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Current Influenza Vaccine Options for 2014

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Abstract Influenza is a virus that causes significant morbidity and mortality in the United States each year. There are multiple vaccine formulations available that can help prevent or decrease the burden of influenza. The Advisory Committee on Immunization Practices (ACIP) recommends that everyone ≥6 months of age receive the influenza vaccine prior to the start of influenza season each year unless contraindicated to help prevent influenza and the spread of infection. The ACIP has developed the best practice guidelines to help assist patients, and providers select the vaccine that will offer the greatest protection against influenza given the patient's age and co-morbid conditions. When administered early, the influenza vaccine can reduce the risk of influenza by 50–60 %. Researchers continue to investigate ways to improve the influenza vaccine to continue to increase its ability to reduce the risk of influenza and prevent influenza-related complications and deaths.

Keywords Influenza · Vaccination · Prevention · Vaccine effectiveness of trivalent inactivated vaccine (VE of the TIV) · Quadrivalent influenza vaccine (QIV)

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Introduction

The influenza virus, an RNA virus made up of 8 single strands, is classified based on antigenic differences between influenza A, influenza B, and influenza C types. Influenza A and B are common causative types leading to seasonal epidemics in humans. Influenza A is further classified according to hemagglutinin (HA) and neuraminidase (NA)—two surface glycoproteins that are critical in the virus cycle [1]. There are two types of influenza B that circulate as seasonal influenza: Victoria lineage and Yamagata lineage [2, 3]. For all influenza subtypes, HA facilitates the virus attachment to host-cell sialic-acid containing proteins which is essential to viral endocytosis and replication while NA cleaves budding virus from the host-cell surface sialic-acid containing proteins [4–6].

Influenza viruses are largely spread from person to person through large-particle respiratory droplet transmission. Close contact with an infected person or contaminated surface is required for transmission as large-particle respiratory droplets do not travel great distances. Once infected, the usual influenza incubation period is 1–4 days. Patients are at risk of spreading influenza ranging from 1 day prior to symptom onset to 5–7 days after displaying symptoms [7, 8]. Young children or immunocompromised patients with prolonged viral shedding may be able to spread influenza for longer periods of time [6]. Influenza should be suspected in patients during times of circulating virus who present with abrupt onset of signs and symptoms consistent with influenza which classically include fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. Most disease is mild in nature and self-limiting, usually 3–7 days with potential for cough and malaise to continue >2 weeks. Patients ≥65 years, young children, and any persons with conditions which put them

at increased risk of influenza complications are at higher risk of hospitalization or even mortality. In more severe cases, influenza can cause viral pneumonia, secondary bacterial infections, or exacerbation of underlying pulmonary or cardiac conditions [7, 8]

Diagnosis of influenza is recommended with the use of RT-PCR tests, if available. This methodology has high sensitivity and high specificity with a rapid turnaround time of 4–6 h. Commercially available rapid influenza diagnostic tests are able to produce results within 10–30 min and display high specificity but very low sensitivity. Laboratory confirmation is not required prior to initiation of therapy, however. Treatment is recommended in hospitalized patients or patients at risk of complications within 48 h of laboratory-confirmed or highly suspected influenza disease. Treatment should be considered in outpatients at high risk of complication >48 h after symptom onset of laboratory-confirmed influenza infection that is not improving or outpatients with laboratory-confirmed influenza presenting <48 h of symptom onset [9].

Five licensed antivirals comprising two therapeutic classes of medication are available in the US for treatment of influenza. Amantadine and rimantadine comprise the adamantane class which is active against influenza A but not influenza B. The adamantanes are no longer recommended for treatment or chemoprophylaxis due to recent trends showing increasing influenza A resistance. Oseltamivir, zanamivir, and peramivir comprise the neuraminidase inhibitor class which inhibits influenza virus neuraminidase from cleaving the budding viral progeny from the cellular envelope attachment point thereby inhibiting virion release and virus spreading. Although all circulating strains of influenza A and B currently show susceptibility to all neuraminidase inhibitors, development of resistance remains a concern that requires surveillance. Rare isolates of 2009 H1N1 have been oseltamivir resistant seen in immunocompromised patients with prolonged viral shedding but have retained zanamivir susceptibility. The usual duration of therapy for oseltamivir (oral) and zanamivir (inhalation) is 5 days, and peramivir is given intravenously as a single dose. Durations of therapy can be extended in patients who are critically ill and have not improved with 5 days of therapy. Neuraminidase inhibitors are generally well tolerated, and renal dose reductions are required for oseltamivir and peramivir [8, 10, 11].

