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Review

Who and when to vaccinate against influenza

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ABSTRACT

Known since Hippocrates and of continuing public health importance, influenza remains a major cause of morbidity and mortality worldwide, and large segments of the human population are affected every year. Vaccination is the most effective means of preventing influenza infection. Today, many countries have implemented annual influenza vaccination programs, and there is increasing awareness of the potential societal and health benefits of vaccinating pregnant women, children aged 6 months to 5 years, older adults, and persons with underlying medical conditions that make them vulnerable to serious complications of influenza. In this non-systematic review, we summarize data on influenza epidemiology and influenza vaccine immunogenicity, efficacy/effectiveness, and safety in the main high-risk groups. We also discuss the optimal time to vaccinate and the effect of pre-existing immunity on vaccine response.

Introduction

In its 2012 recommendations, the World Health Organization (WHO) recognized that decisions on the use of influenza vaccines should be determined by national capacity and resources. However, for countries considering initiation or expansion of seasonal influenza vaccination programs, the WHO recommends that pregnant women should have the highest priority (WHO, 2012). Other risk groups to be considered include children aged 6–23 months, children aged 2–5 years, older adults (≥65 years), persons with specific chronic diseases, and residents of nursing homes and other long-term care facilities. Additionally, several countries recommend vaccination of indigenous populations, such as native Americans and native Alaskans in the United States (Grohskopf et al., 2018), the Aboriginal and Torres Strait Islander people of Australia (Australian Technical Advisory Group on Immunisation (ATAGI), 2018), and the indigenous people of Canada (National Advisory Committee on Immunization (NACI), 2019). Healthcare workers are not at higher risk of the complications of influenza compared to the general population, but should be vaccinated as part of infection control strategies in healthcare facilities. By contrast, infants younger than 6 months are at high risk of severe disease, but are not eligible to receive influenza vaccines due to limited effectiveness in this age group (WHO, 2012).

A large observational study in the United States found that influenza vaccination in at-risk groups provided levels of protection approaching those reported in healthy individuals, particularly in children <18 years, in whom vaccine effectiveness was 51% (95% confidence interval (CI) 39–61%) in those with high-risk conditions versus 52% (95% CI 44–58%) in healthy children (Shang et al., 2018). In adults ≥18 years, vaccine effectiveness was 38% (95% CI 30–45%) in those with a high-risk condition versus 44% (95% CI 38–50%) among those without. Although solid data are not available for all individual high-risk groups, this study supports current recommendations for annual vaccination of patients with high-risk conditions (Shang et al., 2018).

In this non-systematic opinion review we summarize data on influenza epidemiology and influenza vaccine immunogenicity, efficacy/effectiveness, and safety in key high-risk groups. We also discuss the optimal time to vaccinate and the effect of pre-existing immunity on vaccine response (Figure 1).

Pregnant women

Influenza infection is frequent during pregnancy and is estimated to affect up to 11% of pregnant women (Fiore et al., 2009; Irving et al., 2000). Pregnant women are at increased risk of severe and complicated influenza because of the physiological and immunological changes that occur during pregnancy, such as increased heart rate, stroke volume, and oxygen consumption, and

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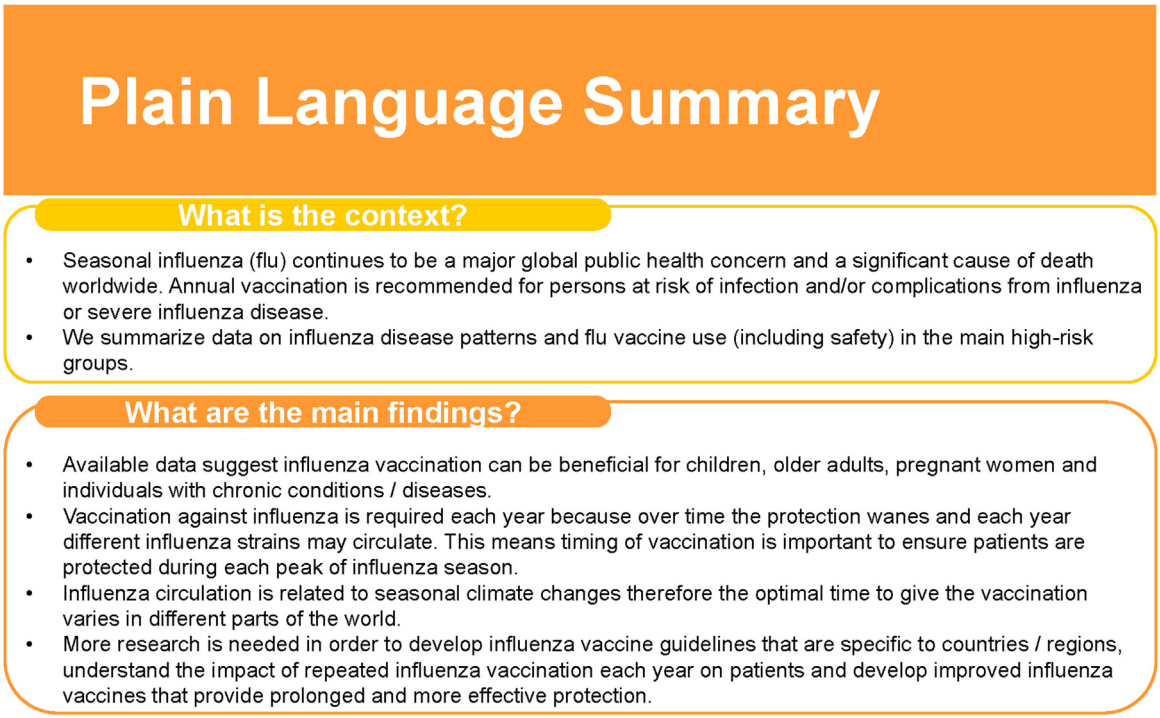

Figure 1.

reduced pulmonary capacity, which increase the risk of hypoxia. Additionally, structural changes, for instance of the endometrium, and modulations of the immune system driven by hormones, cytokines, and immune cells may, together with all the physiological changes, contribute to the increased severity of influenza infections observed in pregnant women (Vojtek et al., 2018). This has been particularly evident during influenza pandemics. Influenza-related mortality in pregnant women reached 27% during the 1918 'Spanish flu' pandemic, and during the 1957 pandemic, 50% of deaths among women of reproductive age were in those who were pregnant (Kourtis et al., 2014). During the 2009 pandemic, pregnant women accounted for 5% of influenza-related deaths in the United States, although they only represented approximately 1% of the population (Rasmussen et al., 2012). A systematic review and meta-analysis of 152 observational studies conducted mostly during the 2009 pandemic concluded that the odds ratio (OR) for hospitalization in influenza-infected pregnant versus non-pregnant women was 2.44 (95% CI 1.22–4.87). The authors did not observe a significantly increased risk of mortality (OR 1.04, 95% CI 0.81–1.33), although four out of the seven ecological studies identified by the review did report higher mortality in pregnant than non-pregnant women (Mertz et al., 2017).

