M, *et al.* Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med* 2014; 371: 635–645.
 58. Izurieta HS, Thadani N, Shay DK, *et al.* Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. *Lancet Infect Dis* 2015; 15: 293–300.
 59. Shay DK, Chillarige Y, Kelman J, *et al.* Comparative effectiveness of high-dose versus standard-dose influenza vaccines among us medicare beneficiaries in preventing postinfluenza deaths during 2012–2013 and 2013–2014. *J Infect Dis* 2017; 215: 510–517.
 60. Kelly H. Letter to the editor: vaccinating healthcare workers: evidence and ethics. *Euro Surveill* 2015; 20: pii: 21006.
 61. Ahmed F, Lindley MC, Allred N, *et al.* Effect of influenza vaccination of healthcare personnel on morbidity and mortality among patients: systematic review and grading of evidence. *Clin Infect Dis* 2014; 58: 50–57.
 62. Potter J, Stott DJ, Roberts MA, *et al.* Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *J Infect Dis* 1997; 175: 1–6.
 63. Carman WF, Elder AG, Wallace LA, *et al.* Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet* 2000; 355: 93–97.
 64. Hayward AC, Harling R, Wetten S, *et al.* Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. *BMJ* 2006; 333: 1241.
 65. Lemaitre M, Meret T, Rothan-Tondeur M, *et al.* Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. *J Am Geriatr Soc* 2009; 57: 1580–1586.
 66. De Serres G, Skowronski DM, Ward BJ, *et al.* Influenza vaccination of healthcare workers: critical analysis of the evidence for patient benefit underpinning policies of enforcement. *PLoS One* 2017; 12: e0163586.
 67. Baay M, Bollaerts K and Verstraeten T. A systematic review and meta-analysis on the safety of newly adjuvanted vaccines among older adults. *Vaccine* 2018; 36: 4207–4214.
 68. Wilkinson K, Wei Y, Szwajcer A, *et al.* Efficacy and safety of high-dose influenza vaccine in elderly adults: a systematic review and meta-analysis. *Vaccine* 2017; 35: 2775–2780.
 69. Nair H, Brooks WA, Katz M, *et al.* Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011; 378: 1917–1930.
 70. Heikkinen T, Booy R, Campins M, *et al.* Should healthy children be vaccinated against influenza? A consensus report of the Summits of Independent European Vaccination Experts. *Eur J Pediatr* 2006; 165: 223–228.
 71. Neuzil KM, Mellen BG, Wright PF, *et al.* The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000; 342: 225–231.
 72. Poehling KA, Edwards KM, Weinberg GA, *et al.* The underrecognized burden of influenza in young children. *N Engl J Med* 2006; 355: 31–40.
 73. Neuzil KM. Influenza: new insights into an old disease. *Curr Infect Dis Rep* 2000; 2: 224–230.
 74. Brotherton J, Wang H, Schaffer A, *et al.* Vaccine preventable diseases and vaccination coverage in Australia, 2003 to 2005. *Commun Dis Intell* 2007; 31(Suppl.): S1–S152.
 75. Centers for Disease Control and Prevention. Severe methicillin-resistant *Staphylococcus aureus* community-acquired pneumonia associated with influenza – Louisiana and Georgia, December 2006–January 2007. *MMWR Morb Mortal Wkly Rep* 2007; 56: 325–329.
 76. Bhat N, Wright JG, Broder KR, *et al.* Influenza-associated deaths among children in the United States, 2003–2004. *N Engl J Med* 2005; 353: 2559–2567.

77. Curson P and McCracken K. An Australian perspective of the 1918–1919 influenza pandemic. *N S W Public Health Bull* 2006; 17: 103–107.
78. Dowell SF, Kupronis BA, Zell ER, *et al.* Mortality from pneumonia in children in the United States, 1939 through 1996. *N Engl J Med* 2000; 342: 1399–1407.
