Chapter 21

Influenza Vaccines and Vaccination Strategies

Kathleen Maletic Neuzil, MD, MPH*, Justin R. Ortiz, MD, MS**
*University of Maryland School of Medicine, Professor of Medicine and Pediatrics, Director, Center for Vaccine Development, Deputy Director, Institute for Global Health, Baltimore, MD, United States; **World Health Organization, Medical Officer, Initiative for Vaccine Research (IVR), Immunization, Vaccines and Biologicals (IVB), Family, Women’s and Children’s Health (FWC) Cluster, Geneva, Switzerland

Chapter Outline

1 Introduction 423
2 The Influenza Virus 424
3 Influenza Disease and Burden of Illness 425
4 Influenza Vaccines 427
5 Non-replicating Influenza Vaccines 428
6 Safety of Non-replicating Vaccines 429
7 Immunogenicity of Inactivated Vaccines 430
8 Efficacy and Effectiveness 431
9 Populations of Interest 433
  9.1 Children 433
  9.2 Pregnant Women 433
10 Live-Attenuated Influenza Vaccines (LAIVs) 434
11 Immunogenicity 434
12 Safety 435
13 Efficacy and Effectiveness 435
14 Influenza Vaccines in Development 436
15 Vaccination Policy and Programs 436
16 Challenges of Influenza 438
17 Summary 440
References 440

1 INTRODUCTION

Influenza is a communicable acute respiratory disease and one of the major infectious disease threats to the human population. Influenza virus affects individuals of all ages, causes repeated infections throughout life, and is responsible for annual worldwide epidemics of varying severity, commonly referred to as “seasonal influenza.” Influenza also causes periodic pandemics that are characterized by a novel virus strain to which the majority of the population is susceptible and which have the capability of causing disease and sustained transmission from person-to-person.
This chapter focuses on seasonal influenza vaccines and vaccination programs. It provides an update on global influenza disease epidemiology and reviews the currently available influenza vaccines, the global recommendations for their use, and the programmatic challenges of delivering them.

2 THE INFLUENZA VIRUS

There are 3 types of influenza viruses that infect humans—A, B, and C— which are classified based on immunologic and biologic properties. Influenza viruses are negative strand RNA viruses with a segmented genome—influenza A and B viruses contain 8 RNA segments, and influenza C contains 7 RNA segments. Type A influenza viruses are further classified into subtypes according to the combinations of the hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins. HA is the major envelope protein and is the protein against which most neutralizing antibodies are directed. NA is important for release of virus particles and viral spread from cell to cell.\(^1,2\) As of 2015, 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes have been identified and distinguished structurally and antigenically—H1 through H18 and N1 through N11, respectively. To date, H1, H2, and H3, and N1 and N2 have been found as components of epidemic viruses in humans. The influenza A subtypes currently circulating among humans are influenza A(H1N1) and A(H3N2).\(^1,2,3\)

Influenza B viruses are mainly, although not exclusively, found in humans and form a single antigenic group. Although the antigenic variation is well-established, influenza B viruses are not divided into subtypes. They are, however, further classified into lineages and strains. Currently circulating influenza B viruses belong to one of two lineages: B/Yamagata and B/Victoria. Type C viruses cause disease much less frequently than type A and B, are not believed to cause epidemics, and are not a target for influenza vaccines.\(^1,2,3\)

The influenza virus undergoes frequent antigenic change. When mutations occur in influenza virus HA and NA surface glycoproteins, they are able to evade immunity induced by infection to previously circulating strains. This is the basis for annual influenza epidemics and necessitates the frequent changes in vaccine composition. A more substantial antigenic change can occur through gene reassortment. As a segmented RNA virus, influenza may reassort with other human and nonhuman influenza viruses. When that gene reassortment occurs in such a way that the virus has major changes to the HA and/or NA antigens, yet retains the capacity to cause disease and transmit among humans, a new strain can emerge, for which immunity in the population is lacking. These reassortment events may create new pandemic influenza viruses that could cause substantial disease, including deaths, globally.

Avian, swine, and other animal influenza viruses may also directly infect humans, and to date human-to-human transmission of these viruses has fortunately been limited.\(^3\) Clearly, these viruses in animals need to be closely monitored, as the human population has little immunity to them. If animal influenza viruses
were to ever efficiently transmit from person-to-person, there would be the potential for a severe influenza pandemic. Because there are many animal reservoirs for influenza, eradication of the influenza virus is not a viable control option.