The few available data describing seasonal influenza disease in pregnant women also support a higher disease burden in this population. In Spain between 2010 and 2016, the risk of hospitalization with severe influenza was almost eight times higher in pregnant than in non-pregnant women of reproductive age (Mazagatos et al., 2018). The presence of comorbidities increased the risk of a respiratory illness among hospitalized pregnant women during influenza seasons by a factor of three (Cox et al., 2006). Women who experience severe influenza during pregnancy are more likely to have adverse fetal outcomes. In 2009, pregnant women admitted to intensive care units (ICU) with H1N1 infection in the United States were more likely to have a preterm delivery (adjusted relative risk (aRR) 3.9, 95% CI 2.7–5.6), a low birthweight infant (aRR 4.6, 95% CI 2.9–7.5), or an infant with a 5-minute Apgar score of $\leq$6 (a clinical score of immediate neonatal well-being determined 5 min after delivery, with a score $\leq$6 indicating that medical attention is needed) (aRR 8.7, 95% CI 3.6–21.2) than women who did not report influenza during pregnancy (Newsome et al., 2019).

Controlled clinical studies in pregnant women are infrequently performed because theoretical safety concerns are outweighed by the risk of disease (Jones and Heath, 2014). The antibody response to influenza vaccine in pregnant and non-pregnant women is similar (Englund et al., 1993; Murray et al., 1979; Sumaya and Gibbs, 1979), except for HIV-infected pregnant women who have a lower and less persistent immune response to vaccination compared with uninfected women (Nunes et al., 2015). Nevertheless, the vaccine efficacy (VE) of trivalent inactivated influenza vaccine (IIV3) appears to be comparable, and was 50.4% (95% CI 14.5–71.2%) in HIV-non-infected women versus 57.7% (95% CI 0.2–82.1%) in HIV-infected pregnant women in South Africa (Madhi et al., 2014). A multi-country study conducted across multiple influenza seasons (2010–2016) found that vaccination prevented 40% (95% CI 12–59%) of laboratory-confirmed influenza hospitalizations during pregnancy (Thompson et al., 2019). This is lower than estimates of 70.3% (95% CI 42.2–85.8%) in preventing laboratory-confirmed influenza in pregnant women in Mali, and 70% (95% CI 66–75) in Norway (Tapia et al., 2016; Haberg et al., 2013), possibly because of antigenic mismatches between the vaccine composition and circulating strains during some seasons (Thompson et al., 2019).

Influenza vaccines have been used in pregnancy in the United States since the 1950s and have a long history of safety assessment (Jones and Heath, 2014). Numerous studies have established the favorable safety profile of administering inactivated influenza vaccines during pregnancy, based on the absence of an increased risk of adverse events in pregnant women, the fetus, and the infant (Nordin et al., 2013; Asavapiriyanont et al., 2018; Tamma et al., 2009; Regan, 2016). For instance, no pattern of adverse outcomes was reported among 2.4 million pregnant women vaccinated in the United States in 2009–2010 (Munoz,

2012), and no increase in fetal death rate was observed in Denmark following the administration of an adjuvanted monovalent H1N1 influenza vaccine to 7000 women during the 2009 pandemic (Pasternak et al., 2012).

Children aged <6 months: maternal immunization

An equally important goal of maternal immunization is the prevention of influenza infections in infants <6 months of age, who are particularly vulnerable to severe disease but too young to receive vaccination. Protection in this age group relies on transplacental transfer of antibodies from the mother (Jones and Heath, 2014; WHO, 2012). In the United States, the hospitalization rate for confirmed influenza in children aged 0–5 months was 4.5 (95% CI 3.4–5.5) per 1000 children, compared with 0.3 per 1000 in children aged 2–5 years (Poehling et al., 2006). Vaccination of pregnant women prevented 56.8%, 63%, and 71% of influenza infections in infants <6 months of age in Denmark, Bangladesh, and England, respectively (Mølgaard-Nielsen et al., 2019; Zaman et al., 2008; Dabrera et al., 2014).

Children aged 6 months to 5 years

A systematic review and meta-analysis estimated that in 2008, in children ≤5 years of age, there were an estimated 90 million new episodes of influenza, 1 million influenza-related acute lower respiratory infections, and 28 000–111 500 deaths worldwide (Nair et al., 2011). The majority of hospitalizations for influenza occurred in otherwise healthy children (Chaves et al., 2014).

Children can be vaccinated with IIVs from the age of 6 months or with live-attenuated influenza vaccines (LAIVs) from the age of 2 years (Table 1), although vaccine availabilities and specific recommendations vary by country. When a child is vaccinated for the first time, two doses given at least 1 month apart are required to ensure protection (Shen et al., 2013). With some exceptions, such as MF59-adjuvanted influenza vaccine in Canada, influenza vaccines including recombinant, adjuvanted, and high-dose influenza vaccines are not approved for use in children at this time (Mameli et al., 2019).

A Cochrane review until 2016 concluded that IIV VE in preventing laboratory-confirmed influenza in healthy children aged 2–16 years was 59% (95% CI 41–71%) (Jefferson et al., 2018). However, only one small study described VE in children aged <2 years (Jefferson et al., 2018). Since the publication of the Cochrane review, a case–control study conducted in the United States in each influenza season from 1999–2000 to 2006–2007, reported IIV3 VE as 86% (95% CI 29–97%) in children aged 6–59 months (Joshi et al., 2009), and other large randomized controlled trials have evaluated VE of quadrivalent inactivated influenza vaccines (IIV4s) in children aged 6–35 months. In a multi-country study of 12 018 children aged 6–35 months conducted between 2011 and 2014, IIV4 VE was 63% (97.5% CI 52–72%) against moderate-to-severe influenza, 78% (97.5% CI 64–87%) against vaccine matched strains, and 50% (97.5% CI 42–57%) against all PCR-confirmed influenza cases (Claeys et al., 2018). In another study conducted in infants 6–35 months old during the 2014–2015 and 2015–2016 Northern hemisphere influenza seasons and 2014 and 2015 Southern hemisphere influenza seasons, IIV4 VE was 51% (97% CI 37–62%) against influenza caused by any A or B type and 68.4% against vaccine-like strains (97% CI 47–82%) (Pepin et al., 2019).

Estimates of VE using LAIVs are variable but overall, LAIVs are thought to reduce the risk of influenza in children 3–16 years of age by between 4% and 18% (Jefferson et al., 2018). LAIVs have a checkered history of use in the United States, where the Advisory Committee on Immunization Practices preferentially recommended LAIV over IIVs for children for 1 year (Grohskopf et al., 2014), withdrew the preferential recommendation the following year (Grohskopf et al., 2015), then withdrew any recommendation at all for several years (2016–2018) on the basis of low VE estimates for some vaccine types (Jhaveri, 2018; Small and Cronin, 2017). LAIV use continued uninterrupted in other countries. In the UK, in the 2015–2016 influenza season, the adjusted vaccine effectiveness in preventing hospitalization due to any influenza types was better for the quadrivalent LAIV (41.9%, 95% CI 7.3–63.6) than for the IIV4 (28.8%, 95% CI −31.1 to 61.3) in 2–16-year-olds, and was 30.0% (95% CI −10.7 to 55.7) in 2–6-year-olds (no estimate for IIV4 provided for this age group) (Boddington et al., 2019). In the following season in the UK (2016–2017), vaccine effectiveness in 2–17-year-olds was 65.8% (Jhaveri, 2018).

