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Live Attenuated Influenza Vaccine (FluMist®; Fluenz™)

A Review of its Use in the Prevention of Seasonal Influenza in Children and Adults

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Data Selection

Sources: Medical literature (including published and unpublished data) on 'intranasal live attenuated influenza vaccine' was identified by searching databases since 1996 (including MEDLINE, EMBASE and inhouse AdisBase), bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'live attenuated intranasal vaccine' or 'intranasal live attenuated influenza vaccine' or ('live' and 'attenuated' and 'intranasal' and 'vaccine' and 'cold-adapted'). Searches were last updated 16 August 2011.

Selection: Studies in children or adults who received intranasal live attenuated influenza vaccine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: intranasal live attenuated influenza vaccine, protective efficacy, reactogenicity, tolerability, immunogenicity.

Contents

Abstract

Live attenuated influenza vaccine (LAIV) is an intranasally administered trivalent, seasonal influenza vaccine that contains three live influenza viruses (two type A [H1N1 and H3N2 subtypes] and one type B).

LAIV was effective in protecting against culture-confirmed influenza caused by antigenically matched and/or distinct viral strains in children aged ≤71 months enrolled in three phase III trials. LAIV was superior to trivalent inactivated influenza vaccine (TIV) in protecting against influenza caused by antigenically-matching viral strains in a multinational phase III trial in children aged 6–59 months. LAIV was also significantly more effective than TIV in decreasing the incidence of culture-confirmed influenza illness in two open-label studies (in children with recurrent respiratory tract illnesses aged 6–71 months and in children and adolescents with asthma aged 6–17 years).

LAIV did not differ significantly from placebo in preventing febrile illnesses in adults (primary endpoint) enrolled in a phase III trial. However, LAIV significantly reduced the incidence of febrile upper respiratory tract illnesses (URTI), severe febrile illnesses, febrile URTI-related work absenteeism and healthcare provider use. In another well designed trial in adults, LAIV significantly reduced the incidence of symptomatic, laboratory-confirmed influenza compared with placebo (but not intramuscular TIV).

LAIV was generally well tolerated in most age groups, with the majority of adverse events being mild to moderate in severity, and runny nose/nasal congestion being the most common. In a large phase III trial, LAIV, compared with TIV, was associated with an increased incidence of medically significant wheezing in vaccine-naive children aged <24 months and an increased incidence of hospitalization in children aged 6–11 months; LAIV is not approved for use in children <24 months.

LAIV was not always associated with high rates of seroconversion/seroresponse, particularly in older children and adults, or in subjects with detectable levels of haemagglutination-inhibiting antibodies at baseline. However, LAIV did elicit mucosal (nasal) IgA antibody responses and strong cell-mediated immunity responses. Only one confirmed case of LAIV virus transmission to a placebo recipient (who did not become ill) occurred in a transmission study conducted in young children. The immunogenic response to LAIV in young healthy children was not affected by concomitant administration with other commonly administered childhood vaccines.

In conclusion, intranasal LAIV seasonal influenza vaccine is effective and well tolerated in children, adolescents and adults. LAIV was more effective than TIV in children, although this advantage was not seen in adults. In the US, LAIV is indicated for the active immunization of healthy subjects aged 2–49 years against influenza disease caused by virus subtypes A and type B contained in the vaccine.

1. Introduction

Seasonal influenza epidemics cause serious illness throughout the world each year.[1] In the US, an estimated 25–50 million cases of influenza occur annually and approximately 225 000 of these cases result in hospitalization.[1] Furthermore, during the last three decades, an estimated 3349–48 614 influenza-related deaths occurred annually in the US.[1]

Annual vaccination is the most effective strategy for the prevention and control of influenza, and the Advisory Committee on Immunization Practices (ACIP; a branch of the US Centers for Disease Control and Prevention [CDC]) recommends that all individuals aged ≥6 months, who are without contraindications, should receive an annual influenza vaccine containing the influenza viral strains that are considered to be the most likely to circulate in the next influenza season.[2]

Trivalent inactivated influenza vaccines (TIVs) have been in use for many decades and may be as much as 60–100% effective in preventing influenza-related morbidity and mortality in healthy adolescents and adults.[3] However, TIVs are least effective in young children and the elderly, two of the populations who are most at risk of developing influenza-related complications (section 6).[4] A variety of other factors may limit the widespread use of TIVs, including their mode of delivery via intramuscular injection, which is invasive and requires administration by trained staff who must adhere to blood and sharps precautions.[4] Other limitations of TIVs include extended production times (which has led to vaccine shortages in the past) and decreased efficacy against influenza viral strains that are antigenically distinct from those contained in the vaccine.[4]

