REVIEW

Flu Myths: Dispelling the Myths Associated With Live Attenuated Influenza Vaccine

PRITISH K. TOSH, MD; THOMAS G. BOYCE, MD; AND GREGORY A. POLAND, MD

Live attenuated influenza vaccine (LAIV), commercially available since 2003, has not gained widespread acceptance among prescribers. This underuse can be traced to several misperceptions and fears regarding LAIV. This review examines both the facts (safety, immunogenicity, and effectiveness) and the most pervasive myths about LAIV. Live attenuated influenza vaccine is a safe, highly immunogenic, and effective vaccine. It is well tolerated; only mild and transient upper respiratory infection symptoms occur with LAIV vs placebo, even in higher-risk patients with asthma or the early stages of human immunodeficiency virus. It is immunogenic, especially in induction of mucosal immunity. In certain populations, LAIV is as effective as, and in some cases more effective than, inactivated influenza in preventing influenza infection. It appears to be more effective in preventing influenza infection than trivalent inactivated influenza vaccine when the vaccine virus strain does not closely match that of the circulating wild-type virus. Many myths and misperceptions about the vaccine exist, foremost among them the myth of genetic reversion. Independent mutation in 4 gene segments would be required for reversion of the vaccine strain of influenza virus to a wild type, an unlikely and as yet unobserved event. Although shedding of vaccine virus is common, transmission of vaccine virus has been documented only in a single person, who remained asymptomatic. In the age groups for which it is indicated, LAIV is a safe and effective vaccine to prevent influenza infection.

Mayo Clin Proc. 2008;83(1):77-84

ACIP = Advisory Committee on Immunization Practices; HAI = hemagglutination inhibition assay; HIV = human immunodeficiency virus; LAIV = live attenuated influenza vaccine; TIV = trivalent inactivated influenza vaccine

Despite the colloquial use of the term *flu* for wintertime infections, influenza is a serious infection causing substantial morbidity and mortality worldwide and resulting in approximately 250,000 to 500,000 deaths per year.[1] Influenza epidemics and pandemics have had disastrous effects on a global scale. For example, the influenza pandemic of 1918 claimed many more lives than World War I, which was being fought at the time.[2] Even in years of relatively mild epidemics, almost 3 times as many Americans die of influenza as of human immunodeficiency virus (HIV) infection and AIDS.[3,4] Safe and effective vaccines have been developed that have been useful in preventing this disease. Influenza vaccines induce an immune reaction to 2 influenza surface glycoproteins, neuraminidase and hemagglutinin, that protect against influenza infection and its complications. Two vaccines, trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV), have been approved by the Food and Drug Administration in the United States.

TRIVALENT INACTIVATED INFLUENZA VACCINE

Intramuscularly injected TIV is the most widely used and studied of the available vaccines. The safety profile of TIV is well established, with mild injection site soreness being the only common adverse effect vs placebo in adults.[5-7] When the surface glycoproteins contained in the vaccine closely match those of the circulating virus, the vaccine is 70% to 90% effective in preventing laboratory-confirmed influenza infection in healthy adults younger than 65 years and reduces symptomatic influenzalike illness by 34% and physician visits by 42%.[8-10] The vaccine is less effective in reducing symptomatic influenzalike illness in healthy children younger than 9 years (45%-70%)[11] and in frail adults 65 years and older (30%-50%).[12]

In addition to being least effective in the 2 populations at greatest risk for severe disease (young children and the elderly), TIV also has other limitations, which include well-publicized vaccine shortages, unfounded though persistent perceptions regarding Guillain-Barré syndrome, the need for needle injection, and extended production time owing to the use of egg-based vaccine production. The value of the vaccine has been established; it has been shown to reduce both documented influenza infections and hospitalization. A meta-analysis of 20 studies involving influenza immunization of elderly people demonstrated an efficacy of 32% to 45% in preventing hospitalization from pneumonia.[12] The effectiveness of TIV can be compromised in years in which the hemagglutinin and neuraminidase proteins contained in the vaccine do not closely match those of circulating viruses. This vaccine has had variable acceptance and use, as evidenced by low vaccination rates among minority ethnic groups, those of low socioeco-

From the Vaccine Research Group (P.K.T., G.A.P.), Division of Infectious Diseases (P.K.T., T.G.B.), and Division of Pediatric Infectious Diseases (T.G.B.), Mayo Clinic, Rochester, MN.

Dr Poland is the chair of a data safety monitoring committee for a novel influenza vaccine being developed by Merck Research Laboratories. He is an investigator for an influenza clinical trial funded by Protein Sciences and has offered consulting advice on influenza vaccines to GlaxoSmithKline, Novartis, CSL Ltd, Novavax, Dynavax, and PowderMed. Dr Boyce is on the Speaker's Bureau for Sanofi-Pasteur and MedImmune.

Individual reprints of this article are not available. Address correspondence to Gregory A. Poland, MD, Vaccine Research Group, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (poland.gregory@mayo.edu).

nomic status, young people with chronic diseases, and health care professionals.[13] The intramuscular route of TIV vaccination has been cited as one of several reasons health care professionals do not seek immunization despite the recommendation by the Centers for Disease Control and Prevention to do so; the nationwide vaccination rate for health care professionals is only approximately 40%.[14-16] In addition, TIV immunization requires trained personnel to administer the vaccine as well as blood and sharps precautions.