Large clinical trials and surveillance studies in several countries and covering a range of seasons support the favorable safety profile of IIV in children. The most common adverse effects reported in children after IIV vaccination are pain, redness, and swelling at the injection site (Wang et al., 2016; Sullivan et al., 2019). In one study of 5806 children aged 6–35 months, the occurrence of systemic symptoms was similar in recipients of IIV4 (48.5%, 95% CI 46.0–51.0), IIV3 (49.7%, 95% CI 44.5–55.0), and placebo (46.5%, 95% CI 44.0–48.9) (Pepin et al., 2019). A study of 45 356 children 6–23 months of age who received IIV3 between 1991 and 2003 in the United States, found no increase in medically attended visits for any serious condition within 14 days after vaccination (Hambidge et al., 2006). Surveillance data from 2015 show that 4.4% of Australian children aged 6 months to 4 years vaccinated with IIV reported fever, and medically attended events were recorded in 1.1% of cases (Pillsbury et al., 2015).

LAIVs are administered intra-nasally and are well tolerated, although they may be associated with the development of fever or rhinorrhea after vaccination (Prutsky et al., 2014; Belshe et al., 2007). Ten years of data from the Vaccine Safety Datalink in the United States confirmed the acceptable safety profile of LAIVs in children and adolescents (Daley et al., 2018). The study found a significant association between LAIV and syncope and anaphylaxis (which are known vaccine-associated adverse events), although these events were rare (8.5 per million doses and 1.7 per million doses, respectively) (Daley et al., 2018). LAIV are contraindicated in immunosuppressed individuals and their close contacts (including caregivers), in young children with asthma, and in persons who have received influenza antiviral treatment within the previous 48 h (Grohskopf et al., 2018).

There is indirect evidence that vaccination of children reduces the burden of influenza amongst the wider community (Jordan et al., 2006). This was illustrated in the United States where the rate of influenza-associated hospitalizations in adults 50–64 years of age was lower in a county where immunization of school-children occurred when compared to a non-intervention county (Talbot et al., 2009), as well as in Japan where vaccination of school-age children was associated with a reduction in influenza-related deaths in adults aged ≥65 years (Reichert et al., 2001) and in the UK where vaccination of school children was associated with a significant reduction in primary care visits for influenza-like illness (ILI) in the non-targeted ≥17 years age group (Pebody et al., 2015).

Adults aged ≥65 years

Influenza has a major impact on morbidity and mortality among older adults who are disproportionately affected by influenza complications including pneumonia, hospitalizations, and death (Hannoun et al., 2004; Szucs, 1996; Simonsen et al., 1998). In total, 90% of all influenza-associated hospitalizations and deaths occur in adults aged >65 years (Thompson et al., 2003; Zhou et al., 2012). Of 291 243 to 645 843 persons who died annually from influenza-associated

Table 1
Key high-risk groups who should benefit from influenza vaccination.

High-risk groups/diseases	Examples (non-exhaustive)	Influenza vaccines recommended or contraindicated[a]
Adults ≥65 years	All	IIV, HD, aIIV recommended LAIV not recommended
Children aged 6 months to 5 years	All, especially those born preterm	IIV from 6 months LAIV from 2 years
Chronic heart disease	Congestive heart failure, congenital heart disease, acute coronary syndromes	As per age group recommendations
Chronic kidney disease	Reduced glomerular filtration rate, increased urinary albumin excretion, or both resulting from diabetes, hypertension, obesity, glomerulonephritis, etc.	As per age group recommendations
Chronic liver disease	Chronic hepatitis B or C, cirrhosis	As per age group recommendations
Chronic neurological disease and neurodevelopmental conditions	Parkinson's disease, multiple sclerosis, cerebral palsy, seizure disorders, stroke, intellectual disability, moderate to severe developmental delay, neuromuscular disorders, spinal cord injury	As per age group recommendations
Chronic respiratory disease	Asthma, chronic obstructive pulmonary disease, cystic fibrosis	In the United States, LAIV is contraindicated in children aged 2–4 years with asthma
Endocrine disorders	Type 2 diabetes, morbid obesity (body mass index ≥40 kg/m^2)	As per age group recommendations
Hospitalized patients (especially in ICUs)	Any	As per age group recommendations
Immunocompromised people	Primary immunodeficiencies: X-linked agammaglobulinaemia, selective IgA deficiency, IgG subclass deficiency, severe combined immunodeficiency diseases, complete DiGeorge syndrome, Wiskott–Aldrich syndrome, ataxia-telangiectasia, persistent complement, properdin or factor B deficiency, chronic granulomatous disease, leucocyte adhesion defect, myeloperoxidase deficiency, Down's syndrome Secondary immunodeficiencies: HIV infections, cancers, transplantations, asplenia (or sickle cell disease) and autoimmune diseases treated with immunosuppressive drugs (corticosteroids, immunomodulators, biological agents) or radiation therapy	LAIV is contraindicated
Metabolic disorders including inherited metabolic disorders, mitochondrial disorders	Phenylketonuria, maple syrup urine disease, urea cycle disorders, classic galactosemia, glycogen storage disease type 1a, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, mitochondrial myopathy, myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, MtDNA depletion syndrome, mitochondrial neuro-gastrointestinal encephalomyopathy	As per age group recommendations
People living in nursing homes, long-term care facilities, and homeless persons		As per age group recommendations
Children receiving long-term aspirin therapy		LAIV is contraindicated
Pregnant women		LAIV is contraindicated
Some ethnic groups	Native Americans, Native Alaskans, Australian Aboriginal and Torres Strait Islander people, Indigenous people of Canada	As per age group recommendations
People in direct contact with poultry infected with avian influenza during culling operations		As per age group recommendations

ICU, intensive care unit; IIV, inactivated influenza vaccine; HD, high-dose influenza vaccine; aIIV, adjuvanted inactivated influenza vaccine; LAIV, live attenuated influenza vaccine.
[a] Recommendations are purely indicative. Reference should always be made to the vaccine label and specific country recommendations.

respiratory complications between 1999 and 2015, adults aged >75 years accounted for 41% of deaths (Iuliano et al., 2018). In the United States alone, influenza is associated with an estimated economic burden of roughly 87 billion US dollars every year (Molinari et al., 2007).

Secondary bacterial infections are a frequent complication of influenza in older persons, and may be associated with high mortality (McElhaney, 2005). Influenza outbreaks are common in care facilities for older adults, with attack rates of 20–40% reported during outbreaks (Booy et al., 2012; Gaillat et al., 2009). Older adults who are not hospitalized can nevertheless experience persistent declines in function and prolonged recovery from influenza. A survey of 5014 older Canadian adults found that 39.3% of those who reported having experienced influenza during the most recent influenza season took longer than 2 weeks to recover, 21.5% reported reduced health and function during the recovery period, 13.9% were admitted to hospital, and 3.1% never fully recovered (Andrew et al., 2019). Such loss of independence imposes a further cost burden on society (Gozalo et al., 2012).

The WHO recommends annual influenza vaccination for the prevention of influenza in adults aged 65 years and older (WHO, 2012). Globally, national vaccination influenza strategies vary widely, and 45% of WHO member states had a policy for the vaccination of older adults in 2014, being lowest in Africa (3/47 member states) and highest in Europe (39/53 member states) (Ortiz et al., 2016).

Influenza vaccines are considered to be well tolerated and have demonstrated an acceptable safety profile in older adults. Serious adverse events are rare. The most common local reactions following IIV are pain, erythema, swelling, and induration at the injection site (Smetana et al., 2018). In one of the first studies to report on safety after IIV, adverse reactions were observed in 23% of patients aged >60 years versus 14% in the placebo group, with no difference in frequency of systemic reactions (11% versus 9.4%, respectively) (Govaert et al., 1993).