3 INFLUENZA DISEASE AND BURDEN OF ILLNESS

Influenza virus infection can result in a spectrum of illness from asymptomatic infection, upper respiratory tract illness with or without fever, lower respiratory tract illness, exacerbation of cardiopulmonary disease, secondary bacterial infection, and progression to severe respiratory failure and death. Classic influenza illness is characterized by a sudden onset of fever, and respiratory symptoms such as cough, sore throat, runny nose, or earache. Systemic symptoms such as headache, muscle and joint pain, and malaise are common. For clinical studies and surveillance purposes, “influenza-like illness” is frequently defined as the sudden onset of fever or feverishness with cough and/or sore throat. Most people recover from influenza illness within a week without requiring medical attention, although the cough may be more prolonged and last for several weeks. However, a subset of individuals develops serious and sometimes fatal disease.

Because influenza symptoms are nonspecific, a definitive diagnosis of infection requires laboratory diagnosis. For example, influenza virus infection could resemble infection by any number of respiratory viruses. Further, influenza may cause nonrespiratory diseases such as nonspecific febrile illness in infants, febrile seizures in children, as well as encephalitis, myositis, and myocarditis/pericarditis in all age groups. Clinicians, researchers, and policy makers often underestimate the incidence of severe influenza due to the underutilization of influenza-specific diagnostic tests.

In general, influenza virus infection is most common in children, while severe complications of influenza virus infection are most common among young children, the elderly, pregnant women, persons of all ages with underlying medical conditions (such as chronic heart or lung disease), and persons with immunosuppressive conditions. While studies conducted in temperate, developed-country settings largely determined these risk conditions, studies have confirmed many of the same factors to be associated with severe disease in Bangladesh and Thailand. Furthermore, there may be additional risk factors associated with severe disease particular to developing-country settings, such as crowding, prevalence and spectrum of chronic illness including HIV, malnutrition, and low birth weight, proximity and proportion of the young to the elderly, and environmental exposures.

In areas where it has been studied, influenza deaths are most frequent in older adults. From 1976 through 2007, a yearly average of 21,098 influenza-related deaths occurred among United States adults 65 years and older. During the period from 1998 to 2005, age-standardized excess mortality among the elderly in South Africa were even higher than in the United States. Importantly, deaths due to influenza may occur at any age. In South Africa, a substantial burden of
influenza mortality has been estimated in children younger than 1 year of age, and in HIV-positive persons of all ages. In South Africa, 28% of influenza-associated deaths at any age occur among HIV-positive individuals, which has important implications for other parts of Africa with high HIV prevalence.\textsuperscript{13}

Deaths can increase during pandemic periods when a population has no pre-existing immunity to the virus. In the United States, between 37 and 171 children in the United States died each year from laboratory-confirmed influenza infection during annual epidemics between 2004 and 2015, as compared to 300 laboratory-confirmed pediatric deaths during the 2009–2010 H1N1 influenza pandemic.\textsuperscript{2,14} These are certainly underestimates given the underutilization of diagnostic testing. The 1918 influenza A (H1N1) pandemic is estimated to have caused 50 to 100 million deaths worldwide.\textsuperscript{15,16} Even so, the cumulative mortality from seasonal influenza exceeds that of pandemic influenza in the United States, and likely throughout the world.\textsuperscript{17}

While countries with temperate climates have conducted intensive influenza surveillance and clinical/epidemiologic research for more than 50 years, influenza in tropical and subtropical climates has been understudied. The World Health Organization (WHO) Global Influenza Surveillance Network has coordinated pandemic planning efforts and influenza surveillance activities since its creation in 1948. During most of this time, influenza surveillance was focused on the collection of virus isolates to inform the influenza vaccine strain selection, with activities mainly concentrated in developed, temperate countries. Since the emergence of avian influenza A (H5N1) in 1996 and the subsequent concern about an imminent pandemic, the global community has strengthened influenza surveillance and research capacity in tropical developed and developing regions around the globe. The increasing availability and use of reverse transcription polymerase chain reaction (RT-PCR) diagnostic techniques has revealed much higher rates of influenza virus infection in developing-country settings than had been demonstrated in prior studies that used less sensitive diagnostic tests. The 2009 influenza A (H1N1) pandemic led to a further intensification of influenza surveillance and research in developing country settings.\textsuperscript{3}

In temperate and subtropical regions, influenza spreads in seasonal epidemics that coincide with the winter season. In tropical regions, many countries have reported peaks in influenza activity associated with rainy and cold seasons and either longer epidemics or year-round transmission.\textsuperscript{18} While attack rates vary substantially by season and locale, influenza typically infects up to 10% of adults and 30% of children each year in temperate regions.\textsuperscript{2,19} Epidemics can result in high levels of worker/school absenteeism and productivity losses. Furthermore, closed populations such as schools, hospitals, and isolated communities may experience much higher attack rates. School-aged children play an important role in the spread of influenza viruses.