LIVE ATTENUATED INFLUENZA VACCINE

Many of the TIV-related limitations have been addressed by the creation of a trivalent, intranasal, cold-adapted LAIV (FluMist; MedImmune, Gaithersburg, MD). The vaccine virus replicates only in the colder temperatures of the upper respiratory tract, inducing both local mucosal and systemic immunity without replicating systemically and causing disease.[17]

Influenza is an enveloped, negative-sense, single-stranded RNA virus composed of 8 segmented genes. The prototype influenza vaccine virus was created by passaging influenza A/Ann Arbor/6/1960 at gradually lower temperatures until the virus mutated to a form ideal for vaccine use.[17] The mutated virus was cold adapted, replicated at 25°C but not at human core body temperatures, remained temperature sensitive, and was attenuated and thus did not produce systemic symptoms of influenza disease in humans.

Annual vaccine strains are created by crossing the cold-adapted donor strains with wild-type influenza strains and selecting for viruses that maintain the attenuation properties of the donor strain and the hemagglutinin and neuraminidase genes of the wild-type strain. This occurs by reassortment of the 8 RNA genomic segments between the crossing strains. The result is a virus strain that retains the 4 gene segments that confer cold adaptivity, temperature sensitivity, and attenuation, as well as the 2 gene segments that code for the antigenically relevant hemagglutinin and neuraminidase of the circulating wild-type influenza virus.

Although LAIV has proven to be safe and effective and has been approved for use in the United States since 2003, it has not gained widespread acceptance among physicians and nurses. Several reasons have been postulated to explain its failure to gain broader acceptance. Live attenuated influenza vaccine is slightly more expensive ($17.95 per dose vs $11.72 to $15.54 per dose of TIV).[18] For storage, the new formulation requires refrigeration, and the previous one required freezing. Short-lived symptoms of mild upper respiratory tract infection can be associated with LAIV and could deter some vaccine recipients.[19-21] However, much of the hesitancy to use this vaccine appears to stem from multiple unsubstantiated fears and misperceptions rather than from established data. Herein we review the literature to address 5 pervasive misconceptions regarding this vaccine.

MYTH 1: THE VACCINE VIRUS WILL REVERT TO WILD TYPE

Underlying the reluctance to use LAIV is the fear that the live virus vaccine can mutate, revert to wild-type virus, and induce disease in the recipient and others. However, no such reversion has ever been observed in preclinical studies, in any of the tens of thousands of participants in vaccine trials during the past 4 decades, or in the millions of people who have received the vaccine since its licensure in 2003. For reversion to occur, the 4 gene segments conferring the attenuation would need to mutate back to wild type.[22] The likelihood of these 4 independent events occurring in the same virus is remote. A 1999 study by Cha et al[23] showed that all 18 viruses recovered from the respiratory secretions of 17 participants after intranasal inoculation were identical to the original vaccine virus. Among 11,800 nucleotides deduced, only 3 nucleotide changes were found. Thus, even after viral replication in human hosts, the vaccine virus retains genetic stability.[23,24] In fact, despite exhaustive testing, reversion to wild type has never been demonstrated.

MYTH 2: VIRAL SHEDDING WILL RESULT IN VIRUS TRANSMISSION

Transmission of high titers of live virus would be necessary to spread virus to others and cause disease. Thus, shedding is not synonymous with transmission. Viral shedding has been well documented after vaccination with attenuated live virus. Peak titers of viral shedding in the respiratory tract range from 0.9 to 4.0 $\log_{10}TCID_{50}$/mL in children and from 0.4 to 3.0 $\log_{10}TCID_{50}$/mL in adults. The mean titers of virus needed for infectivity range from 2.5 to 4.6 $\log_{10}TCID_{50}$ in children and from 4.9 to 6.4 $\log_{10}TCID_{50}$ in adults.[25,26] The amount of virus shed by vaccinated adults is less than the amount needed to infect exposed, susceptible adults. Some overlap exists between the titers associated with viral shedding and the titers needed for infectivity in children; however, large studies conducted with LAIV have shown transmission in only a single instance.[27] A study in a Finnish day care of 197 children aged 8 to 36 months showed that 80% of vaccinated children shed virus for a mean of 7.6 days.[27] Studies in adults suggest that the duration of shedding is considerably shorter.[26] In the previ-

ously mentioned Finnish day care study, 1 child in the placebo group had transiently detectable vaccine-type virus on a single day, indicating transmission from a vaccinated child; the child remained asymptomatic.[27] This is the only documented case of transmission of the vaccine virus to another human. It is also important to remember that transmission is not synonymous with disease. The child in question did not have any signs or symptoms of influenza infection. The vaccine virus retains its attenuation properties after replication and is capable of only limited replication; no disease resulting from the transmission of the vaccine virus has been documented.