79. Fleming DM, Pannell RS and Cross KW. Mortality in children from influenza and respiratory syncytial virus. *J Epidemiol Community Health* 2005; 59: 586–590.
80. Moore DL, Vaudry W, Scheifele DW, *et al.* Surveillance for influenza admissions among children hospitalized in Canadian immunization monitoring program active centers, 2003–2004. *Pediatrics* 2006; 118: e610–e619.
81. Podewils LJ, Liedtke LA, McDonald LC, *et al.* A national survey of severe influenza-associated complications among children and adults, 2003–2004. *Clin Infect Dis* 2005; 40: 1693–1696.
82. van der Wouden JC, Bueving HJ, Poole P, *et al.* Influenza-associated deaths among children. *N Engl J Med* 2006; 354: 1317–1318; author reply: 8.
83. Weber MA, Hartley JC, Ashworth MT, *et al.* Virological investigations in sudden unexpected deaths in infancy (SUDI). *Forensic Sci Med Pathol* 2010; 6: 261–267.
84. Williams AL, Uren EC and Bretherton L. Respiratory viruses and sudden infant death. *Br Med J (Clin Res Ed)* 1984; 288: 1491–1493.
85. Ampofo K, Gesteland PH, Bender J, *et al.* Epidemiology, complications, and cost of hospitalization in children with laboratory-confirmed influenza infection. *Pediatrics* 2006; 118: 2409–2417.
86. Grijalva CG, Weinberg GA, Bennett NM, *et al.* Estimating the undetected burden of influenza hospitalizations in children. *Epidemiol Infect* 2007; 135: 951–958.
87. Ji W, Zhang T, Zhang X, *et al.* The epidemiology of hospitalized influenza in children, a two year population-based study in the People’s Republic of China. *BMC Health Serv Res* 2010; 10: 82.
88. Longini IM, Jr, Koopman JS, Monto AS, *et al.* Estimating household and community transmission parameters for influenza. *Am J Epidemiol* 1982; 115: 736–751.
89. Schanzer D, Vachon J and Pelletier L. Age-specific differences in influenza A epidemic curves: do children drive the spread of influenza epidemics? *Am J Epidemiol* 2011; 174: 109–117.
90. Viboud C, Boelle PY, Cauchemez S, *et al.* Risk factors of influenza transmission in households. *Br J Gen Pract* 2004; 54: 684–689.
91. Shen S, Campitelli MA, Calzavara A, *et al.* Seasonal influenza vaccine effectiveness in pre- and full-term children aged 6–23 months over multiple seasons. *Vaccine* 2013; 31: 2974–2978.
92. Staat MA, Griffin MR, Donauer S, *et al.* Vaccine effectiveness for laboratory-confirmed influenza in children 6–59 months of age, 2005–2007. *Vaccine* 2011; 29: 9005–9011.
93. Jefferson T, Rivetti A, Di Pietrantonj C, *et al.* Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev* 2018; 2: CD004879.
94. Sullivan SG, Feng S and Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. *Expert Rev Vaccines* 2014; 13: 1571–1591.
95. Chiu SS, Kwan MYW, Feng S, *et al.* Influenza vaccine effectiveness against influenza A(H3N2) hospitalizations in children in Hong Kong in a prolonged season, 2016/2017. *J Infect Dis* 2018; 217: 1365–1371.
96. Blyth CC, Jacoby P, Effler PV, *et al.* Effectiveness of trivalent flu vaccine in healthy young children. *Pediatrics* 2014; 133: e1218–e1225.
97. Shinjoh M, Sugaya N, Yamaguchi Y, *et al.* Effectiveness of trivalent inactivated influenza vaccine in children estimated by a test-negative case-control design study based on influenza rapid diagnostic test results. *PLoS One* 2015; 10: e0136539.
98. Fujieda M, Maeda A, Kondo K, *et al.* Inactivated influenza vaccine effectiveness in children under 6 years of age during the 2002–2003 season. *Vaccine* 2006; 24: 957–963.