Many of the limitations of TIVs have potentially been overcome with the more recently available live attenuated influenza vaccine (FluMist®; Fluenz™) [LAIV].[4] LAIV uses novel technology allowing administration of the vaccine via a noninvasive, intranasal route.[3] The vaccine is trivalent, containing three live, cold-adapted (*ca*), temperature-sensitive (*ts*), attenuated (*att*) influenza viruses: two type A strains (subtypes H1N1 and H3N2) and one type B strain (table I).[5,6] Each of the LAIV viruses is a 6 : 2 genetic reassortment virus generated through the process of reverse genetics technology and containing six gene segments from master donor viruses (MDVs) and two gene segments from a wild-type influenza virus that is predicted to be one of the main circulating viruses in the upcoming influenza season.[5,6] The gene segments from the MDVs act as a genetic backbone and give the virus its *ca*, *ts* and *att* phenotype, whereas the other two gene segments encode the haemagglutinin and neuraminidase glycoproteins of the wild-type virus, which are responsible for eliciting a protective immune response to influenza.[5,6]

A trivalent formulated vaccine bulk is prepared by blending three different monovalent bulks of each of the three virus strains. Each monovalent bulk has been prepared from purified harvests derived by the inoculation and growth of a master virus seed into embryonated, specific, pathogen-free eggs.[6]

To induce immune responses, LAIV viruses infect and replicate in mucosal cells of the nasopharynx;[2,6] thus, it is said that LAIV must 'infect to protect'.[10] Of note, LAIV viruses are unable to replicate in the lower respiratory tract and lungs because of the warmer temperature of these tissues.[6] In addition, the LAIV viral proteins are presented to the immune system in their native form and, thus, the immune responses induced by LAIV may be similar to those induced by natural influenza infection.[6,11]

Table I. Influenza viral strains contained in the live attenuated influenza vaccines administered in immunogenicity or clinical studies reviewed in this article. Unless otherwise specified, influenza viral strains stated here were also those recommended by the WHO[7] for the season and hemisphere in which they were administered

Season	H1N1	H3N2	B
Northern Hemisphere			
1995/1996	A/Texas/36/91	A/Shangdong/9/93	B/Panama/45/90
1996/1997	A/Texas/36/91	A/Wuhan/359/95	B/Harbin/7/94
1997/1998	A/Shenzhen/227/95	A/Wuhan/359/95	B/Harbin/7/94
1998/1999	A/Beijing/262/95	A/Sydney/5/97	B/Harbin/7/94
1999/2000	A/Beijing/262/95	A/Sydney/5/97	B/Harbin/7/94 or B/Yamanashi/166/98
2000/2001	A/New Caledonia/20/99	A/Sydney/5/97[a]	B/Yamanashi/166/98
2001/2002	A/New Caledonia/20/99	A/Panama/2007/99	B/Victoria/504/2000[b]
2002/2003	A/New Caledonia/20/99	A/Panama/2007/99	B/Hong Kong/330/2001
2003/2004	A/New Caledonia/20/99	A/Panama/2007/99	B/Hong Kong/330/2001
2004/2005	A/New Caledonia/20/99	A/Wyoming/3/2003	B/Jilin/20/2003
2005/2006	A/New Caledonia/20/99[c]	A/California/7/2004[c]	B/Shanghai/361/2002[c]
2006/2007	A/New Caledonia/20/99[c]	A/Wisconsin/67/2005[c]	B/Malaysia/2506/2004[c]
2007/2008	A/Solomon Islands/3/2006	A/Wisconsin/67/2005	B/Malaysia/2506/2004
2008/2009	A/Brisbane/59/200[c]	A/Brisbane/10/2007[c]	B/Florida/4/2006[c]
2009/2010	A/Brisbane/59/200[c]	A/Brisbane/10/2007[c]	B/Brisbane/60/2008[c]
2010/2011	A/California/7/2009[c]	A/Perth/16/2009[c]	B/Brisbane/60/2008[c]
2011/2012	A/California/7/2009[c]	A/Perth/16/2009[c]	B/Brisbane/60/2008[c]
Southern Hemisphere[d]			
1999	A/Beijing/262/95[c]	A/Sydney/5/97[c]	B/Beijing/184/93[c]
2000	A/New Caledonia/20/99[c]	A/Moscow/10/99[c]	B/Beijing/184/93 or B/Shangdong/7/97[c]
2001	A/New Caledonia/20/99[c]	A/Moscow/10/99[c]	B/Sichuan/379/99[c]
2002	A/New Caledonia/20/99	A/Panama/2007/99	B/Victoria/504/2000
2003	A/New Caledonia/20/99[c]	A/Moscow/10/99[c]	B/Hong Kong/330/2001[c]
2004	A/New Caledonia/20/99[c]	A/Fujian/411/2002[c]	B/Hong Kong/330/2001[c]
2005	A/New Caledonia/20/99[c]	A/Wellington/1/2004[c]	B/Shanghai/361/2002[c]
2006	A/New Caledonia/20/99[c]	A/California/7/2004[c]	B/Malaysia/2506/2004[c]
2007	A/New Caledonia/20/99[c]	A/Wisconsin/67/2005[c]	B/Malaysia/2506/2004[c]
2008	A/Solomon Islands/3/2006[c]	A/Brisbane/10/2007[c]	B/Florida/4/2006[c]
2009	A/Brisbane/59/2007[c]	A/Brisbane/10/2007[c]	B/Florida/4/2006[c]
2010	A/California/7/2009[c]	A/Perth/16/2009[c]	B/Brisbane/60/2008[c]
2011	A/California/7/2009[c]	A/Perth/16/2009[c]	B/Brisbane/60/2008[c]