The combination of immune senescence that occurs with aging and the presence of co-morbidities in older persons, results in a lower immune response and reduced effectiveness of influenza vaccines that worsens with age (McElhaney, 2005). A Cochrane review of randomized clinical trials found that influenza vaccination in older persons may reduce influenza infections by 58% (95% CI 34–73%) (Demicheli et al., 2018), and observational studies

of clinical outcomes suggest that influenza vaccination of older adults is associated with significant benefits. A meta-analysis of 15 studies of community-living adults aged ≥65 years, found that influenza vaccination significantly reduced influenza and pneumonia hospitalization and mortality by 33% (95% CI 27–38%) and 47% (95% CI 25–62%), respectively, and reduced all-cause mortality by 50% (95% CI 45–56%) (Vu et al., 2002).

Providing protection against the influenza A(H3N2) strain currently appears to be a particular challenge for older adults. Immune responses to A(H3N2) appear to be most vulnerable to the negative impacts of repeated annual vaccination on vaccine effectiveness (see below). A combination of high diversity amongst the currently circulating A(H3N2) strains and a higher rate of genetic adaptations acquired *in ovo* can impact on the level of matching between the vaccine strain and circulating strain (Zost et al., 2017). Over the course of five influenza seasons in the United States (2011–2012 to 2015–2016), influenza vaccine effectiveness was similar among adults aged 18–49 years and adults ≥65 years for H1N1 and the vaccine B strain, but was lower in older adults for A(H3N2) (14%, 95% CI −14% to 36% vs 21%, 95% CI 9%–32%) (Russell et al., 2018). Similarly, over the influenza seasons spanning 2011–2012 and 2016–2017 in the UK, no efficacy against A(H3N2) was found among adults aged ≥65 years, with moderate efficacy until age 75 years for other vaccine strains (Pebody et al., 2018).

Even though immune responses to vaccination may be suboptimal in older adults, particularly those who are frail or over 75 years of age, vaccination continues to be an important tool in the prevention of severe outcomes from influenza. Several strategies have been used to improve the immune response of older persons to influenza vaccines (Andrew et al., 2017) (Figure 2). These include vaccines that contain higher amounts of antigen (high-dose), vaccine administration using alternative routes such as the intradermal route, and the inclusion of adjuvants, all of which induce higher antibody responses than standard-dose vaccines in older adults (Ng et al., 2019).

A high-dose IIV containing four times the amount of haemagglutinin antigen (60 μg per antigen) than the standard formulation (15 μg per antigen) has been developed for use in adults from the age of 65 years, but has been licensed in a limited number of countries to date, including the United States, Canada, and Australia. A meta-analysis in 2017 found only two studies that compared vaccine effectiveness of the high- versus the standard-dose vaccine in older adults (Wilkinson et al., 2017). The high-dose vaccine was associated with a 24% reduction in laboratory-confirmed influenza versus the standard-dose vaccine, and other outcomes such as hospitalization and mortality were not studied. In a later database study in the United States, the high-dose influenza vaccine prevented 30.7% (95% CI 8–48%) more hospitalizations due to influenza than the standard-dose vaccine in older adults (Robison and Thomas, 2018). Additional studies are needed to quantify the benefits of the high-dose vaccine in community-living and frail older adults.

An intradermal IIV3 has been licensed for use in older adults since 2010. Intradermal administration aims to enhance innate immune responses by recruiting dermal populations of dendritic cells and their efficient migration to draining lymph nodes via the dermal vascular network (Durando et al., 2011). Despite evidence of improved immunogenicity compared to standard IIV (Ng et al., 2019), evidence of superior effectiveness is lacking to date.

MF59 is a squalene-based oil-in-water emulsion, and the MF59-adjuvanted IIV was specifically developed to improve the immune

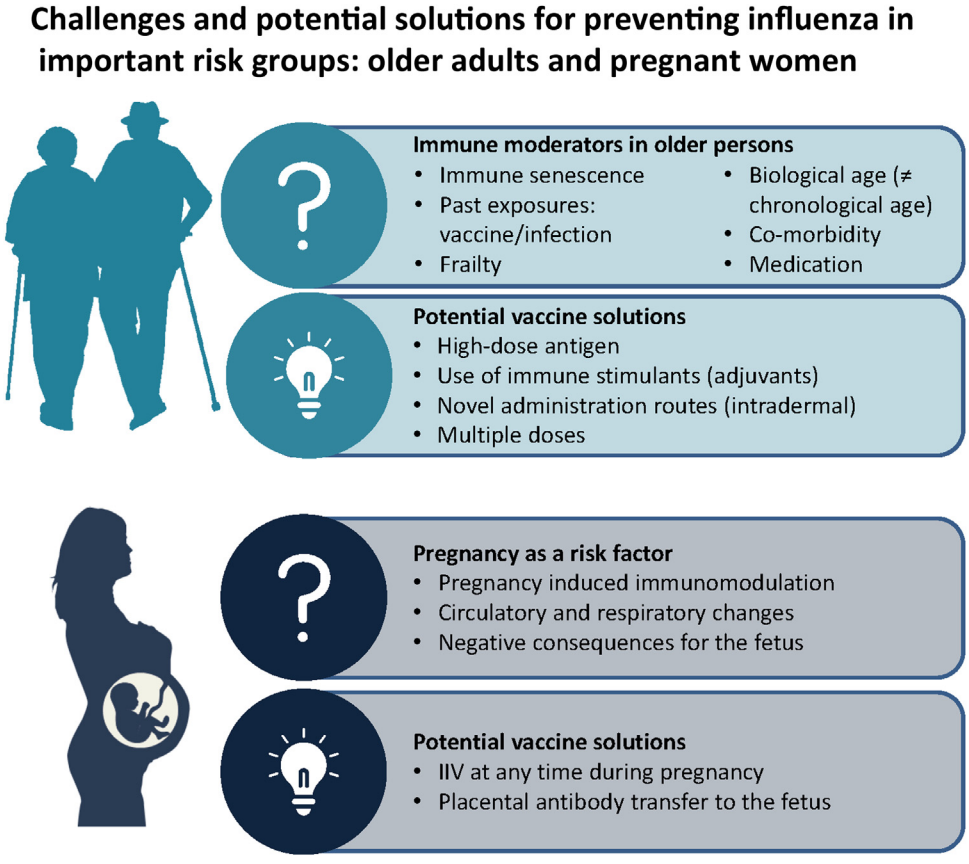

Figure 2. IIV, inactivated influenza vaccine.

response of older adults to influenza vaccination. The MF59-adjuvanted IIV was first licensed in 1997 in Italy for use in adults aged ≥65 years. In a large prospective observational study conducted in northern Italy, MF59-adjuvanted IIV was associated with a 25% lower risk of hospitalization for influenza or pneumonia relative to unadjuvanted IIV (Mannino et al., 2012). MF59 increases the breadth and duration of the immune response (Nicolay et al., 2019), and reduces the risk of hospitalizations for pneumonia and cerebro/cardiovascular events when compared with non-adjuvanted vaccines (Lapi et al., 2019).