Available data are incomplete to estimate influenza incidence in most tropical regions. Recent influenza vaccine studies in pediatric age groups in Senegal and Bangladesh, for example, have revealed attack rates similar or higher than
Influenza Vaccines and Vaccination Strategies  Chapter | 21  427

those seen in the United States.\textsuperscript{20,21} Even higher attack rates have been noted in certain circumstances. For example, investigations of seasonal influenza outbreaks estimated attack rates of clinical infection to be 67\% in Madagascar in 2001 and 47\% in Democratic Republic of Congo in 2002.\textsuperscript{22,23} While much is known about influenza transmission dynamics in temperate regions, many factors in developing regions may alter disease activity where household, community, environmental, and host factors may differ.

Worldwide, the WHO estimates 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths associated with annual influenza epidemics. A 2011 \textit{Lancet} meta analysis in children younger than 5 years of age estimates 20 million (95\% CI 13-32) acute lower respiratory infections (ALRI) associated with influenza, including 1–2 million cases of severe ALRI. This study estimated 28,000–111,500 influenza-attributable deaths annually, with 99\% of early childhood influenza deaths occurring in low- and middle-income countries.\textsuperscript{24}

4  **INFLUENZA VACCINES**

Immunization against influenza serves as the primary means for preventing influenza illness. An unprecedented number of influenza vaccines are available on the global market. (Fig. 21.1). The currently available vaccines are targeted to the HA and NA glycoproteins of the virus, and thus must be reformulated

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{influenza_vaccine_landscape.png}
\caption{Influenza vaccines on the market and in development, 2014. Available at: www.who.int/phi/DAY2_10_Bright_PM_SaoPaulo2015.pdf}
\end{figure}
frequently due to the circulating virus propensity to mutate at key antigenic sites. The strains included in the vaccine are selected based on information derived from globally coordinated epidemiologic and virologic surveillance—WHO’s Global Influenza Surveillance and Response System (GISRS). The GISRS monitors the evolution of influenza viruses and the emergence of influenza viruses with pandemic potential. Twice a year, WHO convenes technical consultations (vaccine composition meetings) to recommend the viruses to be included in influenza vaccines that are termed Northern and Southern Hemisphere formulations. All current vaccines are recommended to contain the selected Influenza A (H1N1) and A (H3N2) strains, and either one (trivalent) or two (quadrivalent) influenza B viruses. Quadrivalent vaccines were developed to protect against both B lineages currently in circulation in humans, as it has been difficult to accurately predict the predominantly circulating influenza B virus lineage. Further, in many parts of the world, both lineages have cocirculated.20,21

Currently, two general classes of influenza vaccines are licensed for production globally: parenterally administered non-replicating virus vaccines and intranasally administered live attenuated vaccines. The non-replicating vaccines may be further divided into manufacturing substrate (eggs, cell culture, fully recombinant), route of administration (intramuscular, intradermal) type of preparation (whole virus, split virus, and subunit vaccines) and by presence of adjuvant (MF-59) (Table 21.1).

The availability of licensed influenza vaccine products is dependent on the age and health status of the individual. For children younger than 6 months of age, there are no currently approved influenza vaccines anywhere in the world. For children younger than 2 years of age, nonadjuvanted inactivated vaccines are the only approved vaccines in most places, although Canada has approved an adjuvanted inactivated vaccine for children from 6 through 23 months of age. For children 2 years of age and over, both nonadjuvanted, inactivated and live-attenuated vaccines are approved and available. The options increase for adults, as intradermal and recombinant vaccines are licensed beginning at 18 years of age. For adults 65 years and over, a high dose inactivated vaccine is available in the United States, while Europe, Canada, and the United States have approved an MF-59 adjuvanted vaccine for this group (Table 21.1).25,26

5 NON-REPLICATING INFLUENZA VACCINES

Inactivated influenza vaccines (IIVs) were first licensed for broad use in 1945. The 15 microgram HA per antigen component of IIVs was determined by consensus in the 1970s after improvements in quantification methods.27 Only recently has the antigen content of such vaccines been altered to optimize immune response in certain populations, for example, higher antigen content vaccines for the elderly, higher antigen content in the recombinant vaccine, and reduced antigen content in intradermal vaccines.
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<thead>
<tr>
<th>Route</th>
<th>Live attenuated</th>
<th>Non-replicating vaccines</th>
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<tr>
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<tr>
<td>Use in pregnant women</td>
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*Approved ages may differ by manufacturer and country.
6 SAFETY OF NON-REPLICATING VACCINES

IIVs have been in use for 70 years, and as a class they have a robust safety profile, as determined in clinical trials as well as large postlicensure surveillance programs. Product-specific information is less available, and the safety databases for the newer products will be more limited until use of the products increase. In general, the most common adverse events associated with IIVs are local injection site reactions.\(^2,25,27\) However, more serious adverse events have been recognized and are described more specifically below.