King et al[28,29] published studies comparing viral shedding in HIV-infected vs non–HIV-infected adults and children after LAIV vaccination. One study randomized 57 HIV-infected adults (HIV class A1-2) and 54 non–HIV-infected adults to receive either LAIV or intranasal placebo. Five days after receipt of vaccine, only one HIV-infected vaccinee had a viral culture positive for LAIV from nasal and throat swab specimens.[28] In another study, 24 HIV-infected children without evidence of immunosuppression (asymptomatic or mild symptoms; >500 CD4 cells) and 25 non–HIV-infected children aged 1 to 7 years were randomized to receive LAIV or placebo; they then crossed over to receive the other vaccine 1 month later. Shedding of vaccine virus occurred in 3 (13%) of the HIV-infected children and 7 (28%) of the non–HIV-infected children. Shedding of vaccine virus is reduced in those who have been vaccinated previously with TIV; thus, it was unsurprising that less shedding of vaccine virus occurred in HIV-infected children, who had a higher rate of previous TIV vaccination.[29]

MYTH 3: LIVE VIRUS VACCINATION LEADS TO SERIOUS ADVERSE REACTIONS

The safety of LAIV has been extensively studied. No serious complications caused by vaccination with LAIV have been reported in those for whom the vaccine is licensed. Belshe et al[19] conducted a trial comparing cold-adapted influenza vaccination with placebo in 1602 healthy children aged 15 to 71 months. The only significant differences found were that vaccinees had more rhinorrhea (58% vs 47%; $P<.001$) and more fever (15% vs 11%; $P=.05$) than placebo recipients after the first dose. The fever was low grade (mean temperature, 38.2°C) and lasted a mean of 1.4 days. After a second vaccine dose, no difference in adverse effects was observed between vaccinees and placebo recipients.

A recent trial by Belshe et al[30] randomized 8352 healthy children aged 6 to 59 months to receive TIV and an intranasal saline spray as placebo or a refrigerator-stable formulation of LAIV that was recently approved by the Food and Drug Administration and an intramuscular injection of saline as placebo. Children who received LAIV and intramuscular placebo had higher rates of runny or stuffy nose (57.0% vs 46.3%; $P<.001$) and elevated temperature (>37.8°C) (5.4% vs 2.0%; $P<.001$) than those receiving TIV and intranasal placebo. Overall, no significant difference in other adverse events was noted between the 2 groups; however, those younger than 24 months in the LAIV treatment arm were found to have an increased rate of clinically remarkable wheezing in the 42 days after vaccination (3.2% vs 2.0%; adjusted difference, 1.2%; 95% confidence interval, 0.1%-2.3%). In post hoc analysis, children aged 6 to 11 months who were receiving LAIV had a higher rate of hospitalization for any cause (6.1% vs 2.6%; difference, 3.5%; 95% confidence interval, 1.4%-5.8%). These data suggest that the vaccine is well tolerated by those older than 24 months but could potentially cause some adverse events in those younger than 24 months.

The safety of LAIV has also been evaluated in adults. Nichol et al[20] studied the response to cold-adapted influenza vaccine vs placebo in 4561 healthy, working adults. Vaccine recipients were more likely to have sore throat and rhinorrhea within a week of vaccination ($P<.05$). The symptoms were well tolerated and lasted a mean of 2 days. No serious complications were observed, and symptoms spontaneously resolved.

Another study that included both children and adults supported the above findings. Edwards et al[21] compared an investigational bivalent LAIV (not the currently licensed formulation or dose), TIV, and placebo in more than 5000 healthy participants aged 1 to 65 years. A saline placebo was administered intramuscularly in those receiving LAIV, intranasally in those receiving TIV, and both intramuscularly and intranasally in those receiving placebo alone. Compared with placebo controls, recipients of LAIV had higher rates of sore throat (21% vs 10%; $P<.00005$), coryza (26% vs 20%; $P<.00005$), lethargy (22% vs 17%; $P<.00005$), headache (23% vs 20%; $P<.005$), and muscle ache (15% vs 13%; $P<.05$). No serious complications and no difference in fever, chills, nausea, or cough were observed. However, compared with controls, TIV recipients had significantly higher rates of sore throat (12% vs 10%; $P<.05$), lethargy (18% vs 17%; $P<.05$), injection site redness (11% vs 8%; $P<.00005$), induration (12% vs 7%; $P<.00005$), and tenderness (51% vs 36%; $P<.00005$). No other serious complications were observed with TIV.

The safety of LAIV has also been evaluated in higher-risk individuals, and no safety concerns have yet been identified. King et al[28] randomized 57 volunteers with mild HIV disease (asymptomatic or with mild symptoms; >200 CD4 cells) and 54 non–HIV-infected volunteers to receive

LAIV or placebo. A statistically significant increase in rhinorrhea was noted in vaccine recipients, regardless of HIV status, but no other adverse effects were observed. No increase in influenza vaccine viral shedding or HIV RNA levels and no decrease in CD4 counts were reported among patients in the LAIV treatment arm vs those who received placebo. Similar results were found in a study of 24 HIV-infected children aged 1 to 7 years.[29]

The use of LAIV in patients with asthma remains controversial and is not currently recommended by the Advisory Committee on Immunization Practices (ACIP), although this policy is being reviewed. In a randomized controlled trial of LAIV in 48 children aged 9 to 17 years with moderate to severe asthma, LAIV was well tolerated, with no serious complications and no significant difference between the 2 groups in symptoms including fever, rhinorrhea, sore throat, and fatigue (all, $P>.99$). No significant change in forced expiratory volume in the first second of expiration ($P=.78$), peak flow ($P=.24$), β-adrenergic rescue medication use ($P=.49$), or asthma exacerbations ($P=.49$) were observed with the vaccine vs the placebo group.[31]