Pandemic influenza occurs when the population is unexposed and therefore has little to no immunity, to a new circulating virulent strain of influenza. During times of pandemic influenza, one can expect rapid transmission from person to person worldwide with no available vaccine early in the emergence [12]. To cause a pandemic, influenza A will have undergone an antigenic shift meaning a novel HA and/or NA subtype virus [13]. Influenza B will not cause pandemics. Four confirmed influenza pandemics have occurred in the past 100 years [14, 15]. Most recently, the 2009 A(H1N1) influenza pandemic is estimated to have killed 284,400 people worldwide [16]. Once a virus has caused pandemic, it will become a regularly circulating seasonal influenza strain [12].

Variant and zoonotic influenza occurs when humans are infected with virus that normally circulates in animals [2]. The World Health Organization (WHO) has stated that highly pathogenic avian influenza (HPAI) H5N1 is the zoonotic influenza virus of greatest concern to human health. Since reemergence in late 2003, 55.1 % of laboratory-confirmed cases of H5N1 in humans have been fatal [17]. In the US, HPAI H5 infections have only been reported in poultry [18].

Influenza Vaccine

The primary method for prevention and control of influenza worldwide is vaccination with the goal of reducing the number of illnesses and limiting the disease severity. As of February 2015 in the US, approximately 147.8 million doses of the 2014–2015 influenza vaccine had been distributed with the majority occurring by the end of October 2014 [19]. The process of seasonal influenza vaccine virus selection is a global process orchestrated by the WHO. Based on the information obtained through the Global Influenza Surveillance and Response System, the WHO makes twice yearly recommendations for influenza virus strains that should be included in the seasonal influenza vaccine. This information is published approximately 6–8 months prior to influenza season for each hemisphere to allow for vaccine manufacturing and distribution. Although the WHO makes recommendations highlighting the most likely causative strains of the seasonal flu, it is the national regulatory agencies in each country that make the final decision regarding strain-specific vaccine make up [20].

Classical reassortment techniques are utilized in seasonal influenza vaccine manufacturing to produce high-growth H1N1 and H3N2 viruses. Wild type influenza A viruses do not grow efficiently in eggs which poses a manufacturing hurdle as this method is still the most predominant today. To overcome this reluctance to grow, genes from a high-growth virus are combined with two genes encoding HA and NA from the recommended virus resulting in high-growth reassortants. Currently, wild type influenza B viruses are utilized for manufacturing. These high-growth reassortants undergo genetic characterization to ensure laboratory manipulation has not resulted in any gene alterations and analysis to determine whether they induce the same antigenicity as wild type virus for optimal

protection. Final steps include evaluating growth property to ensure yield is sufficient for manufacturing and developing a standard reagent for potency requirements [20].

Three types of seasonal influenza vaccines are commercially available in the United States: inactivated influenza vaccine (IIV), live attenuated influenza vaccine (LAIV), and recombinant HA vaccine (RIV_3) (Table 1) [21]. Current influenza vaccine practices rely on the patient to form antibodies to HA proteins which results in strain-specific influenza vaccines [22]. IIVs contain a split virion or subunit with the major HA antigen particle which leads to immunogenicity but has been chemically inactivated and detergent washed for envelope disruption. IIVs induce a strain-specific IgG immune response. Patients will receive 15 μg of each purified HA protein intramuscularly or 9 μg of each purified HA protein intradermal. To overcome immunosenescence in elderly patients, a high-dose IIV is available that delivers 60 μg of each purified HA protein intramuscularly [21, 23••]. IIVs are available as trivalent, two influenza A strains and the dominant circulating influenza B lineage, or quadrivalent, two influenza A strains and an influenza B strain from each lineage [15, 21]. A cell culture-based trivalent IIV vaccine ($ccIIV_3$) is commercially available and utilizes technology that grows influenza A and B viruses in mammalian cultured cells to bypass some of the disadvantages of egg-based vaccine production [23••].