In children, across multiple large studies, IIVs are generally considered to be safe for all ages and all risk groups. In clinical trials, fever and injection-site reactions are the most common events, and tend to be mild and transient.\(^2,28,29\) In 2010, a IIV-trivalent (IIV-T) formulation from a single manufacturer in Australia was strongly associated with increased febrile seizures in children.\(^30\) This led to varying recommendations in countries precluding the use of this vaccine in younger children, and enhanced surveillance for febrile seizures in the United States and elsewhere. The febrile seizure risk among children in the United States was noted to be elevated in some years and not others, and more so when IIV was coadministered with PCV-13 vaccines. In all cases the risk for febrile seizures in the United States was determined to be substantially lower than observed in 2010 in Australia.\(^30,31\)

Likewise, in adults, IIVs have a strong safety record. In placebo-controlled trials, only injection site soreness is consistently associated with receipt of IIVs.\(^27\) The adjuvanted IIVs and newer high-dose vaccines are associated with increased injection site reactions and mild systemic events, although these are generally mild and transient.\(^32,33\) Safety of IIVs has also been well-studied among pregnant women, again realizing a general lack of product-specific and limited randomized clinical trial data.\(^34–37\)

Safety surveillance in pregnancy is particularly challenging, as the background incidence of rare pregnancy-related adverse events is not well-established, particularly in low resource countries. However, multiple studies to date have not identified consistent, unexpected serious acute events, adverse pregnancy outcomes, or congenital anomalies associated with receipt of influenza vaccine during pregnancy.\(^25,34–36\)

The oculorespiratory syndrome (ORS) is an acute, self-limited reaction associated with bilateral red eyes, facial edema and/or respiratory symptoms such as coughing, wheezing, hoarseness, sore throat, chest tightness or difficulty breathing occurring within 2–24 h of receiving IIV. It is more common in adults and in women. It was first described in Canada in the 2000–2001 influenza season and was strongly associated with one specific preparation manufactured in Quebec. Subsequently, enhanced surveillance did identify lesser associations with other vaccines in Canada, the United States, and Europe. While the pathogenesis is not known, it is not IgE-mediated. Thus, persons with previous ORS may be safely revaccinated if IgE hypersensitivity events can be excluded.\(^25,38\)
Individuals with egg allergy may experience hypersensitivity reactions after receipt of influenza vaccines given the residual egg protein that may exist in most vaccines. While the cell culture-based vaccines do not use eggs in the manufacturing process, influenza seed viruses are passaged in eggs so very small amounts of residual egg proteins may still remain in cell culture vaccines. The new recombinant vaccine, FluBlok, is the only product to be entirely egg-free. Thus, the risk for reaction in egg-allergic individuals will vary based on the product and the individual’s history, and the manufacturer’s package insert and country-specific recommendations should be consulted.

In 1976, there was concern in the United States regarding an imminent swine influenza pandemic, which resulted in mobilization of public health resources and development of a specific vaccine. The swine influenza vaccine was associated with an increased frequency of Guillain–Barre syndrome (GBS), an acute inflammatory polyneuropathy. No subsequent study of influenza vaccines and GBS has demonstrated a risk of the magnitude seen in 1976, which was estimated at one additional case of GBS per 100,000 persons vaccinated. While not consistently noted, studies have identified risks on the magnitude of 1 additional case of GBS per 1 million persons vaccinated, such as the 1992–93 and 1993–94 seasons in the United States. Multiple studies during other seasons have identified no association.

During the 2009 pandemic, several countries demonstrated an increased risk of narcolepsy following receipt of ASO3-adjuvanted influenza vaccine in children, adolescents and young adults. The ASO3 adjuvant is in the oil-in-water adjuvant class, and is not approved for use in any seasonal influenza vaccine. MF-59 is also an oil-in-water adjuvant. MF59 adjuvanted seasonal influenza vaccines have not been associated with narcolepsy.

7 IMMUNOGENICITY OF INACTIVATED VACCINES

Currently licensed IIV are designed to elicit immunity predominantly against the virus hemagglutinin (HA), the surface glycoprotein critical for virus attachment to host cells. Specific antibodies to the HA are believed to be the best correlate of protection against influenza virus infection, and they are the primary endpoint used by regulatory agencies to evaluate vaccine immunogenicity. However, the influenza virus, and particularly the HA glycoprotein, undergo constant genetic and antigenic change. Thus, antibody elicited by vaccination is generally strain-specific, such that antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype. In addition, nonadjuvanted inactivated influenza vaccines are less likely to confer protection against antigenic variants of the same virus that arise by antigenic drift.