Individuals with chronic respiratory disease

The global prevalence of chronic obstructive pulmonary disease (COPD) is close to 12% in persons aged 30 years and older, and COPD causes approximately 2.9 million deaths each year (Adeloye et al., 2015; GBD 2013 Mortality and Causes of Death Collaborators, 2015). Exacerbations triggered by respiratory infections contribute to faster disease progression, hospitalization, and to COPD-associated morbidity and mortality. Influenza viruses are detected in between 2.5% to 11.6% of COPD exacerbations (Kostikas et al., 2016; Mohan et al., 2010). During the 2009 H1N1 pandemic, 32.7% of patients hospitalized in ICUs in Australia and New Zealand had pre-existing asthma or COPD (ANZIC Influenza Investigators et al., 2009). Although impaired immune responses have been reported, most studies have shown that influenza vaccination appears immunogenic in persons with COPD, meeting the criteria of the Committee for Medicinal Products for Human Use of the European Medicines Agency (reviewed in Bekkat-Berkani et al., 2017). For seasonal vaccines, these criteria are a seroconversion rate >40% in subjects aged 18–60 years and >30% in subjects older than 60 years (Committee for Proprietary Medicinal Products (CPMP), 1997). Despite sometimes contrasting results (Poole et al., 2006), numerous studies suggest a beneficial effect of influenza vaccination on clinical outcomes in patients with COPD, including a reduction in the risk of acute respiratory infection, hospitalization due to COPD, all-cause mortality, and death associated with respiratory episodes (Bekkat-Berkani et al., 2017; Sanei and Wilkinson, 2016; Kopsaftis et al., 2018). In Taiwan, persons older than 55 years with COPD who received an influenza vaccine had a lower risk of hospitalization for acute coronary syndrome, and the risk was the lowest in those who received the highest number of influenza doses during the follow-up period (adjusted hazard ratio (aHR) 0.48 (95% CI 0.38–0.62) versus 0.20 (95% CI 0.14–0.28) after 2–3 and ≥4 vaccinations, respectively) (Sung et al., 2014).

Influenza is thought to cause a proportion of acute asthma exacerbations, but estimates of this proportion vary widely due to differences in study design and illness definitions (Schwarze et al., 2018). While a Cochrane review published in 2013 did not establish that influenza vaccination was able to prevent asthma exacerbations (Cates and Rowe, 2013), a subsequent systematic review and meta-analysis found that vaccination was associated with a 59–78% reduction in asthma episodes leading to emergency visits or hospitalizations (Vasileiou et al., 2017). A study in Japan suggested that among children with asthma, the risk of physician-diagnosed influenza was significantly higher in children who had not received H1N1 vaccination compared to vaccinated children (OR 13.2, 95% CI 5.6–32.1). Vaccine effectiveness against physician-diagnosed influenza was estimated to be 92% (95% CI 81–96%) in children with asthma (Yokouchi et al., 2014).

The authors of a recent systematic review reported the acceptable safety profile of influenza vaccines in persons with COPD (Bekkat-Berkani et al., 2017). In Thailand, a randomized clinical trial detected an increased frequency of local adverse events in COPD patients who received influenza vaccine versus placebo, but there was no increased risk of systemic adverse reactions or COPD exacerbations, reduced lung function, dyspnea, or reduced exercise capacity of the vaccinees (Wongsurakiat et al., 2004). Two trials that included 2238 children and adults in total, excluded clinically important increases in asthma exacerbations in the 2 weeks following influenza vaccination (Cates and Rowe, 2013).

In addition to the WHO and US Centers for Disease Control and Prevention (CDC) recommendations for the influenza vaccination of persons with chronic pulmonary disease, the Global Initiative for Chronic Obstructive Lung Disease also recommends vaccination for all patients with COPD (Global Initiative for Chronic Obstructive Lung Disease, 2019). The Global Initiative for Asthma recommends influenza vaccination for persons with moderate to severe asthma (Global Initiative for Asthma, 2018).

Individuals with cardiovascular disease

In 2016, an estimated 17.9 million people died of cardiovascular disease, representing 31% of all deaths globally. Myocardial infarction and cerebrovascular accident accounted for 85% of these deaths (WHO, 2017a). Influenza infection can have adverse impacts on individuals with underlying cardiovascular disease. Deaths by stroke and myocardial infarction increase by approximately 10–15% during the winter months when influenza is circulating in the Northern hemisphere (Johnstone et al., 2012). The risk of myocardial infarction was six times higher within 7 days of detection of influenza, compared with control intervals spanning 1 year before or 1 year after infection (Kwong et al., 2018).

The mechanisms through which influenza increases cardiovascular risk are not fully elucidated and may include, among others, modifications to the inflammatory and coagulation pathways, autoimmune mechanisms, endothelium dysfunction, and fever-induced tachycardia (Nguyen et al., 2016; Howard and Kleoppel, 2013). The response to IIV has been investigated in patients with heart failure, and although seroprotection rates were not statistically different compared with healthy controls, the humoral response was lower for the A(H3N2) antigen, interleukin-10 production was higher (Vardeny et al., 2009), and titres waned faster in those with heart failure (Albrecht et al., 2014).

In a Cochrane review conducted in 2015, influenza vaccination significantly reduced overall cardiovascular mortality in patients with coronary heart disease (RR 0.45, 95% CI 0.26–0.76) (Clar et al., 2015). In a large multi-country study enrolling over 8000 patients with heart failure, influenza vaccination was associated with a reduction in all-cause mortality (HR 0.81, 95% CI 0.67–0.97) (Vardeny et al., 2016). More recently, Mosheni et al. demonstrated that patients with heart failure were 27% less likely to be hospitalized for cardiovascular disease if they were vaccinated against influenza (Mosheni et al., 2017). A systematic review and meta-analysis of observational studies evaluating 179 158 patients with heart failure observed that influenza vaccination was associated with a lower risk of all-cause mortality (HR 0.83, 95% CI 0.76–0.91) (Rodrigues et al., 2020).

In addition to the WHO and US CDC guidelines, influenza vaccination is recommended for persons with cardiovascular disease by a range of societies, such as the American Heart Association and the European Society of Cardiology (American Heart Association, 2015; Piepoli et al., 2016).

Individuals who are obese

The WHO estimated that in 2016, more than 650 million adults >18 years of age, or approximately 13% of the global adult population, were obese (WHO, 2018a). The prevalence of obesity has tripled since 1975. Obesity in children is also increasing, and affected 6% and 8% of 5–19-year-old girls and boys, respectively, in

2016 (WHO, 2018a). Obesity is often associated with other co-morbidities such as type 2 diabetes and cardiovascular disease, which are documented risk factors for morbidity and mortality following influenza infection (Tagliabue et al., 2016). Mechanical and physiological changes such as altered ventilation, reduced expectoration, and gastroesophageal reflux are frequently associated with obesity and predispose patients to respiratory infections (Tagliabue et al., 2016). Obesity also leads to complex modifications of the immune response, resulting from the effects ofadipokines, cytokines, free fatty acids, and infiltration of adipose tissue by some immune cells causing low-grade chronic inflammation (Fisher-Hoch et al., 2013). The H1N1 pandemic highlighted obesity as a major risk factor for mortality from influenza infection. In a large international study conducted during the last influenza pandemic, 6% of hospitalized patients, 11.3% of patients admitted to ICUs, and 12% of those who died were obese (Van Kerkhove et al., 2011).