As mentioned above, clinically remarkable wheezing was found in those younger than 24 months who received LAIV.[25] Furthermore, a post hoc subgroup analysis of a study randomizing 9689 healthy children (1-17 years) found that children aged 18 to 35 months receiving LAIV were 4 times more likely than placebo recipients to have an office visit coded as being due to asthma in the 42 days after vaccination.[32] However, this result was not statistically significant at the 95% confidence limit, and the design of the study had several serious flaws. More than 1500 statistical tests were performed without adjusting for multiple comparisons, leading to the implausible conclusion that recipients of LAIV were more likely to experience 24 types of adverse events (including warts and enuresis) and less likely to experience 51 other types of adverse events (including trauma and constipation). Other evidence points to the association between LAIV and asthma being spurious: asthma events were evenly distributed in the 42 days after vaccination with no clustering of events around the time of viral replication (the first 7-10 days). Furthermore, children aged 18 to 35 months did *not* have an increased risk of wheezing in the 42 days after vaccination. No increased risk of asthma events within 42 days of vaccine receipt was observed in a review by Piedra et al[33] of the safety data from a nonrandomized, open-label trial of 11,096 children aged 18 months to 4 years, 5 to 9 years, and 10 to 18 years. Furthermore, a recently published trial randomizing more than 2200 children (6-17 years) with asthma to receive either LAIV or TIV showed no difference in asthmatic complications between the 2 groups, including rates of asthma exacerbations, changes in peak flows, and changes in asthma symptom score.[34]

The use of LAIV in elderly people with chronic respiratory illness was evaluated by Gorse et al[35] in a trial that randomized 2215 persons older than 50 years with chronic obstructive pulmonary disease to receive TIV and LAIV or TIV and intranasal saline placebo. Those receiving TIV and LAIV were found to have significantly longer duration of stuffy or runny nose (1.9 vs 1.5 days; $P<.001$), increased shortness of breath (1.0 vs 0.75 day; $P<.0001$), chills (0.35 vs 0.29 day; $P<.05$), headache (0.86 vs 0.69 day; $P<.05$), and intramuscular injection site soreness (0.13 vs 0.08 day; $P<.05$); however, these differences, which consisted only of fractions of days, were not thought to be clinically relevant.

A study by Jackson et al[36] examined the safety of LAIV in 200 persons older than 65 years with chronic medical conditions, including chronic cardiovascular disease, chronic pulmonary disease, and diabetes. Participants were randomized to receive either intramuscular TIV and LAIV or intramuscular TIV and placebo. In this population, a statistically significant difference in adverse effects was noted only for sore throat in the LAIV intervention group (15% vs 2%; $P=.001$). Four people in the trial, 2 who were receiving LAIV and 2 who were receiving placebo, had a serious adverse event that was a complication of an underlying chronic condition and so was considered to be unrelated to the receipt of vaccine or placebo. For those older than 50 years, LAIV is not currently recommended by ACIP; however, this policy is under review.

MYTH 4: LAIV IS EFFECTIVE ONLY WHEN THE VACCINE STRAIN IS IDENTICAL TO CIRCULATING VIRUS

Vaccines protect against infection by simulating the presence of the pathogen and allowing the development of cellular and humoral immunity. Variables that affect the immune response to vaccines include age, allelic variations, preexisting immunity, number of doses, and vaccine antigen.

Studies in children and elderly adults have shown that TIV is more likely to produce seroconversion and higher serum hemagglutination inhibition assay (HAI) titers than is LAIV.[37-47] However, the immune response to LAIV is designed to mimic that to natural influenza infection. The immune protection conferred by natural infection is thought to result in a broader immunologic response, including induction of local IgA nasal mucosal antibodies, cell-mediated cytotoxicity, and serum antibodies.[37-47]

Although TIV induces high serum HAI titers, it does not effectively induce mucosal immune responses.[40,41,44-46] In

contrast, LAIV has been shown to induce mucosal immunity in children, young adults, and chronically ill adults.[43,44,47,48] Furthermore, the induction of mucosal immunity occurred with equal frequency among previously seropositive and seronegative participants. By neutralizing the virus at the portal of entry before replication, infection, and dissemination can occur, mucosal immunity could confer better protection against influenza than serum antibodies; however, this superior protection has not been established conclusively.