The immunogenicity of influenza vaccines varies with the influenza strain, the age and underlying condition of the recipient, prior exposure to antigenically similar influenza viruses or vaccines, and the vaccine formulation used. In general, young and middle-aged healthy adults, including pregnant women,
have robust antibody responses. Antibody responses may be diminished in young children, the elderly, and those with underlying chronic or immunocompromising condition. Adults and older children require one dose of vaccine each season to induce immunity. Unimmunized young children require two doses of IIV given at least 4 weeks apart to produce sufficient immunity. Based on studies conducted in 1976, children were traditionally administered one-half the standard dose of influenza vaccines, to minimize reactogenicity. More recently, with the use of less reactogenic vaccines, certain countries are recommending full dose vaccines be used even in the youngest children to enhance immunogenicity. Improving the immunogenicity and performance of vaccines has stimulated new product development for specific age groups, including adjuvanted vaccines for young children and the elderly, and high dose vaccines for the elderly.

8 EFFICACY AND EFFECTIVENESS

IIVs have demonstrated efficacy and effectiveness across broad age groups and among different populations over many influenza seasons. In general, the term efficacy is used to describe a vaccine’s performance to prevent influenza disease in clinical trials, while effectiveness is used to describe a vaccine’s performance in observational, nonrandomized settings. Specific efficacy and effectiveness estimates vary considerably from study to study, as they are influenced by many variables—age and underlying health condition of the recipient, the inherent immunogenicity of the vaccine, the match between vaccine virus and circulating strain, and the design characteristics of the studies (eg, surveillance method, outcome measures, placebo versus active controlled trials versus observational studies). Caution should be exercised in comparing efficacy across studies. For example, comparing efficacy among different age groups is problematic unless individuals of different ages are included in the same study season and receive the same study product. Likewise, different vaccine formulations are best compared in head-to-head trials.

A recent metaanalysis of eight United States randomized controlled trials in healthy adults from 2004 to 2008 estimated the pooled efficacy of IIV against culture-confirmed influenza to be 59% (95% CI, 51–67%) among those aged 18 through 64 years. Efficacy estimates are significantly higher in years when vaccine match to circulating strains is higher, and may be lower in years with vaccine-circulating strain mismatch. From the public health context, it is important to consider that even a vaccine with modest efficacy can have important benefits against a disease as common as influenza. Due to the variability in influenza seasons and vaccine match, monitoring for influenza efficacy or effectiveness is best done over multiple influenza seasons.

The now rapidly changing landscape of influenza vaccines, coupled with the unpredictable aspects of influenza epidemics, necessitates a nimble system to monitor and evaluate the impact of individual vaccines and policy decisions. A
growing number of surveillance systems in the United States, Canada, Australia, and Europe monitor influenza effectiveness annually and have the ability to produce early, in-season estimates of vaccine performance.\textsuperscript{47,48} Annual estimates of influenza vaccine efficacy are critical to guide policy decisions and public health communications, and should be expanded to allow for more robustly powered investigations of the relative performance of particular vaccines against influenza types or subtypes, across age groups and risk groups, and over multiple years.

\section*{9 POPULATIONS OF INTEREST}

\subsection*{9.1 Children}

Estimates of the efficacy or effectiveness of IIV among children vary by season and study design. In a randomized, controlled trial in healthy children aged 6–23 months, vaccine efficacy was 66\% (95\% CI, 34–82\%) in the first year, but could not be assessed in the second year due to a low influenza attack rates.\textsuperscript{49} Using a case-control design, influenza vaccination was associated with a 75\% reduction in the risk of life-threatening influenza illness in children during the 2010–11 and 2011–12 seasons in the United States. In this study, there was no effectiveness demonstrated among children receiving influenza vaccine for the first time who did not receive the recommended 2 doses.\textsuperscript{50}

A clinical trial in Europe in 2007–08 and 2008–09 randomized healthy influenza vaccine-naive children aged 6 months to less than 72 months to receive IIV, MF-59 adjuvanted IIV, or a noninfluenza control vaccine. Vaccine efficacy was 43 and 86\%, respectively, for IIV and adjuvanted IIV versus the noninfluenza control vaccine against all laboratory-confirmed influenza illness across both influenza seasons. The adjuvanted IIV was 75\% better than the IIV comparator vaccines used in the study.\textsuperscript{29}