99. Maeda T, Shintani Y, Nakano K, *et al.* Failure of inactivated influenza A vaccine to protect healthy children aged 6–24 months. *Pediatr Int* 2004; 46: 122–125.
100. Joshi AY, Iyer VN, St Sauver JL, *et al.* Effectiveness of inactivated influenza vaccine in children less than 5 years of age over multiple influenza seasons: a case-control study. *Vaccine* 2009; 27: 4457–4461.
101. Shuler CM, Iwamoto M, Bridges CB, *et al.* Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003–2004. *Pediatrics* 2007; 119: e587–e595.
102. Sugaya N, Shinjoh M, Kawakami C, *et al.* Trivalent inactivated influenza vaccine effective

- against influenza A(H3N2) variant viruses in children during the 2014/15 season, Japan. *Euro Surveill* 2016; 21: 30377.
103. Osterholm MT, Kelley NS, Sommer A, *et al.* Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; 12: 36–44.
104. Kreijtz JH, Fouchier RA and Rimmelzwaan GF. Immune responses to influenza virus infection. *Virus Res* 2011; 162: 19–30.
105. Oshansky CM and Thomas PG. The human side of influenza. *J Leukoc Biol* 2012; 92: 83–96.
106. Khan AS, Polezhaev F, Vasiljeva R, *et al.* Comparison of US inactivated split-virus and Russian live attenuated, cold-adapted trivalent influenza vaccines in Russian schoolchildren. *J Infect Dis* 1996; 173: 453–456.
107. Webster RG, Braciale TJ, Monto AS, *et al.* *Textbook of influenza*. 2nd ed. Chichester, West Sussex; Hoboken, NJ: Wiley-Blackwell, 2013.
108. Ambrose CS, Levin MJ and Belshe RB. The relative efficacy of trivalent live attenuated and inactivated influenza vaccines in children and adults. *Influenza Other Respir Viruses* 2011; 5: 67–75.
109. INFLUENZA in the United Kingdom, 1953–6; report to the Medical Research Council Committee on Clinical Trials of Influenza Vaccine by the Public Health Laboratory Service. *Br Med J* 1957; 2: 8–10.
110. Pebody R, Warburton F, Ellis J, *et al.* Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. *Euro Surveill* 2016; 21: 30348.
111. Nohynek H, Baum U, Syrjanen R, *et al.* Effectiveness of the live attenuated and the inactivated influenza vaccine in two-year-olds – a nationwide cohort study Finland, influenza season 2015/16. *Euro Surveill* 2016; 21: 30346.
112. Jackson ML, Chung JR, Jackson LA, *et al.* Influenza vaccine effectiveness in the United States during the 2015–2016 season. *N Engl J Med* 2017; 377: 534–543.
113. Zimmerman RK, Nowalk MP, Chung J, *et al.* 2014–2015 Influenza vaccine effectiveness in the United States by vaccine type. *Clin Infect Dis* 2016; 63: 1564–1573.
114. Grohskopf LA, Olsen SJ, Sokolow LZ, *et al.* Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States, 2014–15 influenza season. *MMWR Morb Mortal Wkly Rep* 2014; 63: 691–697.
115. Ambrose CS, Bright H and Mallory R. Letter to the editor: potential causes of the decreased effectiveness of the influenza A(H1N1)pdm09 strain in live attenuated influenza vaccines. *Euro Surveill* 2016; 21: pii: 30394.
116. Penttinen PM and Friede MH. Decreased effectiveness of the influenza A(H1N1)pdm09 strain in live attenuated influenza vaccines: an observational bias or a technical challenge? *Euro Surveill* 2016; 21: 30350.
117. Pebody R, McMenamin J and Nohynek H. Live attenuated influenza vaccine (LAIV): recent effectiveness results from the USA and implications for LAIV programmes elsewhere. *Arch Dis Child* 2018; 103: 101–105.