Influenza vaccines work best when the hemagglutinin and neuraminidase contained in the vaccine are antigenically similar to that of the circulating influenza virus. In children, LAIV has the advantage of conferring better protection against heterologous (drifted) strains than TIV.[20,21,49-51] Improved cross-protection likely occurs because the live virus presents not only the surface glycoproteins but also other viral antigens in their native conformation, providing more antigenic targets for induction of immunity. In a 2-year study by Belshe et al,[50] participants were given the influenza A/Wuhan/359/1995(H3N2) LAIV strain during the first year of the study. The circulating virus strain during the second year of the trial was influenza A/Sydney/05/1997(H3N2), which was antigenically different from the influenza A/Wuhan/359/1995(H3N2) strain contained in the LAIV of the previous year. Nonetheless, the efficacy of LAIV in preventing culture-confirmed influenza A/Sydney/05/1997(H3N2) infection was found to be 86%. Protection against heterologous challenge has also been shown by other studies, with LAIV protecting better against drifted strains than TIV (relative reduction, 58%).[30] In contrast, the immunogenicity of TIV to drifted strains in children is generally poor.[20,21,49,51]

A recently published study of 1247 adults (18-47 years) compared the efficacy of LAIV and TIV in prevention of culture- or polymerase chain reaction–confirmed influenza infection during a period when the vaccines were not closely matched to the circulating virus.[52] The study found no statistically significant difference between the 2 vaccines in protection against heterologous challenge. It remains unclear why LAIV, which has been shown to provide superior protection against heterologous challenge in children, did not do so in this study in adults.

MYTH 5: LAIV IS NOT AS EFFECTIVE AS TIV IN PREVENTING INFLUENZA INFECTION

The efficacy of LAIV against influenza infection has been measured using different parameters. Efficacy refers to reduction of culture-positive influenza disease, and effectiveness to other favorable vaccine outcomes, such as fewer cases of symptomatic febrile respiratory illness, fewer days of missed work, and fewer physician visits. Trials evaluating efficacy have been more commonly conducted in children, who shed more virus and do so for longer than adults.

In a 1996-1997 multicenter trial, Belshe et al[19] studied 1602 children (15 to 71 months) who were randomized to receive either 1 or 2 doses (60 days apart) of LAIV or placebo. In the second year of the study, vaccine or placebo were readministered. In the first year, the vaccine was found to be 87% efficacious against the influenza A(H3N2) strain and 91% efficacious against influenza B in vaccinees receiving a single dose; in vaccinees receiving 2 doses, the efficacy was 95% against the influenza A(H3N2) strain and 91% against influenza B. During the second year of the trial, an efficacy of 86% was still observed although the circulating virus was dissimilar to the influenza A(H3N2) vaccine strain. The vaccine was also effective in reducing febrile illness by 21%, febrile otitis media by 33%, and physician visits by 13%.

Influenza A(H1N1) virus was not among the circulating strains of wild-type influenza during the years of the aforementioned study. To evaluate the efficacy of the vaccine against influenza A(H1N1), a subset of 222 children from the study were challenged with the influenza A/Shenzhen/227/95-like(H1N1) vaccine strain. The vaccine was 83% efficacious in preventing viral shedding. An independent correlation was noted between the presence of serum HAI or nasal wash IgA titers before challenge and a reduction in viral shedding.[53]

An efficacy trial has also been performed in adults. Treanor et al[54] randomized 103 adults aged 18 to 45 years to receive LAIV, TIV, or placebo. The participants were then challenged with wild-type influenza A/Shangdong/9/1993(H3N2) and influenza A/Texas/36/1991 as well as influenza B/Panama/45/1990. Infection was defined as a respiratory illness with either a positive culture for influenza or a 4-fold increase in influenza HAI titers. Of the 2 vaccines, LAIV had greater efficacy (85% for LAIV vs 71% for TIV), a difference that was not statistically significant. The study was not sufficiently powered and did not compare LAIV to TIV directly but rather combined the data from a placebo-controlled study of LAIV with those from a placebo-controlled study of TIV.

Nichol et al[20] studied the effectiveness of LAIV vaccine in the prevention of febrile illness in adults (18-64 years) by randomizing 4561 healthy adults to receive LAIV or placebo. During the peak influenza outbreak period, vaccinees had episodes of viral illness that were similar to those seen in the placebo group. However, they experienced significantly fewer incidences of severe febrile illness (19% reduction; $P=.002$) and febrile upper respiratory illness (24% reduction; $P<.001$) and shorter

periods of febrile illness (23% reduction; $P<.001$) and severe febrile illness (27% reduction; $P<.001$). The vaccine also effectively reduced the days of work lost and the number of health care professional visits due to severe febrile illness by 18% and 25%, respectively, and due to febrile upper respiratory illness by 28% and 41%, respectively.

Recently published randomized trials in children suggest that LAIV is more efficacious than TIV in preventing influenza. Ashkenazi et al[55] randomized 2187 children aged 6 to 71 months with recurrent respiratory tract infections to receive 2 doses (a month apart) of either LAIV or TIV. During the subsequent influenza season, the number of culture-confirmed cases of influenza in the LAIV group was half that in the TIV group (3% vs 6%). Fleming et al[34] randomized 2229 children (6-17 years) with asthma to receive either LAIV or TIV. The incidence of culture-confirmed influenza illness was reduced by 35% in the LAIV vs TIV arm (4% vs 6%). Belshe et al[30] randomized 8352 children (6-59 months) to LAIV or TIV and found 55% fewer cases of culture-confirmed influenza in those who received LAIV vs TIV ($P<.001$).

The efficacy of LAIV used in conjunction with TIV in elderly people was studied by Treanor et al.[56] During the 3-year trial, 532 nursing home residents were randomized to receive TIV and cold-adapted influenza A(H3N2) LAIV or TIV and placebo. Compared with those who received TIV alone, those randomized to receive both vaccines had a 61% greater reduction in laboratory-documented influenza A infection.