a This strain was used instead of the WHO recommended strain (A/Moscow/10/99) because of industry-wide technical problems.[8,9]

b This strain was replaced with B/Yamanashi/166/98 in one study because of manufacture delays.[8]

c No LAIV studies were conducted in this season and hemisphere. Therefore, strains given here are those recommended by the WHO for inclusion in seasonal influenza vaccines for this season and hemisphere.[7]

d No LAIV studies were conducted in the Southern Hemisphere prior to 2001, and WHO recommended influenza viral strains pre-dating 1999 were not available.

LAIV is approved in various countries, including the US,[12] the EU[13] and Canada.[14] In the US, LAIV is approved for use in subjects aged 2–49 years as an active immunization against influenza disease caused by the influenza virus strains contained in the vaccine.[12] Initial approval of LAIV in the US was for the frozen formulation of the vaccine.[15,16] However, some providers had difficulties storing a frozen vaccine, and a new refrigerator-stable formulation

was developed in an effort to ameliorate this problem.[15,16] The refrigerator-stable formulation was approved in the US in 2007, and has been in use since the 2007/2008 influenza season in the Northern Hemisphere.[15]

This review focuses on the protective efficacy, reactogenicity and immunogenicity of both the frozen and refrigerator-stable formulations of LAIV in children, adolescents and adults. The approval of LAIV in the US is only for individuals aged 2–49 years;[12] although some of the studies upon which the US approval of this vaccine was based included children younger, or adults older, than the approved age range.

Unless otherwise stated, each dose of LAIV administered in the studies discussed in this review contained $10^{6.5–7.5}$ fluorescent focus units (FFUs) of live attenuated influenza virus reassortants of each of the three virus strains recommended for the season and hemisphere in which it was administered (table I). The frozen formulation of LAIV was administered at a dose of 0.5 mL, and the refrigerator-stable formulation was administered at a dose of 0.2 mL.

2. Protective Efficacy

LAIV provides direct protective efficacy (see table II for definitions) in children (section 2.1) and in healthy adults (section 2.2) and indirect (herd) protective efficacy in a community (section 2.3).

2.1 In Children

Various placebo- and active-comparator trials have investigated the efficacy of LAIV in children (see table III for study design details and the age of the children).[8,9,17-22]

Most vaccine-naive children aged 2–8 years received the recommended two doses of LAIV, administered ≥1 month apart (section 5); one study included an additional treatment arm in which vaccine-naive children aged 6 to <36 months received only one dose of LAIV[18] (see table III for further details).