LAIVs are created through combining a stable, attenuated master donor virus plus HA and NA from the chosen seasonal influenza strains of concern [15]. Once combined, this new virus is called the master virus strain. Attenuated virus means that virus will replicate in hosts but will cause little to no disease as it has been weakened in the laboratory. The master donor virus donates the temperature sensitive properties to the master virus strain resulting in a virus that cannot replicate in the warmer temperatures of the lower respiratory tract, but is freely replicating in the cooler temperatures of the upper respiratory tract [21]. LAIVs are able to induce an IgG strain-specific antibody response as well as mucosal IgA and T cell responses. These additional immune properties of the LAIV, compared to the IIV, confer protection against some antigenic drift strains. LAIVs are quadrivalent containing both the recommended influenza A H1N1 and H3N2 as well as predominant circulating influenza B strains from each lineage [15].

The only commercially vaccine that is guaranteed to be egg-free is the RIV_3, which is trivalent [23••]. From the strains of concern, the HA is sequenced, and proteins are cloned and expressed in insect cells from baculovirus vectors. Utilizing recombinant technology allows for a shorter production time which can provide benefit during seasons of pandemic influenza [21].

The recommendations for the 2015–2016 Northern Hemisphere seasonal influenza virus vaccine were detailed in February 2015. The seasonal influenza vaccine should contain the following coverage: an A/California/7/2009 (H1N1)pdm-09-like virus; an A/Switzerland/9715293/2013 (H3N2)-like virus; and a B/Phuket/3073/2013-like virus (Yamagata lineage). For quadrivalent IIV and LAIV, a B/Brisbane/60/2008-like virus (Victoria lineage) should be included [24].

There are short comings with the current process for seasonal influenza vaccine development. Firstly, patients

Table 1 Vaccines available for the 2014–2015 flu season

Brand Name	Manufacturer	Administration route	Strain coverage	LAIV?	Recommended ages (years)
Afluria	bioCSL	IM	Trivalent	No	≥5[a]
Fluarix	GlaxoSmithKline	IM	Trivalent/quadrivalent	No	≥3
FluBlok	Protein Sciences	IM	Trivalent	No	≥18
Flucelvax	Novartis	IM	Trivalent	No	≥18
FluLaval	GlaxoSmithKline	IM	Trivalent/quadrivalent	No	≥3
FluMist	MedImmune	IN	Quadrivalent	Yes	2–49
Fluvirin	Novartis	IM	Trivalent	No	≥4
Fluzone	Sanofi Pasteur	IM	Trivalent/quadrivalent	No	≥6
Fluzone high-dose	Sanofi Pasteur	IM	Trivalent	No	≥65
Fluzone intradermal	Sanofi Pasteur	ID	Trivalent	No	18–64

IM intramuscular, *ID* intradermal, *IN* intranasal, *LAIV* live attenuated influenza vaccine

[a] Age indication per package insert is ≥5 years; however, ACIP recommends Afluria not be used in children aged 6 months through 8 years because of increased risk for febrile reactions noted in this age group. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5 through 8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine. Afluria may be used in persons aged ≥9 years

with reported egg allergies require careful consideration of product choice and potential consultation with an allergy specialist. The ACIP provided guidance on influenza vaccination in egg-allergic patients for the 2014–2015 influenza season. As previously mentioned, ccIIV$_3$ and RIV$_3$ are not manufactured in eggs, but RIV$_3$ is the only guaranteed egg-free product and is currently approved for use in adults 18–49 years. According to the ACIP, the IIV can be administered to people who have had a mild reaction to egg or egg products (i.e., hives), if administered by a healthcare provider familiar with the management of an allergic reaction and monitored for 30 min for signs of a reaction. For people with a known severe allergy to eggs (i.e., angioedema), the IIV vaccine should be administered under observation of a licensed healthcare provider trained to manage severe allergic reactions. LAIV is not in the ACIP recommendations for egg-allergic patients secondary to little data supporting its safety in this population [23••]. In addition to allergic potential, vaccine manufacturing in sterile embryonated chicken eggs is a lengthy process. In times of pandemic, there is a delay in producing the vaccine for vulnerable populations as well as the potential for short supplies of embryonated chicken eggs [21].

The necessity for annual revaccination makes the seasonal influenza vaccine unique compared to vaccines for other diseases. Antigenic drift, partially due to error prone proteases, is a key factor in the need for yearly reevaluation of vaccine components. Current focus is on creating a universal vaccine targeting highly conserved viral proteins to ensure that immunity is cross-reactive among the viral subtypes as well as producing cell-mediated immunity rather than humoral immunity alone. The HA stem and matrix 2 ion channel protein are examples of highly conserved vial protein targets [15, 22].