Gorse et al[35] similarly randomized 2215 patients (>50 years) with chronic obstructive pulmonary disease to receive TIV and LAIV or TIV and intranasal saline placebo. No significant difference in efficacy was noted between the 2 groups; however, the study, which enrolled 1800 participants, did not accrue the 4000 patients projected to be needed to detect a statistical difference in efficacy.

CURRENT RECOMMENDATIONS AND INDICATIONS

Currently, LAIV is approved in the United States for use in healthy, nonpregnant people aged 2 to 49 years.[57,58] Those with underlying medical conditions such as pulmonary disease, cardiovascular disease, metabolic disease, renal disease, or hemoglobinopathies should receive TIV instead. According to the guidelines from the ACIP, either TIV or LAIV is acceptable for the vaccination of health care professionals.[58] However, the use of LAIV in health care professionals is particularly encouraged during times of TIV shortage. For health care professionals in contact with severely immunocompromised patients (ie, those for whom reverse isolation is required), TIV is preferred over LAIV because of the theoretical risk of transmission. The ACIP recommends that health care professionals receiving LAIV refrain from contact with severely immunosuppressed patients (those requiring protective isolation) for 7 days after vaccination.

CONCLUSION

Influenza continues to be one of the largest infectious killers in the United States and throughout the world. Indeed, it results in more deaths in the United States than all other vaccine-preventable diseases combined. On average, it is responsible for the deaths of 36,000 Americans and 250,000 to 500,000 people worldwide each year. Although safe and effective vaccines are available, they are underused. In particular, health care professionals are poorly informed about LAIV. Live attenuated influenza vaccine more closely mimics the immunity induced by natural infection than other vaccine formulations, with minimal adverse effects. The vaccine has been shown to be very effective in preventing infection and to be safe even in higher-risk populations; however, larger studies in these populations are needed. Because it can be administered intranasally, LAIV should be more practical than TIV, which is injected intramuscularly, particularly when mass dispensing is required, such as during major epidemics and pandemics, and for use in children. The National Institutes of Health has recently awarded a multimillion-dollar contract to develop live attenuated candidate pandemic influenza vaccines.[59]

Despite a wealth of data to the contrary, there continues to be hesitancy to use this vaccine, largely due to unfounded fears regarding transmissibility, safety, and efficacy. In actuality, LAIV has several characteristics that favor its use, including its inability to replicate at core body temperatures (requiring instead the cooler temperatures of the upper airway) and its induction of immunity at the portal of virus entry, which mimics the immune response to wild-type infection. Compared with TIV, it offers better protection against disease in years in which the antigenic match between circulating and vaccine strains is incomplete. In young children, it is more effective than TIV, regardless of whether there is antigenic match between the circulating and vaccine strain. This characteristic holds promise for eventual mass vaccination of children, with resultant herd immunity and indirect protection of adults in the community.[60] Wider appreciation of these advantages could lead to wider acceptance of LAIV, resulting in better protection against influenza infection and reduction in the substantial morbidity and mortality with which it is associated.