Obese individuals generally respond adequately to influenza vaccination and achieve antibody titres that are not significantly different from healthy weight individuals (Callahan et al., 2014). However, higher body mass index appears to be associated with a faster decline in antibody titres at 12 months post-vaccination (Sheridan et al., 2012). Nevertheless, a prospective observational study found that compared with vaccinated healthy weight adults, vaccinated obese individuals were twice as likely to develop influenza or ILI compared with healthy weight individuals (RR 2.01, 95% CI 1.12–3.60) (Neidich et al., 2017). The authors suggested that current correlates of protection may not be relevant for obese persons. On the other hand, a study in children observed similar levels of protection provided by influenza vaccination in obese and healthy weight individuals (Smit et al., 2016). Local and systemic adverse events occurred with a comparable frequency in obese and healthy weight children after IIV vaccination, and no serious adverse events were recorded (Esposito et al., 2016).

Individuals with diabetes

The WHO reports that diabetes affected 422 million persons in 2014 and caused the death of an estimated 1.6 million persons in 2016. The global prevalence of diabetes almost doubled between 1980 and 2014, from 4.7% to 8.5% (WHO, 2018b). Diabetes is believed to cause a chronic inflammatory syndrome that adversely affects both innate and adaptive immunity and the ability to effectively control infections (Fisher-Hoch et al., 2013).

During the 2009 H1N1 pandemic among Canadian patients hospitalized with influenza, the risk of ICU admission was 4.3-fold higher in patients with diabetes (OR 4.3, 95% CI 1.3–14.3) (Allard et al., 2010). Among 252 fatal influenza cases associated with laboratory-confirmed influenza during the 2009 H1N1 pandemic in Germany, patients with diabetes were 2.3 (95% CI 1.5–3.6) times as likely to die from pandemic H1N1 virus infection than individuals without diabetes (Wilking et al., 2010).

There have been several reviews and a meta-analysis that have evaluated studies reporting the immunogenicity, safety, and effectiveness of influenza vaccine in persons with diabetes versus without diabetes (Dos Santos et al., 2018; Remschmidt et al., 2015). In the most recent review of 15 studies, the authors concluded that the immune response and safety profile following vaccination were similar in persons with and without diabetes (Dos Santos et al., 2018). A systematic review and meta-analysis of 11 observational studies that included 170 924 participants found that in persons aged 18–64 years with diabetes, pooled vaccine effectiveness was 58% (95% CI 6–81%) against all-cause hospitalization and 43% (95% CI 28–54%) against hospitalization for influenza or pneumonia (Remschmidt et al., 2015). No impact on all-cause mortality was observed. In older adults aged 65 years or over with diabetes, the pooled vaccine effectiveness was 38% (95% CI 32–43%) against all-cause mortality, 45% (95% CI 34–53%) against hospitalization due to influenza or pneumonia, and 13% (95% CI 10–16%) against ILI (Remschmidt et al., 2015). In the United States, adjusted vaccine effectiveness against any influenza infection was not different in persons with diabetes (46%, 95% CI 30–58%) compared with persons without high-risk conditions (48%, 95% CI 43–52%) (Shang et al., 2018).

Influenza vaccine appears to be well-tolerated in persons with diabetes (Seo et al., 2015).

Individuals with chronic kidney disease

Worldwide, chronic kidney disease (CKD) affects 8–16% of the adult population (Jha et al., 2013). It is estimated that 5–10 million persons die each year from kidney disease, including 2.7 to 7.1 million persons who die annually from end-stage renal disease without access to chronic dialysis (Luyckx et al., 2018). CKD is associated with alterations of the immune system due to reductions in the number of B and CD4+ T lymphocytes, impaired T-cell response to antigens, and impaired neutrophil function, including decreased phagocytic capacity and increased rates of apoptosis (Ishigami and Matsushita, 2019). Patients receiving dialysis who developed A(H1N1) infection experienced higher hospitalization rates (34% versus 6–7%) and mortality (approximately 5% versus 0.2–0.5%) than historical cohorts of the general population (Marcelli et al., 2009).

Most studies report lower seroprotection and seroconversion rates as well as lower geometric mean antibody titres after influenza vaccination in persons with end-stage renal disease compared to healthy individuals (Principi et al., 2015). Interestingly, Sharpé et al. found than more than 80% of persons receiving hemodialysis reached seroprotective levels after vaccination, which was comparable with the response observed in healthy individuals (Sharpé et al., 2009). In a study of patients with CKD undergoing dialysis in Korea, the seroconversion rate after MF59-adjuvanted influenza vaccine was significantly higher than after non-adjuvanted IIV at 1 month post-vaccination (47.7% versus 17.4% for A(H1N1), 42.0% versus 16.3% for A (H3N2), and 31.8% versus 7.0% for B), although the increase was only significant for type B in patients aged $\geq$65 years (33.3% versus 7.1% for B) (Noh et al., 2016). In patients with end-stage renal disease, booster doses do not significantly improve the immune response obtained after the first dose, even when an adjuvanted vaccine is used (Tanzi et al., 2007; Versluis et al., 1985).

In a systematic review, influenza vaccine effectiveness in persons with end-stage renal disease was 32% (95% CI 24–39%) against all-cause mortality, 16% (95% CI 1–29%) against cardiac death, 81% (95% CI 63–86%) against ICU admission, and 14% (95% CI 7–20%) against hospitalization for influenza or pneumonia (Remschmidt et al., 2014). In patients with CKD aged 55 years or older, the risk of hospitalization for heart failure decreased with the number of influenza vaccines received during the study follow-up. The aHR was 0.60 (95% CI 0.47–0.77) in those who received one influenza vaccination during the follow-up period, 0.30 (95% CI 0.23–0.41) for two to three vaccinations, and 0.10 (95% CI 0.06–0.16) for at least four vaccinations (Fang et al., 2016).

The reactogenicity and safety profile of influenza vaccines administered to adults and children with end-stage renal disease appear to be similar to those observed in healthy individuals (Principi et al., 2015). No association has been observed between influenza vaccination and acute rejection in patients with kidney transplant, or vaccination and decreased renal function in those with CKD (Principi et al., 2015).

Individuals with chronic liver disease

Worldwide, liver disease causes an estimated 2 million deaths per year, 1 million of which are from cirrhosis and 1 million a

consequence of viral hepatitis and liver cancer (Asrani et al., 2019). In 22 patients with chronic liver disease (CLD), mortality caused by pneumonia or acute respiratory syndrome was 81.8% in those persons with influenza A(H1N1) infection compared with 40% in persons with a respiratory infection unrelated to influenza (Premkumar et al., 2019). During the 2017–2018 influenza epidemic in Germany, patients with liver cirrhosis infected by an influenza virus had higher liver-specific and non-specific organ failure scores, experienced more severe influenza, and a higher proportion died (two deaths, 18%) compared with patients with no underlying liver disease (one death, 3%). Additionally, five out of 11 patients with CLD and influenza infection developed acute-on-chronic liver failure (Schütte et al., 2019). Influenza virus may damage the liver directly or through immune-mediated mechanisms (Premkumar et al., 2019).