118. Grohskopf LA. *Review of effectiveness of live attenuated influenza vaccine*. Presented at the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) Meeting, 21 February 2018, Atlanta, GA.
119. McLean HQ, Caspard H, Griffin MR, *et al.* Association of prior vaccination with influenza vaccine effectiveness in children receiving live attenuated or inactivated vaccine. *JAMA Network Open* 2018; 1: e183742.
120. Grohskopf LA, Sokolow LZ, Fry AM, *et al.* Update: ACIP recommendations for the use of quadrivalent live attenuated influenza vaccine (LAIV4) – United States, 2018–19 influenza season. *MMWR Morb Mortal Wkly Rep* 2018; 67: 643.
121. Grohskopf LA, Sokolow LZ, Fry AM, *et al.* Update: ACIP recommendations for the use of quadrivalent live attenuated influenza vaccine (LAIV4) – United States, 2018–19 influenza season. *MMWR Morb Mortal Wkly Rep* 2018; 67: 643–645.
122. Vesikari T, Kirstein J, Devota Go G, *et al.* Efficacy, immunogenicity, and safety evaluation of an MF59-adjuvanted quadrivalent influenza virus vaccine compared with non-adjuvanted influenza vaccine in children: a multicentre, randomised controlled, observer-blinded, phase 3 trial. *Lancet Respir Med* 2018; 6: 345–356.
123. Vesikari T, Knuf M, Wutzler P, *et al.* Oil-in-water emulsion adjuvant with influenza vaccine in young children. *N Engl J Med* 2011; 365: 1406–1416.
124. Sylvester G. *Study results of an adjuvanted quadrivalent influenza vaccine in young children Meeting of the Advisory Committee on Immunization*

- Practices (ACIP)*. Atlanta, Georgia: Centers for Disease Control and Prevention, 2018.
125. Castilla J, Moran J, Martinez-Artola V, *et al*. Effectiveness of the monovalent influenza A(H1N1)2009 vaccine in Navarre, Spain, 2009–2010: cohort and case-control study. *Vaccine* 2011; 29: 5919–5924.
 126. Wijnans L, Dieleman J, Voordouw B, *et al*. Effectiveness of MF59 adjuvanted influenza A (H1N1) pdm09 vaccine in risk groups in the Netherlands. *PLoS One* 2013; 8: e63156.
 127. Lansbury LE, Smith S, Beyer W, *et al*. Effectiveness of 2009 pandemic influenza A(H1N1) vaccines: a systematic review and meta-analysis. *Vaccine* 2017; 35: 1996–2006.
 128. Hambidge SJ, Glanz JM, France EK, *et al*. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. *JAMA* 2006; 296: 1990–1997.
 129. Pillsbury A, Cashman P, Leeb A, *et al*. Real-time safety surveillance of seasonal influenza vaccines in children, Australia, 2015. *Euro Surveill* 2015; 20: 30050.
 130. Belshe RB, Edwards KM, Vesikari T, *et al*. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med* 2007; 356: 685–696.
 131. Stassijns J, Bollaerts K, Baay M, *et al*. A systematic review and meta-analysis on the safety of newly adjuvanted vaccines among children. *Vaccine* 2016; 34: 714–722.
 132. Nohynek H, Jokinen J, Partinen M, *et al*. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. *PLoS One* 2012; 7: e33536.
 133. Miller E, Andrews N, Stellitano L, *et al*. Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis. *BMJ* 2013; 346: f794.
 134. Winstone AM, Stellitano L, Verity C, *et al*. Clinical features of narcolepsy in children vaccinated with AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine in England. *Dev Med Child Neurol* 2014; 56: 1117–1123.
 135. European Centre for Disease Prevention and Control. *Narcolepsy in association with pandemic influenza vaccination (a multi-country European epidemiological investigation)*. Stockholm: European Centre for Diseases Prevention and Control, 2012.