REFERENCES

1. World Health Organization. Influenza. www.who.int/mediacentre/factsheets/fs211/en/. Revised March 2003. April 2006. Accessed November 2, 2007.
2. Reid AH, Fanning TG, Hultin JV, Taubenberger JK. Origin and evolution of the 1918 "Spanish" influenza virus hemagglutinin gene. *Proc Natl Acad Sci U S A*. 1999;96(4):1651-1656.
3. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*. 2003; 289(2):179-186.
4. CDC Centers for Disease Control and Prevention. CDC HIV/AIDS Fact Sheet: a glance at the HIV/AIDS epidemic. http://img.thebody.com/legacyAssets/71/03/hiv_epidemic.pdf. Updated April 2006. Accessed November 2, 2007.
5. Nichol KL, Margolis KL, Lind A, et al. Side effects associated with influenza vaccination in healthy working adults: a randomized, placebo-controlled trial. *Arch Intern Med*. 1996;156(14):1546-1550.
6. Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccine in the elderly: a randomized, placebo-controlled trial [published correction appears in *JAMA*. 1991;265(21):2810]. *JAMA*. 1990; 264:1139-1141.
7. Govaert TME, Dinant GJ, Aretz K, Masurel N, Sprenger MJW, Knottnerus JA. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. *BMJ*. 1993;307(6910):988-990.
8. Wilde JA, McMillan JA, Serwint J, Butta J, O'Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized trial. *JAMA*. 1999;281(10):908-913.
9. Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: a randomized controlled trial. *JAMA*. 2000;284(13):1655-1663.
10. Demicheli V, Jefferson T, Rivetti D, Deeks J. Prevention and early treatment of influenza in healthy adults. *Vaccine*. 2000;18(11-12):957-1030.
11. Zangwill KM, Belshe RB. Safety and efficacy of trivalent inactivated influenza vaccine in young children: a summary for the new era of routine vaccination. *Pediatr Infect Dis J*. 2004;23(3):189-197.
12. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. *Ann Intern Med*. 1995;123(7):518-527.
13. Centers for Disease Control and Prevention (CDC). Influenza and pneumococcal vaccination levels among adults aged greater than or equal to 65 years—United States, 1997. *MMWR Morb Mortal Wkly Rep*. 1998;47(38):797-802.
14. Weingarten S, Riedinger M, Bolton LB, Miles P, Ault M. Barriers to influenza vaccine acceptance: a survey of physicians and nurses. *Am J Infect Control*. 1989;17(4):202-207.
15. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP) [published correction appears in *MMWR Recomm Rep*. 2004;53(32):743]. *MMWR Recomm Rep*. 2004;53(RR-6):1-40.
16. Poland GA, Tosh P, Jacobson RM. Requiring influenza vaccination for health care workers: seven truths we must accept. *Vaccine*. 2005;23(17-18): 2251-2255.
17. Maassab HF. Biologic and immunologic characteristics of cold-adapted influenza virus. *J Immunol*. 1969;102(3):728-732.
18. Centers for Disease Control and Prevention. Influenza vaccine price list. www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm#flu. Updated September 18, 2007. Accessed Nov 9, 2007.
19. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. *N Engl J Med*. 1998;338(20):1405-1412.
20. Nichol KL, Mendelman PM, Mallon KP, Jackson LA, Gorse GJ, Belshe RB, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial. *JAMA*. 1999;282(2): 137-144.
21. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccine for the prevention of influenza A disease. *J Infect Dis*. 1994;169(1):68-79.
22. Snyder MH, Betts RF, DeBorde D, et al. Four viral genes independently contribute to attenuation of live influenza A/Ann Arbor/6/60 (H2N2) cold-adapted reassortant virus vaccines. *J Virol*. 1988;62(2):488-495.
23. Cha TA, Kao K, Zhao J, Fast PE, Mendelman PM, Arvin A. Genotypic stability of cold-adapted influenza virus vaccine in an efficacy clinical trial. *J Clin Microbiol*. 2000;38(2):839-845.
24. Buonagurio DA, O'Neill RE, Shutyak L, et al. Genetic and phenotypic stability of cold-adapted influenza viruses in a trivalent vaccine administered to children in a day care setting. *Virology*. 2006 Apr 10;347(2):296-306. Epub 2006 Jan 18.
25. Talbot TR, Crocker DD, Peters J, et al. Duration of virus shedding after trivalent intranasal live attenuated influenza vaccination in adults. *Infect Control Hosp Epidemiol*. 2005;26(5):494-500.
26. Murphy BR, Coelingh K. Principles underlying the development and use of live attenuated cold-adapted influenza A and B virus vaccines. *Viral Immunol*. 2002;15(2):295-323.
27. Vesikari T, Karvonen A, Korhonen T, et al, CAIV-T Transmission Study Group. A randomized, double-blind study of the safety, transmissibility and phenotypic and genotypic stability of cold-adapted influenza virus vaccine. *Pediatr Infect Dis J*. 2006;25(7):590-595.
28. King JC Jr, Treanor J, Fast PE, et al. Comparison of the safety, vaccine virus shedding, and immunogenicity of influenza virus vaccine, trivalent, types A and B, live cold-adapted, administered to human immunodeficiency virus (HIV)-infected and non-HIV-infected adults. *J Infect Dis*. 2000;181(2):725-728.
29. King JC Jr, Fast PE, Zangwill KM, et al, HIV Influenza Study Group. Safety, vaccine virus shedding and immunogenicity of trivalent, cold-adapted, live attenuated influenza vaccine administered to human immunodeficiency virus-infected and noninfected children. *Pediatr Infect Dis J*. 2001;20(12):1124-1131.
30. Belshe RB, Edwards KM, Vesikari T, et al, CAIV-T Comparative Efficacy Study Group. Live attenuated versus inactivated influenza vaccine in infants and young children [published correction appears in *N Engl J Med*. 2007;356(12):1283]. *N Engl J Med*. 2007;356(7):685-696.
31. Redding G, Walker RE, Hessel C, et al. Safety and tolerability of cold-adapted influenza virus vaccine in children and adolescents with asthma. *Pediatr Infect Dis J*. 2002;21(1):44-48.
32. Bergen R, Black S, Shinefield H, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. *Pediatr Infect Dis J*. 2004;23(2):138-144.
33. Piedra PA, Gaglani MJ, Riggs M, et al. Live attenuated influenza vaccine, trivalent, is safe in healthy children 18 months to 4 years, 5 to 9 years, and 10 to 18 years of age in a community-based, nonrandomized, open-label trial. *Pediatrics*. 2005;116(3):e397-e407.
34. Fleming DM, Crovari P, Wahn U, et al, CAIV-T Asthma Study Group. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. *Pediatr Infect Dis J*. 2006;25(10):860-869.
35. Gorse GJ, O'Connor TZ, Young SL, et al. Efficacy trial of live, cold-adapted and inactivated influenza virus vaccines in older adults with chronic obstructive pulmonary disease: a VA cooperative study. *Vaccine*. 2003;21(17-18):2133-2144.
36. Jackson LA, Holmes SJ, Mendelman PM, Huggins L, Cho I, Rhorer J. Safety of a trivalent live attenuated intranasal influenza vaccine, FluMist, administered in addition to parenteral trivalent inactivated influenza vaccine to seniors with chronic medical conditions. *Vaccine*. 1999;17(15-16):1905-1909.
37. Keitel WA, Couch RB, Quarles JM, Cate TR, Baxter B, Maassab HF. Trivalent attenuated cold-adapted influenza virus vaccine: reduced viral shedding and serum antibody responses in susceptible adults. *J Infect Dis*. 1993;167(2):305-311.
38. Edwards KM, King JC, Steinhoff MC, et al. Safety and immunogenicity of live attenuated cold-adapted influenza B/Ann Arbor/1/86 reassortant virus vaccine in infants and children. *J Infect Dis*. 1991;163(4):740-745.
39. Tomoda T, Morita H, Kurashige T, Maassab HF. Prevention of influenza by the intranasal administration of cold-recombinant, live-attenuated influenza virus vaccine: importance of interferon-gamma production and local IgA response. *Vaccine*. 1995;13(2):185-190.
40. Treanor JJ, Betts RF. Evaluation of live, cold-adapted influenza A and B virus vaccines in elderly and high-risk subjects. *Vaccine*. 1998;16(18):1756-1760.
41. Powers DC, Sears SD, Murphy BR, Thumar B, Clements ML. Systemic and local antibody responses in elderly subjects given live or inactivated influenza A virus vaccines. *J Clin Microbiol*. 1989;27(12):2666-2671.
42. Gorse GJ, Campbell MJ, Otto EE, Powers DC, Chambers GW, Newman FK. Increased anti-influenza A virus cytotoxic T cell activity following vaccination of the chronically ill elderly with live attenuated or inactivated influenza virus vaccine. *J Infect Dis*. 1995;172(1):1-10.