In persons with chronic hepatitis C, a single dose of monovalent H1N1 pandemic vaccine induced seroconversion in 72% of patients with a mean fold increase in antibodies of 10.3. A lower humoral response was associated with older age, low body mass index, and use of steroid-like medicines (such as Stronger Neo-Minophagen C) (Ohfuji et al., 2013). In a small study, immunogenicity of adjuvanted IIV was compared between patients with chronic hepatitis B or C and healthy age-matched controls. Seroconversion (defined as a four-fold increase in hemagglutinin-inhibition antibody titres) was observed in 75% to 85% of persons with liver disease versus 100% of controls (Gaeta et al., 2002). In a later study, the authors compared the immune response to IIV in three different groups of patients with CLD. Seroconversion for each vaccine strain was present in 42.1% to 68.4% of persons with cirrhosis receiving treatment, 37.5% to 56.3% of liver transplant recipients, and 43.5% to 91.3% of persons with cirrhosis who were not receiving treatment (Gaeta et al., 2009).

During the 2009 pandemic, vaccination of patients with chronic hepatitis C with a monovalent inactivated H1N1 pandemic vaccine decreased the likelihood of hospitalization. Of 28 patients hospitalized with chronic hepatitis C, six were vaccinated and 22 were unvaccinated (OR 0.43, 95% CI 0.16–1.17) (Ohfuji et al., 2014). In patients with chronic hepatitis B virus infection, influenza vaccination was associated with a lower risk of hospitalization (aHR 0.56, 95% CI 0.50–0.62), pneumonia and influenza (aHR 0.79, 95% CI 0.67–0.92), ICU admission (aHR 0.33, 95% CI 0.25–0.43), and mortality (aHR 0.19, 95% CI 0.15–0.24) (Su et al., 2016). Protection against ILI and culture-positive influenza infection was clearly demonstrated in patients with liver cirrhosis vaccinated with IIV in Korea: influenza virus was isolated in 2.3% of vaccinated persons versus 8.8% of those who were unvaccinated (OR 0.24, 95% CI 0.07–0.82). The incidence of ILI was 14.3% in vaccinees versus 23.3% in unvaccinated persons (p = 0.064) (Song et al., 2007).

The reactogenicity and safety profile of an adjuvanted influenza vaccine was similar in vaccine recipients with chronic hepatitis B and C and in healthy control subjects, with mild and transient erythema at the injection site following vaccination (Gaeta et al., 2002). Persons with cirrhosis or liver transplant vaccinated with an unadjuvanted IIV3 developed mild erythema and local pain in 35% of cases, and there were no alterations in liver function tests or clinically significant events related to liver disease (Gaeta et al., 2009).

Individuals with chronic neurological disease

Neurological disorders account for an estimated 9.4 (95% CI 9.1–9.7) million deaths per year worldwide, representing the second leading cause of death (16.8% of global deaths). The global prevalence of Alzheimer's disease and other dementias, stroke, Parkinson's disease, epilepsy, and multiple sclerosis is estimated at 46 million, 42.4 million, 6.2 million, 23.4 million, and 2 million cases, respectively (GBD 2015 Neurological Disorders Collaborator Group, 2017GBD 2015 Neurological Disorders Collaborator Group, 2017). In a large cohort of patients, multiple sclerosis was associated with an increased aRR of hospitalization for influenza of 3.57 (95% CI 3.06–4.15) (Montgomery et al., 2013). During the 2009 pandemic in the United States, 43% of the children who died from influenza had underlying neurological disorders (Blanton et al., 2012). In patients with relapsing–remitting multiple sclerosis, influenza was associated with an acute relapse in 33% of infected patients (De Keyser et al., 1998). Persons with neurological diseases, especially those suffering from neuromuscular disorders, may experience difficulties with respiratory secretions, putting them at higher risk of developing severe influenza (Krammer et al., 2018).

Individuals with immunocompromising conditions

Primary immunodeficiency disorders can be hereditary or genetic and encompass a broad range of defects of varying severity, such as disorders that impact B cells and the production of antibodies (e.g., X-linked agammaglobulinaemia, selective IgA deficiency, and IgG subclass deficiency), T cells and cell-mediated and humoral responses (e.g., severe combined immunodeficiency diseases, complete DiGeorge syndrome, Wiskott–Aldrich syndrome, ataxia-telangiectasia), complement (e.g., persistent complement, properdin, or factor B deficiency), and phagocytic function (e.g., chronic granulomatous disease, leucocyte adhesion defect, myeloperoxidase deficiency). Secondary immunodeficiencies are generally acquired and result from a disease or its treatment. These include HIV infections, cancers, transplantation, asplenia (or sickle cell disease), and autoimmune diseases treated with immunosuppressive drugs (corticosteroids, immunomodulators, biological agents) or radiation therapy. HIV-infected adults with a CD4+ T-cell count <200 cells/mm^3, persons with advanced Hodgkin's disease, and recipients of hematopoietic stem transplants are considered among the most immunocompromised groups (Miller and Rathore, 2012; Rubin et al., 2014; Doherty et al., 2016).

Influenza-related hospitalization rates are four-times higher and mortality rates are 10-times higher among people with cancer compared with the general population (Cooksley et al., 2005). Influenza and its complications may also delay or lead to cancellation of chemotherapy, with possible consequences for cancer outcomes (Eliakim-Raz et al., 2013). During the 2009 pandemic, H1N1 infections were associated with a high incidence of pneumonia (66%) and 30-day mortality (18.5%) in patients with hematological cancers and solid tumors treated by chemotherapy or stem cell transplantation (Dignani et al., 2014).

As anticipated, the immunogenicity of influenza vaccines is overall reduced in immunocompromised persons (Zbinden and Manuel, 2014). The immunogenicity of a monovalent influenza A(H1N1) vaccine was compared in Thailand between healthy individuals, HIV-infected individuals undergoing antiretroviral therapy, and kidney transplant recipients. The seroconversion and seroprotection rates were respectively 70.8% and 74.2% amongst healthy individuals, 29.6% and 42% amongst HIV-infected persons, and 32.3% and 37.1% in kidney transplant recipients (Watcharananan et al., 2014). Standard-dose and high-dose IIV3s were compared in children and young adults with cancer or HIV. The high-dose vaccine was more immunogenic than the standard-dose vaccine in persons with leukemia or solid tumor, but not in persons with HIV (Hakim et al., 2016).

Despite the low number of studies included, a Cochrane review reported that the evidence is in favor of vaccinating immunosuppressed adults with cancer against influenza, and that vaccination has an acceptable safety profile in this population (Bitterman et al., 2018). In an observational study in cancer patients undergoing active chemotherapy treatment, influenza vaccination was associated with an aHR for death of 0.88 (95% CI 0.77–0.99) (Earle, 2003).

In a study of persons with solid malignancies undergoing chemotherapy or hematological malignancies, influenza vaccination was associated with an adjusted OR for death of 0.43 (95% CI 0.26–0.71) (Vinograd et al., 2013). In a randomized controlled trial, vaccinated patients with multiple myeloma undergoing active treatment experienced significantly fewer ILI episodes and reduced rates of pneumonia and hospitalization than unvaccinated patients (Musto and Carotenuto, 1997). In Canadian adults with cancer (mean age 70 years), influenza vaccine effectiveness was 25% (95% CI 18–31%) in persons with solid tumors and 8% (95% CI −5% to 19%) in those with hematological malignancies. Active chemotherapy did not significantly affect vaccine effectiveness (Blanchette et al., 2019). In children with cancer, the effectiveness of IIV3 was 72% (95% CI 26–94%). No serious adverse events were observed and few children (3%) reported symptoms after vaccination (Kotecha et al., 2016).