\subsection*{9.2 Pregnant Women}

The immunogenicity of IIV is generally considered to be similar among healthy pregnant women and nonpregnant women of similar age. In comparison to a noninfluenza vaccine in a randomized trial, IIV reduced febrile respiratory illness by 36\% among pregnant women in Bangladesh.\textsuperscript{51} Among HIV-uninfected and HIV-infected pregnant women in South Africa, influenza vaccine was 50.4\% (14.5–71.2) and 57.7\% (0.2–82.1) efficacious, respectively, against laboratory-confirmed influenza illness. Importantly, in both Bangladesh and South Africa, infants born to mothers who received influenza vaccine had fewer laboratory-confirmed influenza illnesses.\textsuperscript{37,51}

\subsection*{9.3 Older Adults}

A single randomized placebo-controlled study of IIV-3 was conducted in persons 60 years and over and demonstrated a vaccine efficacy against
laboratory-confirmed influenza illness of 58% (95% CI, 26–77%).\textsuperscript{52} Concerns about suboptimal performance of influenza vaccine are based on immunogenicity studies that demonstrate that older individuals, and particularly those with poor health status, have poor immune responses to vaccines. Thus, new vaccines have been developed to improve performance in older individuals. In Europe, an adjuvanted influenza vaccine has been approved for use in persons 65 and over since 1997, and in the United States the vaccine was approved in Nov., 2015. Regulatory approval was based on immunogenicity, and no head-to-head trials with unadjuvanted IIV are currently available. However, such studies are ongoing, and observational studies have demonstrated superior immunogenicity and effectiveness of the adjuvanted formulation.\textsuperscript{53,54}

A high dose inactivated influenza vaccine, with 4 times the antigen content as standard-dose vaccine, was approved in 2009 for use in persons 65 years, based on superior immunogenicity as compared to standard dose IIV.\textsuperscript{32} A postlicensure study demonstrated that among nearly 32,000 older adults, most of whom had at least one chronic medical condition, the high-dose vaccine had a relative efficacy of 24.2% against laboratory-confirmed influenza as compared to the standard dose product. Based on the incidence rates reported during the two study seasons, this relative efficacy translated into approximately 1 additional case of influenza prevented for every 200 persons vaccinated.\textsuperscript{33}

10 LIVE-ATTENUATED INFLUENZA VACCINES (LAIVs)

LAIVs rely on viral replication and immune activation within vaccine recipients. The replication mechanism is altered such that the vaccine virus grows below normal body temperature (ie, cold-adapted), ensuring that virus selectively replicates in the mucosa of the nasopharynx. The vaccine virus is also temperature-sensitive, meaning that replication is hindered at the higher temperatures of the lower respiratory tract. There is no accepted correlate of immunity for LAIVs and in contrast to IIVs, the HA antibody response cannot be used to predict vaccine performance. LAIV is administered intranasally.

There are currently two LAIVs in use worldwide. One was developed in the former Soviet Union from an attenuated influenza A/Leningrad/134/57 backbone and has been manufactured and used in Russia for over 30 years.\textsuperscript{55} More recently, through a program spearheaded by the WHO, these Russian attenuated seed strains were provided to developing country manufacturers. Serum Institute of India, one of those manufacturers, now has a licensed trivalent LAIV for seasonal use.\textsuperscript{56} The second vaccine was developed in the United States from an attenuated influenza A/Ann Arbor/6/60 backbone and has been approved since 2003.\textsuperscript{55,57}

11 IMMUNOGENICITY

A number of systemic and mucosal immune responses have been routinely assessed following administration of LAIV.\textsuperscript{58,59} LAIV immunogenicity data have lacked correlation between efficacy and standard immunogenicity
measures. For this reason, there is no correlate of protection recognized by regulatory agencies for LAIV vaccines, highlighting the importance of clinical efficacy studies for licensure and vaccine policy determination. A single study described cell-mediated immunity as determined by ELISPOT assays that measure gamma-interferon as correlating with protection following LAIV in children, however the results have not been corroborated and this measurement is not yet considered to be standard for LAIV vaccine trials.

12 SAFETY

LAIV receipt is associated with mild increases in signs and symptoms of upper respiratory tract infection including runny nose, nasal congestion, headache, low grade fever, and myalgia. In clinical trials, an increased risk for wheezing illness was observed in LAIV/Ann Arbor backbone recipients aged <24 months (3.8% LAIV vs. 2.1% IIV). An increase in hospitalizations also was observed in children aged <12 months after vaccination with LAIV/Ann Arbor. For these reasons, LAIV/Ann Arbor is approved for use beginning at 24 months of age. Postlicensure surveillance data from North America and Europe has not demonstrated an increased frequency of wheezing illness after administration of LAIV/Ann Arbor among healthy children over 2 years of age. Clinical trials of the LAIV/Leningrad in Russia were done prior to the recognition of the wheezing signal, and did not prospectively solicit this event. In Bangladesh, a Phase 2 trial of the LAIV/Leningrad found no imbalance of medically important wheezing events in 300 children aged 2 through 4 years prospectively followed for the outcome.