In the majority of trials, children were included if they were in good health;[8,9,17-19,22] children with a history of mild or moderate asthma were included in one trial[19] and another trial specified that children attend daycare at least 12 hours/week.[9] Two trials were conducted in special patient populations: one in children with a history of recurrent respiratory tract infections (RTIs)[20] and the other in children with a clinical diagnosis of asthma.[21]

Table II. Definition of absolute and relative vaccine efficacy

Absolute efficacy	Relative efficacy
1 minus the relative risk of developing influenza (or the incidence of influenza) in the active vaccine group vs the placebo group × 100	1 minus the relative risk of developing influenza (or the incidence of influenza) in one active vaccine group vs the other active vaccine group × 100

In general, exclusion criteria were underlying chronic illness,[8,9,17,18,20-22] known or suspected immune system disorder[8,9,18-22] (or a household member with immunosuppression[9,18,20]), immunosuppressive therapy[20,21] and/or treatment with immunoglobulins,[9,20] aspirin or aspirin-containing products[9,19,20,22] or previous treatment with an influenza vaccine (either LAIV, TIV or investigational vaccines).[9,18,20] Some studies specifically excluded children with clinically diagnosed respiratory illness with wheezing within the previous 2[9] or 6[19] weeks.

Generally, in the placebo-controlled trials, the influenza strains circulating during an influenza season were well matched with those contained in the season's LAIV.[8,9,17] However, two influenza type B viruses antigenically distinct from that in LAIV were in circulation in year 2 of two studies[8,9] and caused >77% of cases of influenza B illness in that year in one of the studies.[8] An antigenically distinct strain of H3N2 caused 66 of 71 cases of influenza in year 2 of another study.[17]

2.1.1 Placebo-Controlled Studies

Culture-confirmed influenza caused by strains antigenically matching those contained in the vaccine occurred in 2–3% of LAIV recipients and 11–13% of placebo recipients in year 1, and 2–3% of LAIV recipients and 10–30% of placebo recipients in year 2 (table IV).[8,9] Across all studies, culture-confirmed influenza caused by any viral strain (including antigenically matching or non-antigenically matching strains) occurred in 1–5% of LAIV recipients and 13–18% of placebo

Table III. Design of key live attenuated influenza vaccine (LAIV) studies conducted in healthy children or in special populations of children

Study (location)	Subject age (season[s]; hemisphere)	Trial design	Dosage regimen	Primary endpoint
Placebo-controlled studies				
Belshe et al.[17,23,24] (US)	15–71 mo (1996/1997, 1997/1998; NH)	r, db, mc	1 or 2 doses of IN F-LAIV or PL (y1);[a] 1 dose of IN F-LAIV or PL (y2)[b]	First episode of culture-confirmed influenza illness in each year
Bracco Neto et al.[18] (South Africa and South America)	6 to <36 mo (2001 and 2002; SH)	r, db, mc	2 doses of RS-LAIV, 1 dose of RS-LAIV + PL_S or 2 doses of PL_E or PL_S (y1); 1 dose of RS-LAIV or PL_S (y2)	First episode of culture-confirmed influenza illness caused by community-acquired influenza subtypes similar to those contained in y1 vaccine
Tam et al.[8] (Asia)	12 to <36 mo (2000/2001, 2001/2002; NH)	r, db, mc	2 doses of IN RS-LAIV or PL (y1) 1 dose IN RS-LAIV or PL (y2)	First episode of culture-confirmed influenza illness caused by a subtype antigenically similar to that in the vaccine after receipt of the second dose of vaccine (or PL) during y1
Vesikari et al.[9] (Europe and the Middle East)	6 to <36 mo (2000/2001, 2001/2002; NH)	r, db, mc	2 doses of IN RS-LAIV or PL (y1) 1 dose IN RS-LAIV or PL (y2)	Efficacy of a primary series of 2 doses of LAIV vs PL against culture-confirmed influenza caused by subtypes antigenically similar to those contained in the vaccine in the first season
Active-comparator studies				
Ashkenazi et al.[20] (Europe and Israel)[c]	6–71 mo (2002/2003; NH)	r, ol, mc	2 doses of IN RS-LAIV or IM TIV	First episode in a study child of culture-confirmed influenza illness caused by a community-acquired subtype antigenically similar to those contained in the vaccine
Belshe et al.[19] (US, Asia, Europe and the Middle East)	6–59 mo (2004/2005; NH)	r, db, mc	1 or 2 doses of IN RS-LAIV or IM TIV[d]	Efficacy of LAIV vs TIV in preventing culture-confirmed influenza-like illness (using CDC definition and modified for age) caused by a well matched influenza strain
Fleming et al.[21] (Europe and Israel)[c]	6–17 y (2002/2003; NH)	r, ol, mc	1 dose of IN RS-LAIV or IM TIV	Incidence of culture-confirmed influenza illness caused by a community-acquired subtype antigenically similar to those contained in the vaccine
Coadministration study				
Lum et al.[22] (Europe, Asia and Mexico)	11 to <24 mo (2002/2003; NH)	r, db, mc	2 doses of IN RS-LAIV or IN PL + 1 dose SC MMR	First episode (occurring ≥15 d after last vaccine dose) of culture-confirmed influenza illness caused by a subtype antigenically similar to those contained in the vaccine