Considering the increased morbidity and mortality of influenza in immunocompromised persons and the suboptimal response to influenza vaccination in these populations, novel vaccine strategies such as the use of adjuvants, multiple doses, or high-dose vaccines, as well as different routes of administration (e.g., intradermal), warrant exploration through further studies (Zbinden and Manuel, 2014).

Inactivated influenza vaccines are generally well tolerated in persons who are immunocompromised, with reactogenicity limited to local inflammatory reactions in the majority (Zbinden and Manuel, 2014). In most cases, IIV are recommended and can be used safely, except in some specific situations such as in patients with cancer undergoing intensive chemotherapy or those who are receiving or have received anti-B cell antibodies within the last 6 months. In solid organ transplant recipients, IIV can be given $\geq$1 month after transplantation in response to a disease outbreak (Doherty et al., 2016). Live-attenuated vaccines are contraindicated in severely immunocompromised persons because of the risk of disseminated viral infection.

Considering the wide variety of immunocompromising conditions, it is prudent to refer to national or international guidelines such as those edited by the Infectious Diseases Society of America (IDSA) before vaccinating (Rubin et al., 2014). Healthcare workers and close contacts of immunocompromised persons may be sources of influenza transmission and should also be vaccinated (Bosaeed and Kumar, 2018).

Timing of influenza vaccination

Studies on influenza vaccine effectiveness have observed lower effectiveness as the interval since vaccination increases, suggesting that vaccine protection wanes somewhat over time during an influenza season (Ferdinands et al., 2019). These findings raise the question of optimal vaccination timing, especially for older adults and those with chronic diseases. Influenza surveillance can provide important information to policymakers, but due to regional variations in seasonal influenza activity, identifying the optimal time for vaccination is not always straightforward. The optimal period for vaccination could most appropriately be addressed at the level of individual countries, based on their own climate and seasonal influenza patterns, rather than on global recommendations. This is particularly the case in the sub-tropics and tropical countries, where influenza transmission often occurs year-round, sometimes with multiple peaks, thereby making it challenging to determine the optimal time for vaccination if vaccination only occurs annually. In these countries, the WHO recommends that seasonal influenza vaccination should occur before the start of the primary period of increased influenza activity, usually after October or April (WHO, 2017b). Semi-annual vaccination may improve immune responses in older adults living in tropical countries (Young et al., 2019). However, another study of older adults in Hong Kong showed reduced immune responses in a twice-annual vaccination group in a setting where the vaccine strains did not change (Tam et al., 2018). International travelers who move between the Northern and Southern hemispheres before their respective seasonal influenza peaks are another population in whom the timing of vaccination can be challenging. Semi-annual influenza vaccination may be beneficial in some settings and in some seasons, depending upon circulating strains, but the programmatic feasibility and cost-effectiveness of a twice-annual vaccination strategy has not been explored.

Impact of pre-existing immunity on influenza vaccine effectiveness

Influenza vaccines are unique among vaccines because they are updated semi-annually in response to viral antigenic changes and circulating strains, and they provide only brief immunity, requiring annual administration. There are data suggesting that repeated annual influenza vaccination can blunt future vaccine-induced antibody responses, particularly to A(H3N2) strains, and possibly reduce clinical VE in some seasons, although the evidence is conflicting (Belongia et al., 2017; Ramsay et al., 2019). Contributing to limited knowledge is that vaccine trials typically follow-up participants for only 1 year, and prior influenza vaccination history is often not reported. Disentangling the impact of immunosenescence from the impact of repeated vaccination in antibody response blunting and/or on VE is particularly challenging.

Several meta-analyses of repeated annual vaccination studies have not concluded that prior seasonal influenza vaccination has negative impacts on vaccine effectiveness, with the possible exception of seasons where the vaccine antigens remain unchanged and distinct to the circulating strain (Belongia et al., 2017; Ramsay et al., 2019). However, the underlying mechanisms and the interplay between differing seasonal disease burdens and negative interference with antigenic drift in more severe seasons are not well understood. A case–control study in Spain found that repeated annual vaccination of older adults from age 65 years was moreeffective in preventing severe influenza outcomes compared to a single vaccination in the current season (Casado et al., 2018). Conversely, mechanistic studies of repeated annual influenza vaccination have shown suppression of vaccine-specific B cell responses, and decreases in the production and affinity binding of anti-hemagglutinin antibodies after annual IIV vaccination (Sanyal et al., 2019; Khurana et al., 2019; He et al., 2011). The results support that B cells that are activated in response to influenza vaccines are short-lived. Subsequent responses may be reduced due to so-called 'antigenic sin', whereby antibody responses following vaccination are directed towards previously encountered epitopes, which are less effective against circulating strains (Henry et al., 2018).

Thus, it seems apparent that the characteristics of activated plasma cells and the antibodies secreted in response to influenza vaccination are highly dependent on a complex interplay between currently administered antigens and the imprinting of past immune exposures. Further studies are needed to better define the effects of previous exposure history at the individual level. While the 'one size fits all' approach to annual influenza vaccination is currently the best option to protect the population against influenza, in the future, personalized vaccines that account for past exposure history may prove more effective, but are likely to be considerably more expensive (Biswas et al., 2019). Many newer influenza vaccines (high-dose or adjuvanted) are not available or not yet licensed in many countries globally.

Conclusions

Influenza is a complex illness with wide-ranging clinical implications and its prevention is equally complex. Despite improvements in influenza vaccines with the use of higher doses, adjuvants, and alternative administration routes, seasonal influenza continues to be a major global public health concern and a significant cause of death worldwide, particularly in those susceptible to severe or complicated disease. Despite very large seasonal variations in effectiveness, the available data support current recommendations to vaccinate at-risk groups against influenza and to perform this annually. Nevertheless, the complexity of factors that influence influenza vaccine immunogenicity and protective capacity from season to season means that numerous questions remain unanswered. The most pressing issues include confirmation of the effectiveness of enhanced compared to standard influenza vaccines, and evidence-based consideration of their potential benefits if used more widely in influenza prevention in at-risk populations. Do we need different correlates of protection for some medical conditions, such as obesity or end-stage renal failure? What are the risks and benefits of semi-annual vaccination?

The relationship between immune responses and influenza VE is affected by a whole range of virus, host, and vaccine-specific factors, including the match between vaccine strains and circulating strains, the age of vaccine recipients, and the extent of past exposures and pre-existing immunity. Meta-analyses of the effectiveness of influenza vaccines in specific populations are limited by the large number of studies prone to bias or unable to account for potential confounding factors that can markedly influence study outcomes. Therefore, it is critical to extend the available data to well-designed studies conducted in larger populations during several influenza seasons. It is also important to gain a better understanding of the long-term effects of repeated influenza vaccination on the future efficacy of influenza vaccination. Finally, while the evidence indicates that influenza vaccines can play a role in reducing morbidity and mortality due to influenza infection, VE remains suboptimal and the need to continually update formulations on a semi-annual basis places a significant burden on public health resources and manufacturers. The ideal influenza vaccine would be administered once and provide prolonged or even life-long protection against all influenza strains, regardless of the effects of antigenic shift and drift. Such a universal influenza vaccine would make a major contribution to global public health, particularly among persons with conditions that place them at high risk of severe and complicated influenza disease, but has to date proved elusive.

Author contributions

All authors reviewed the literature, provided substantial input, and reviewed the paper. All authors approved the final article and are accountable for all aspects of the work.

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Conflict of interest

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