13 EFFICACY AND EFFECTIVENESS

LAIV/Ann Arbor has demonstrated high efficacy in children, including during years with a vaccine-circulating strain mismatch. The efficacy of LAIV/Ann Arbor was superior to IIV in children in 3 randomized efficacy trials. A meta-analysis of these 3 trials and a nonrandomized clinical trials using LAIV/Ann Arbor calculated 46% fewer cases of influenza in children who first received LAIV compared with children first receiving inactivated vaccine. For older children, vaccination with LAIV/Ann Arbor caused 35% fewer cases of influenza compared to children receiving IIV. Based on these results, several countries, including the United States, United Kingdom, Canada, Germany, and Israel preferentially recommended LAIV over IIV for young children. The United States subsequently rescinded this recommendation after effectiveness studies in the 2013–2014 influenza season demonstrated that LAIV did not perform well in young children. The United States currently recommends that either IIV or LAIV be given to young children. Similar to IIV, young children receiving LAIV/Ann Arbor for the first time should be given two doses of LAIV, separated by at least 4 weeks.
In adults up to 50 years of age, most comparative studies suggest either similar efficacy of LAIV and IIV, or that IIV is more efficacious.\textsuperscript{27,69,70} As with other influenza studies, the relative efficacy of LAIV and IIV among adults may vary depending on the influenza season and the vaccine match as well as the influenza and vaccine exposure history of the population.

14 INFLUENZA VACCINES IN DEVELOPMENT

The development of improved influenza vaccines is a public health priority. The Global Vaccine Action Plan calls for progress toward a universal influenza vaccine by 2020.\textsuperscript{71} A universal vaccine that protects against all influenza A virus subtypes would be transformative. In the shorter term, vaccines are being designed to be more effective at preventing influenza illness and severe infection, to be more broadly protective, and to have longer lasting immunity. It is also important to consider ways in which the vaccine production process could be improved, or timelines shortened to permit a more rapid response to an emerging outbreak. Ultimately, an influenza vaccine that elicits broad immunity could preclude the need for the continuous chasing of evolutionary changes seen with influenza. If significant cross-protective immunity could be induced, influenza vaccines would be more effective against novel strains and could be manufactured and delivered throughout the year or even stockpiled for rapid use in the event of an outbreak of a drifted or reassortant virus. These factors could ease the stress placed on vaccine manufacturers and health-care providers in such situations.\textsuperscript{72}

The limitations of current influenza vaccines have stimulated an unprecedented pipeline of new vaccine candidates. (Fig. 21.1). Many of these candidates are directed at more conserved regions of the influenza virus, including the stem portion of the HA antigen. While the need for an improved vaccine is clear, and the efforts remarkable, the development pathway is challenging. Substantial investment will be required as multiyear head-to-head trials with currently available products will likely be needed to ensure that enhancing cross-protection, for example, does not diminish vaccine performance during a season in which vaccine is matched with circulating virus strains. Likewise, any new seasonal influenza vaccine will need to have a robust safety record in targeted populations.

15 VACCINATION POLICY AND PROGRAMS

Many countries throughout the world have seasonal influenza vaccine policy recommendations (Fig. 21.2). Policies and implementation of such policies will be dependent on the availability of national or regional data, and the capacity, resources, and priorities of the individual country. In temperate industrialized countries with seasonal outbreaks, influenza vaccine is given annually, prior to the influenza season, and generally targeted to individuals with the highest risk of severe disease and to those who may be important in the transmission
of virus to such high-risk individuals. Health care workers are recommended to receive influenza vaccine in many countries both to limit transmission to vulnerable patients as well as to maintain the health-care work force during influenza outbreaks.