a The majority of study centres used a 2-dose vaccination regimen in y1.

b Subjects received the same vaccine in y1 as y2[9,17,18] or were rerandomized in y2.[8]

c In special populations; in children with asthma[21] or recurrent respiratory tract infections.[20]

d Subjects received 1 dose of vaccine if they had previously received an influenza vaccination and 2 doses if they had not.

CDC = Centers for Disease Control and Prevention; **db** = double-blind; **F-LAIV** = frozen LAIV; **IM** = intramuscular; **IN** = intranasal; **mc** = multicentre; **MMR** = measles, mumps and rubella vaccine; **NH** = northern hemisphere; **ol** = open-label; **PL** = placebo; $\mathbf{PL_E}$ = excipient PL; $\mathbf{PL_S}$ = saline PL; **r** = randomized; **RS-LAIV** = refrigerator-stable LAIV; **SC** = subcutaneous; **SH** = southern hemisphere; **TIV** = trivalent inactivated vaccine; **y*x*** = year *x*.

recipients in year 1, and 2–5% of LAIV recipients and 12–32% of placebo recipients in year 2 (table IV).[8,9,17]

LAIV was 73–84% more effective than placebo in year 1 (primary endpoint in one trial[9]) and 74–89% more effective in year 2 with regard to

preventing culture-confirmed influenza caused by an influenza subtype antigenically similar to those contained in the vaccine (see table IV for the trials that assessed this endpoint and for 95% CIs).[8,9,18] Furthermore, in all trials, LAIV was 70–93% more effective than placebo in year 1 and 47–87% more effective in year 2 in preventing culture-confirmed influenza of any subtype (see table IV for 95% CIs).[8,9,17,18]

When results of one study were stratified according to H3N2 influenza strain type, LAIV was 100% effective in protecting against H3N2 strains contained in the vaccine, and 86% effective in protecting against the antigenically distinct H3N2 strain that became the predominant cause of illness in the second study year.[17] In another study, LAIV was 48% effective against all influenza strains (predominantly influenza B viruses) that were determined to be antigenically distinct from those contained in the vaccine.[8]

Although a single dose of LAIV was clinically effective (56–58% vs placebo) in preventing culture-confirmed influenza in the trial that compared the efficacy of one versus two doses of LAIV in vaccine-naive children, two doses of LAIV was shown to be more effective than one dose (table IV), confirming the additive protection that the recommended two-dose regimen (section 5) provides to children.[18]

2.1.2 Comparator Studies

LAIV was superior to TIV in protecting against culture-confirmed influenza-like illness in children and adolescents, according to data from a large, phase III study in children aged 6–59 months[19] and from open-label studies in children with recurrent RTIs[20] or in children and adolescents with asthma[21] (table IV).

Phase III Trial

Relative to TIV, LAIV reduced the attack rate of culture-confirmed influenza-like illness caused by well matched influenza strains by 44.5% (95% CI 22.4, 60.6) and the attack rate of culture-confirmed influenza-like illness caused by any viral strain (either well matched or mismatched) by 54.9% (95% CI 45.4, 62.9) [see table IV for actual attack rates].[19] The statistical superiority of LAIV over TIV for both of these endpoints was established when the lower bound of the 95% CI was greater than the prespecified level of zero. When stratified according to patient age, LAIV continued to be superior to TIV after one dose for preventing culture-confirmed influenza-like illness caused by matching viral strains in subjects aged 36–59 months (reduction in attack rate 65.6%; 95% CI 36.3, 82.4), but not in those aged 6–23 months (29.1%; 95% CI −21.2, 59.1) or 24–35 months (32.6%; 95% CI −25.8, 64.5).[19]