The CDC conducts vaccine effectiveness (VE) studies every year to assess the performance and benefit of seasonal influenza vaccines. VE is a measure of how well a seasonal influenza vaccine prevents influenza virus infection in the general population during a given influenza season. Strain changes for the 2014–2015 season led to 19 % adjusted overall effectiveness [25]. The WHO attributes this vaccine mismatch to H3N2 influenza strains that began to emerge in March 2014 after recommendations were put forth for the virus strains of concern for 2014–2015. Vaccination still provides benefit for the population even if it does not closely relate to the leading circulating virus [26].

High-Dose Versus Standard-Dose

In December 2009, the high-dose, trivalent, inactivated influenza vaccine (IIV$_3$-HD) was licensed for use in the US [27•]. The need for a high-dose influenza vaccine arose after observing a lower antibody response and decreased immunity against influenza in adults ≥65-year old [28]. This age group has the highest incidence of influenza-related hospitalizations and deaths [29] prompting researchers to investigate the efficacy of a four time increased amount of HA in the high-dose influenza vaccine compared to the standard-dose, trivalent, inactivated influenza vaccine (IIV$_3$-SD).

In the phase IIIb, multicenter, randomized, double-blind, controlled trial, DiazGranados et al., sought to demonstrate superior efficacy when comparing the IIV$_3$-HD to IIV$_3$-SD in 9172 medically stable participants ≥65-year old at 99 US centers. No participants who received either vaccine developed laboratory-confirmed influenza caused by strains of influenza found in the vaccine, and there was no difference in the incidence of influenza caused by strains not covered by the vaccine when comparing IIV$_3$-HD and IIV$_3$-SD. Patients who received IIV3-HD had higher titers at day 28 post-vaccination compared to participants who received IIV$_3$-SD. There were no adverse effect differences between groups [30]. This study demonstrated that IIV$_3$-HD is well tolerated and provides a greater immune response compared to IIV$_3$-SD.

DiazGranados et al. next conducted a phase IIIb-IV, multicenter, randomized, double-blind, active-controlled trial to compare the efficacy and safety of IIV$_3$-HD to IIV$_3$-SD in 31,989 adults ≥65-year old from 126 US and Canadian centers. Of these participants, 228 participants who received IIV$_3$-HD (1.4 %) and 301 participants who received IIV$_3$-SD (1.9 %) developed laboratory-confirmed influenza. Of the participants who received the IIV$_3$-HD, 8.3 % had a serious adverse event compared to 9.0 % of participants who received the IIV$_3$-SD. Antibody titers 28 days after vaccination were significantly higher after vaccination with IIV$_3$-HD compared to IIV$_3$-SD [27•]. This trial further demonstrated that IIV$_3$-HD offers better protection against influenza when compared to IIV$_3$-SD in subjects ≥65-year old.

Since the approval of the IIV$_3$-HD, there have been retrospective trials published trying to quantitate the clinical efficacy of the vaccine in a variety of patient populations ≥65 years of age. Richardson et al. retrospectively evaluated community dwelling patients ≥65 years of age who received the influenza vaccine during the 2010–2011 influenza season and received care at a Veteran Health Administration medical center. Of the 25,714 patients who received IIV$_3$-HD and the 139,511 patients who received IIV$_3$-SD, 0.3 % was the rate of hospitalization for influenza or pneumonia in both groups. There was also no difference between hospitalization for any cause and death. When stratifying patients by age, patients who were ≥85-year old and received IIV$_3$-HD had a decreased incidence of hospitalization for influenza or pneumonia compared to

patients who received IIV3-SD ($p = 0.02$) [31]. Slzurieta et al. retrospectively evaluated IIV_3-HD and IIV_3-SD in a Medicare population ≥65-year old during the 2012–2013 influenza season. When comparing the 929,730 patients who received IIV_3-HD to the 1,615,545 patients who received IIV_3-SD, the IIV_3-HD was found to be 22 % more effective for the prevention of probable influenza infections in all patients and 36 % more effective in patients ≥85-year old. The IIV_3-HD was 22 % more effective for prevention of influenza hospital admissions and emergency department visits compared to the IIV_3-SD for all age groups [32•]. This retrospective data confirms that IIV_3-HD is more clinically effective than IIV_3-SD in adults ≥65-year old.