Influenza vaccine programs are more complex in tropical and subtropical countries. Given the varying influenza circulation patterns in the tropics, it is not yet clear if a Southern or Northern Hemisphere vaccine administered in annual campaigns would provide year-round protection against the diverse strains that may be seen in such countries. Further, the optimal formulation or timing of immunization is still uncertain in many countries with limited historical influenza surveillance. In the Americas, for example, some tropical countries use Southern Hemisphere vaccine while others use the Northern Hemisphere formulation. (Fig. 21.3)

Recognizing the complexity of influenza and influenza vaccination programs, and the importance of country-specific data and decision-making, WHO updated its recommendations on use of influenza vaccine in 2012.\(^1\)\(^8\) For countries considering the initiation or expansion of programs for season influenza vaccination, WHO recommends that pregnant women should have the highest priority for vaccine receipt. This recommendation was based on the risk of severe disease, evidence on the safety of the vaccine during pregnancy, the potential for benefit to the women and infant, and the operational feasibility. Additional groups to be considered, in no particular order of priority, are children aged 6 through 59 months, the elderly, individuals with specific medical conditions, and health-care workers. As no vaccines are approved for children

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**FIGURE 21.2** Countries with seasonal influenza vaccine recommendations. Available at: www.who.int/immunization/sage/meetings/2015/april/Hombach_SAGE_13April2015.pdf
younger than 6 months of age, protection of these vulnerable infants can only be achieved through vaccination of the mother during pregnancy and vaccination of close contacts to limit transmission.¹⁸

### 16 CHALLENGES OF INFLUENZA VACCINE PROGRAMS IN LOW RESOURCE SETTINGS

Most low resource countries have no recommendations for influenza vaccine, and limited capacity to initiate such programs. (Fig. 21.2). Adolescent and adult preventive health services are poorly developed in many countries. Even strategies that target those in the population with regular access to medical care, such as pregnant women or young children, may be logistically difficult. Unlike other vaccines, influenza vaccine formulations change up to twice annually, and may not be available year-round. Young vaccine-naive children require 2 doses of vaccine. Further, due to the nonspecific nature of the clinical illness, health-care providers and patients lack an understanding of the risks of influenza disease. Influenza vaccine package inserts are often vaguely written with regard to the risks and use during pregnancy because pregnant women are seldom included in prelicensure vaccine trials.

Vaccine financing is always an important consideration, and currently, other than the Pan-American Health Organization Revolving Fund for Vaccine Procurement, financing mechanisms do not exist to support influenza vaccine
programs for low resource countries. In 2013, GAVI the Vaccine Alliance reviewed maternal influenza for investment in low-income countries worldwide. GAVI chose not to open a funding window due to the logistical challenges, the low country awareness, and the uncertain health benefits of influenza vaccine in comparison to other vaccines. However, GAVI will reconsider opening a funding window for maternal influenza vaccination in 2018, when additional data from clinical trials will be available. Further, a number of programmatic initiatives are underway to understand and facilitate maternal influenza vaccine delivery in low resource countries. Lessons may be learned from the Latin American experience, as well, where influenza vaccine of pregnant women has been a priority. (Fig. 21.4)

Recognizing that there will be challenges in adding seasonal influenza vaccine to routine childhood vaccination schedules in low resource countries, a better understanding of the burden of severe disease attributable to influenza has emerged as a key area for data generation. Influenza vaccine trials in low resource countries have generally been designed to show efficacy against laboratory-confirmed influenza infection of any severity. In contrast, other recent childhood vaccine introductions, such as rotavirus and pneumococcal vaccines, had supportive data from much larger, randomized controlled trials that demonstrated efficacy of the vaccines against severe disease. Such data have been instrumental in influencing policy and financing decisions on childhood vaccines. Unfortunately, no definitive data exist for the vaccine-preventable

FIGURE 21.4 Influenza vaccine coverage for pregnant women, Latin America. Available at: www.paho.org/hq/images/stories/AD/FCH/IM/Influenza_vaccine/maps/influenza_pregnant_2013.jpg?ua=1
burden of severe influenza illness in low resource settings, nor have studies to date examined the possible causal role of influenza in the progression of other respiratory diseases, such as bacterial pneumonia, to severe respiratory illness and death. This is particularly important for children younger than 2 years of age, for whom acute respiratory illness remains a major cause of morbidity and mortality.

17 SUMMARY

Influenza is a common respiratory illness that accounts for substantial global morbidity, mortality and lost productivity on an annual basis. Currently available influenza vaccines are safe and effective, although absolute efficacy varies by year and will be influenced by the virus, the vaccine, and the population. Increasing the use of influenza vaccines can reduce the impact of influenza illness, and high risk groups have been identified that would benefit most from influenza vaccine. Vaccination schedules of the future are likely to be more nuanced in regard to the use of specific vaccines for specific age and risk groups. While HA-based non-replicating and live-attenuated vaccines will be the primary options in the near-term, the influenza vaccine development pipeline is robust. It is critically important that additional data be generated in tropical and subtropical regions to understand how to best deliver influenza vaccines to pregnant women, young children, and other high risk populations. Influenza vaccine probe studies with severe disease outcomes in young children will be important to guide funding priorities and country level decision making on routine pediatric influenza vaccine in low resource settings.

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