43. Clements ML, Betts RF, Tierney EL, Murphy BR. Serum and nasal wash antibodies associated with resistance to experimental challenge with influenza A wild-type virus. *J Clin Microbiol*. 1986;24(1):157-160.

44. Gorse GJ, Otto EE, Powers DC, Chambers GW, Eickhoff CS, Newman FK. Induction of mucosal antibodies by live attenuated and inactivated influenza virus vaccines in the chronically ill elderly. *J Infect Dis*. 1996; 173 (2):285-290.

45. Gorse GJ, Belshe RB, Munn NJ. Local and systemic antibody responses in high-risk adults given live-attenuated and inactivated influenza A virus vaccines. *J Clin Microbiol*. 1988;26(5):911-918.

46. Johnson PR, Feldman S, Thompson JM, Mahoney JD, Wright PF. Immunity to influenza A virus infection in young children: a comparison of natural infection, live cold-adapted vaccine, and inactivated vaccine. *J Infect Dis*. 1986;154(1):121-127.

47. Boyce TG, Gruber WC, Coleman-Dockery SD, et al. Mucosal immune response to trivalent live attenuated intranasal influenza vaccine in children. *Vaccine*. 1999;18(1-2):82-88.

48. Gorse GJ, Belshe RB, Munn NJ. Superiority of live attenuated compared with inactivated influenza A virus vaccines in older, chronically ill adults. *Chest*. 1991;100(4):977-984.

49. Clover RD, Crawford S, Glezen WP, Taber LH, Matson CC, Couch RB. Comparison of heterotypic protection against influenza A/Taiwan/86 (H1N1) by attenuated and inactivated vaccines to A/Chile/83-like viruses. *J Infect Dis*. 1991;163(2):300-304.

50. Belshe RB, Gruber WC, Mendelman PM, Cho I, Reisinger K, Block SL, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. *J Pediatr*. 2000;136(2):168-175.

51. Belshe RB, Mendelman PM. Safety and efficacy of live attenuated, cold-adapted, influenza vaccine-trivalent. *Immunol Allergy Clin North Am*. 2003;23 (4):745-767.

52. Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *N Engl J Med*. 2006;355(24):2513-2522.

53. Belshe RB, Gruber WC, Mendelman PM, et al. Correlates of immune protection induced by live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine. *J Infect Dis*. 2000;181(3):1133-1137.

54. Treanor JJ, Kotloff K, Betts RF, et al. Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. *Vaccine*. 1999;18(9-10): 899-906.

55. Ashkenazi S, Vertruyen A, Aristegui J, et al, CAIV-T Study Group. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. *Pediatr Infect Dis J*. 2006;25(10):870-879.

56. Treanor JJ, Mattison HR, Dumyati G, et al. Protective efficacy of combined live intranasal and inactivated influenza A virus vaccines in the elderly. *Ann Intern Med*. 1992;117(8):625-633.

57. US Food and Drug Administration. FDA approves nasal influenza vaccine for use in younger children [news release]. Rockville, MD: US Department of Health and Human Services; September 19, 2007. www.fda.gov/bbs /topics/NEWS/2007/NEW01705.html. Accessed November 9, 2007.

58. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP) [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2005;54(30):750]. *MMWR Recomm Rep*. 2005;54(RR-8):1-40.

59. Rosenwald MS. MedImmune, NIH team up on bird flu vaccines. *Washington Post*. September 29, 2005:D04. www.washingtonpost.com/wp-dyn/content/article /2005/09/28/AR2005092802197.html. Accessed November 9, 2007.

60. King JC Jr, Stoddard JJ, Gaglani MJ, et al. Effectiveness of school-based influenza vaccination. *N Engl J Med*. 2006;355(24):2523-2532.