Trivalent Versus Quadrivalent

VE of the TIV is reduced if the influenza B lineage prevalent during influenza season does not match the influenza B lineage chosen for the seasonal TIV. Kieninger et al. conducted a phase III, randomized, partially blind study in six countries during the 2010–2011 influenza season to evaluate the immunogenicity, reactogenicity, and safety of the QIV and TIV in adults ≥18 years of age. After evaluating the geometric mean titer (GMT) ratio and seroconversion rate (SCR) difference of the enrolled 4659 subjects, the QIV demonstrated non-inferior immunogenicity when compared to the TIV for the shared strains and demonstrated superiority for the added alternate-lineage B strains. Subjects who received the QIV were highly immunogenic overall compared to those subjects who received either TIV, having a >1.5-fold higher mean hemagglutination inhibition (HI) antibody response over each TIV. The reactogenicity and reported adverse events were similar when comparing the QIV and TIV groups [33].

During the 2010–2011 influenza season, Domachowske et al. compared the QIV to two TIVs (either B/Yamagata or B/Victoria) in a phase III, double-blind, randomized trial in 3027 children 3–17 years of age located in five countries. As was seen in adult subjects, children exhibited non-inferior immunogenicity when comparing QIV to TIV for shared strains and superior immunogenicity against alternate-lineage B strains when comparing QIV to TIV based on GMTs and SCRs. Children who received the QIV were highly immunogenic having a >twofold higher mean HI antibody response over each TIV for the influenza B strain of alternate lineage. In an open-label subgroup of this analysis, the investigators evaluated the QIV in children 6–35 months of age and found that QIV was also immunogenic in this population despite GMTs being lower than those found in the older group. In both the older group and the younger, open-label group, there was no difference between the QIV and the TIV in terms of reactogenicity and safety [34].

Although these studies have demonstrated that immunogenicity improves when QIV is administered versus TIV, it is unclear if this correlates with a clinical benefit. The results of these investigations suggest that a QIV could eliminate the risk of B lineage mismatch thus improving the protection that a vaccine can offer against influenza. In two published studies evaluating the cost-effectiveness of the QIV compared to the TIV in high risk patients for influenza in Hong Kong and the United Kingdom, an indirect and direct cost-benefit was seen with administration of the QIV. In Hong Kong, the cost benefit was dependent upon the difference in cost between the QIV and TIV and the amount of unmatched influenza B lineages with the TIV [35, 36].

Live Versus Inactive

The TIV has been used in the US since 1978 and is still the most widely administered influenza vaccine type in this country. In 2003, the LAIV was approved for use in the US as a TIV but is now QIV. Monto et al. performed a randomized, double-blind, placebo-controlled trial of trivalent inactivated and LAIVs in 1952 healthy adults 18–49 years of age during the 2007–2008 influenza season. The absolute efficacy was 68 % for the inactivated vaccine and 36 % for the LAIV when using culture, real-time PCR, or both to confirm influenza cases. Comparing those patients who received the inactivated vaccine or the LAIV and had culture or PCR confirmed influenza, there was a 50 % reduction in influenza overall and a 60 % reduction in influenza A in patients who received the inactivated vaccine. No serious adverse events occurred in either group [37]. The results from this study suggest that in a healthy adult population ages 18–49-year old, the inactivated influenza vaccines may offer superior protection against influenza.

The Cold-Adapted Live Attenuated Influenza Vaccine, Trivalent (CAIV-T) study group compared the efficacy and safety of the intramuscular inactivated TIV to the intranasal LAIV in 8352 children 6–59 months of age during the 2004–2005 influenza season. Children who received the LAIV had 54.9 % fewer cases of culture-confirmed influenza compared to those children who received the inactivated TIV ($p < 0.001$). The superiority of the LAIV compared to the inactivated vaccine persisted whether the vaccine and the virus were antigenically well-matched or not. Children who received the LAIV had higher rates of hospitalizations for any cause and of wheezing, both noted especially in children 6–11 months of age [38]. Ashkenazi

et al. confirmed the results of the CAIV-T study group, by comparing the efficacy of LAIV to inactivated TIV in children 6–71 months of age with a history of recurrent respiratory tract infections. LAIV reduced the number of antigenically similar influenza cases and respiratory tract infection related visits to healthcare providers compared to inactivated TIV. Children who received either vaccine had a similar incidence of wheezing [39].