 136. Vaarala O, Vuorela A, Partinen M, *et al*. Antigenic differences between AS03 adjuvanted influenza A (H1N1) pandemic vaccines: implications for pandemrix-associated narcolepsy risk. *PLoS One* 2014; 9: e114361.
 137. Sarkanen T, Alakuijala A, Julkunen I, *et al*. Narcolepsy associated with pandemrix vaccine. *Curr Neurol Neurosci Rep* 2018; 18: 43.
 138. Kelly HA, Skowronski DM, De Serres G, *et al*. Adverse events associated with 2010 CSL and other inactivated influenza vaccines. *Med J Aust* 2011; 195: 318–320.
 139. Rockman S, Dyson A, Koernig S, *et al*. Evaluation of the bioactivity of influenza vaccine strains in vitro suggests that the introduction of new strains in the 2010 Southern Hemisphere trivalent influenza vaccine is associated with adverse events. *Vaccine* 2014; 32: 3861–3868.
 140. Rockman S, Becher D, Dyson A, *et al*. Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine. *Vaccine* 2014; 32: 3869–3876.
 141. Therapeutic Goods Administration. *Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination: status report as at 2 July 2010 (updated 24 September 2010)*. Canberra: Therapeutic Goods Administration, 2010.
 142. Gold MS, Effler P, Kelly H, *et al*. Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. *Med J Aust* 2010; 193: 492–493.
 143. Mertz D, Geraci J, Winkup J, *et al*. Pregnancy as a risk factor for severe outcomes from influenza virus infection: a systematic review and meta-analysis of observational studies. *Vaccine* 2017; 35: 521–528.
 144. Munoz FM. Safety of influenza vaccines in pregnant women. *Am J Obstet Gynecol* 2012; 207: S33–S37.
 145. Zaman K, Roy E, Arifeen SE, *et al*. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med* 2008; 359: 1555–1564.
 146. World Health Organization. Weekly Epidemiological Record, 2012, vol. 87, 21 [full issue]. *Wkly Epidemiol Rec* 2012; 87: 201–216.
 147. Ortiz JR, Perut M, Dumolard L, *et al*. A global review of national influenza immunization policies: analysis of the 2014 WHO/UNICEF Joint Reporting Form on immunization. *Vaccine* 2016; 34: 5400–5405.
 148. Bardaji A, Steinhoff M, Macete E, *et al*. The burden of vaccine-preventable diseases in

- pregnancy in low-resource settings. *Lancet Glob Health* 2016; 4: e152–e153.
149. Katz MA, Gessner BD, Johnson J, *et al.* Incidence of influenza virus infection among pregnant women: a systematic review. *BMC Pregnancy Childbirth* 2017; 17: 155.
 150. Ohfuji S, Deguchi M, Tachibana D, *et al.* Estimating influenza disease burden among pregnant women: application of self-control method. *Vaccine* 2017; 35: 4811–4816.
 151. Dodds L, McNeil SA, Fell DB, *et al.* Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ* 2007; 176: 463–468.
 152. Tempia S, Walaza S, Cohen AL, *et al.* Mortality associated with seasonal and pandemic influenza among pregnant and nonpregnant women of childbearing age in a high-HIV-prevalence setting – South Africa, 1999–2009. *Clin Infect Dis* 2015; 61: 1063–1070.
 153. Centers for Disease Control and Prevention. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1) – United States, April 2009–August 2010. *MMWR Morb Mortal Wkly Rep* 2011; 60: 1193–1196.
 154. Häberg SE, Trogstad L, Gunnes N, *et al.* Risk of fetal death after pandemic influenza virus infection or vaccination. *N Engl J Med* 2013; 368: 333–340.
 155. Barakat A, Ihazmad H, El Falaki F, *et al.* 2009 Pandemic influenza A virus subtype H1N1 in Morocco, 2009–2010: epidemiology, transmissibility, and factors associated with fatal cases. *J Infect Dis* 2012; 206(Suppl. 1): S94–S100.