A meta-analysis of nine trials evaluating the efficacy and safety of the LAIV in children aged 6-month to 17-year old compared to either placebo or inactivated TIV demonstrated that the LAIV resulted in 44 % fewer cases of influenza caused by similar strains and 48 % fewer cases against all strains compared to the inactivated TIV. Investigators also found that the LAIV reduced the incidence of influenza-related acute otitis media and the severity of influenza illness in children between the ages of 24–71 months [40]. This meta-analysis further supports the preferential use of LAIV compared to inactivated TIV to vaccinate children ≥2 years of age.

Recommendations

Advisory Committee on Immunization Practices

The ACIP is a group consisting of medical and public health experts who make recommendations in regards to the appropriate use of vaccines in the US to control diseases. Their recommendations are passed on to the director of the CDC for ultimate approval and publication. For the 2014–2015 influenza season, the ACIP recommends that everyone ≥6 months of age receive the influenza vaccine annually in the absence of contraindications to the vaccine. They recommend that the vaccine be administered prior to the influenza season and as soon as the vaccine becomes available to the community. For the 2014–2015 influenza season, two doses of the influenza vaccine are recommended in children between the ages of 6 months and 8 years, if they did not receive at least one dose of the 2013–2014 influenza vaccine or at least two influenza vaccines since July 1, 2010. The first dose should be administered as soon as possible after the influenza vaccine becomes available for the season, and the second dose should be administered ≥4 weeks later [23••].

Despite the debate surrounding the efficacy when comparing the LAIV and the IIV, the ACIP still recommends either for adults. In children 2–8-year old, the ACIP recommends administering the LAIV over the IIV as long as there are no contraindications to the LAIV. People who should not receive the LAIV include people <2-year-old and >49-year-old pregnant women, immunocompromised, children 2–17-year-old taking aspirin, children 2–4-year-old with asthma or wheezing episodes, and people with an egg allergy. Despite literature suggesting that IIV_3-HD is superior to IIV_3-SD, the ACIP recommends that further data be published to support these findings before they solely recommend IIV_3-HD in adults ≥65-year-old [23••].

Given the superiority data regarding immunogenicity when comparing QIV to TIV for influenza B lineages and the availability of QIVs approved for use in people ≥6-month-old, the ACIP recommends receiving a QIV over TIV to provide broader protection against influenza [23••]. Of the 156 million doses of influenza vaccine available for the 2014–2015 influenza season, only approximately 50 % of these doses will be the QIV [41]. The ACIP recommends that if a QIV is not available at the time of influenza vaccine administered, the TIV should be administered [23••].

The ACIP strongly recommends influenza vaccination of populations identified as being at greater risk for developing influenza-related complications including adults ≥65 years of age and children <2 years of age, pregnant women, nursing home, and long-term care facility residents and American Indians and Alaskan Natives. Also people with the following medical conditions are at greater risk of influenza-related complications: asthma, chronic lung disease, immunocompromised, morbid obesity, kidney disease, liver disease, diabetes, heart disease, neurological disease, and metabolic disorders [23••].

American Academy of Pediatrics

The American Academy of Pediatrics' (AAP) committee on infectious disease is comprised of pediatric specialists who provide expert opinion consensus guidance on seasonal influenza. The AAP recommends that all people ≥6 months of age be vaccinated annually with the influenza vaccine. The recommendations regarding the influenza vaccine for the 2014–2015 influenza season are in line with the recommendations from ACIP including no preference for TIV or QIV; LAIV should preferentially be administered to children 2–8-year old, and children 6-month to 8-year old need two doses of the influenza vaccine ≥4 weeks apart unless they received at least one dose of the 2013–2014 influenza vaccine or ≥2 doses of the influenza vaccine since July 1, 2010 [42].

Conclusion

The CDC estimates the influenza vaccine to be 19 % effective this season [43], which is very low compared to previous seasons, but is likely due to an antigenic mismatch between circulating viruses and virus strains contained in the vaccine. This low efficacy emphasizes the

need for ongoing influenza vaccine research and the importance of vaccination to reduce influenza-related complications and mortality, especially in at-risk populations.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

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