 156. Grohskopf LA, Sokolow LZ, Broder KR, *et al.* Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices – United States, 2017–18 influenza season. *Am J Transplant* 2017; 17: 2970–2982.
 157. Steinhoff MC, Omer SB, Roy E, *et al.* Influenza immunization in pregnancy – antibody responses in mothers and infants. *N Engl J Med* 2010; 362: 1644–1646.
 158. Madhi SA, Nunes MC and Cutland CL. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med* 2014; 371: 2340.
 159. Omer SB. Maternal immunization. *N Engl J Med* 2017; 376: 1256–1267.
 160. Regan AK, de Klerk N, Moore HC, *et al.* Effectiveness of seasonal trivalent influenza vaccination against hospital-attended acute respiratory infections in pregnant women: a retrospective cohort study. *Vaccine* 2016; 34: 3649–3656.
 161. Thompson MG, Li DK, Shifflett P, *et al.* Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010–2011 and 2011–2012 influenza seasons. *Clin Infect Dis* 2014; 58: 449–457.
 162. Palmeira P, Quinello C, Silveira-Lessa AL, *et al.* IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol* 2012; 2012: 985646.
 163. Katz J, Englund JA, Steinhoff MC, *et al.* Impact of timing of influenza vaccination in pregnancy on transplacental antibody transfer, influenza incidence, and birth outcomes: a randomized trial in rural Nepal. *Clin Infect Dis* 2018; 67: 334–340.
 164. Dabrera G, Zhao H, Andrews N, *et al.* Effectiveness of seasonal influenza vaccination during pregnancy in preventing influenza infection in infants, England, 2013/14. *Euro Surveill* 2014; 19: 20959.
 165. Benowitz I, Esposito DB, Gracey KD, *et al.* Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis* 2010; 51: 1355–1361.
 166. Black SB, Shinefield HR, France EK, *et al.* Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. *Am J Perinatol* 2004; 21: 333–339.
 167. Naleway AL, Irving SA, Henninger ML, *et al.* Safety of influenza vaccination during pregnancy: a review of subsequent maternal obstetric events and findings from two recent cohort studies. *Vaccine* 2014; 32: 3122–3127.
 168. Nordin JD, Kharbanda EO, Benitez GV, *et al.* Maternal influenza vaccine and risks for preterm or small for gestational age birth. *J Pediatr* 2014; 164: 1051–1057. e2.
 169. Omer SB, Goodman D, Steinhoff MC, *et al.* Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. *PLoS Med* 2011; 8: e1000441.
 170. Donahue JG, Kieke BA, King JP, *et al.* Association of spontaneous abortion with receipt of inactivated influenza vaccine containing

- H1N1pdm09 in 2010–11 and 2011–12. *Vaccine* 2017; 35: 5314–5322.
171. Chambers CD, Xu R and Mitchell AA. Commentary on: “Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12”. *Vaccine* 2017; 35: 5323–5324.
172. Ault KA and Riley LE. Response to Donahue et al. 2017 in press article. *Vaccine* 2018; 36: 2230.
173. Regan AK, Moore HC and Sullivan SG. Does influenza vaccination during early pregnancy really increase the risk of miscarriage? *Vaccine* 2018; 36: 2227.
174. Savitz DA, Fell DB, Ortiz JR, *et al.* Does influenza vaccination improve pregnancy outcome? Methodological issues and research needs. *Vaccine* 2015; 33: 6430–6435.
175. Steinhoff MC, Katz J, Englund JA, *et al.* Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. *Lancet Infect Dis* 2017; 17: 981–989.
176. Fell D, Platt R, Lanes A, *et al.* Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. *BJOG* 2015; 122: 17–26.
177. Hutcheon JA, Fell DB, Jackson ML, *et al.* Detectable risks in studies of the fetal benefits of maternal influenza vaccination. *Am J Epidemiol* 2016; 184: 227–232.