With respect to the reduction in attack rate, LAIV was superior to TIV in the subgroups with culture-confirmed influenza-like illness caused by influenza A/H1N1 (3 cases; 89.2% reduction; $p < 0.001$) and influenza A/H3N2 (37 cases; 79.2% reduction; $p < 0.001$), but there was no statistically significant difference between the two vaccines in those with culture-confirmed influenza-like illness caused by influenza B ($n = 115$ cases; 16.1% reduction; $p = 0.19$).[19]

An additional analysis of data from this trial indicated that LAIV recipients with breakthrough influenza may have had less severe disease than TIV recipients with breakthrough influenza.[25] For example, significantly fewer LAIV than TIV recipients had febrile disease (78% vs 88%, $p = 0.001$).

Special Patient Populations

Culture-confirmed influenza caused by antigenically matching strains occurred in 24 of 1050 LAIV recipients and 50 of 1035 TIV recipients with recurrent RTIs,[20] and in 46 of 1109 LAIV recipients and 70 of 1102 TIV recipients with asthma[21] (primary endpoint in both trials; see table IV for corresponding attack rates). This translated into a relative efficacy, that was significantly in favour of LAIV, of 52.7% (90% CI 27.2, 69.8; 95% CI 21.6, 72.2) in the recurrent RTI study,[20] and 34.7% (90% CI 9.4, 53.2; 95% CI 3.9, 56.0) in the asthma study[21] (table IV).

In both studies, when primary endpoint results were stratified according to influenza subtype, the relative vaccine efficacy remained significantly in favour of LAIV in participants with influenza A/H1N1 (100.0%; 90% CI 55.2, 100.0[20] and 100.0%;

Table IV. Efficacy of intranasal live attenuated influenza vaccine (LAIV) in preventing influenza A or B in children enrolled in phase III studies (see table III for study design details and vaccine dosage regimens). Children were randomized to receive intranasal LAIV, intramuscular trivalent inactivated influenza vaccine (TIV) or placebo (PL).[8,9,17-22] Analyses were conducted in the intent-to-treat[9,17] or per-protocol[8,18-22] population

Study	Vaccine [no. of doses]	No. of subjects	No. of influenza cases	Attack rate (%)	Absolute vaccine efficacy (%) [95% CI] LAIV vs PL		Relative vaccine efficacy (%) [95% CI] LAIV vs TIV unless otherwise stated	
			a/m viral strain [any viral strain]	a/m viral strain [any viral strain]	a/m viral strain	any viral strain	a/m viral strain	any viral strain
Placebo-controlled studies								
Belshe et al.[17,23,24]	F-LAIV	y1: 1070	[14[d]]	[1.3]		93 [87, 96]		
	PL	y1: 532	[94[d]]	[17.7]				
	F-LAIV	y2: 917	[15[d]]	[1.6]		87 [78, 93]		
	PL	y2: 441	[56[d]]	[12.7]				
Bracco Neto et al.[18]	RS-LAIV [2]	y1: 944			73.5 [63.6, 81.0]	72.0 [61.9, 79.8]	37.3 [9.5, 56.9][a]	36.0 [8.5, 55.6][a]
	RS-LAIV [1] + PL	y1: 935			57.7 [44.7, 67.9]	56.3 [43.1, 66.7]		
	RS-LAIV [2 (y1); 1 (y2)]	y2: 338			73.6 [33.3, 91.2]	46.6 [14.9, 67.2]	24.1 [–104.2, 75.7][b]	0.5 [–57.7, 38.5][b]
	RS-LAIV [1 + PL (y1); 1 (y2)]	y2: 684			65.2 [31.2, 82.8]	46.4 [21.1, 63.5]		
Tam et al.[8][c]	RS-LAIV	y1: 1653	56[d] [81]	3.4 [4.9]	72.9 [62.8, 80.5]	70.1 [60.9, 77.3]		
	PL	y1: 1111	139[d] [182]	12.5 [16.4]				
	RS-LAIV	y2: 771	12 [33]	1.6 [4.3]	84.3 [70.1, 92.4]	64.2 [44.2, 77.3]		
	PL	y2: 494	49 [59]	9.9 [11.9]				
Vesikari et al.[9]	RS-LAIV	y1: 1059	19 [23]	1.8 [2.2]	83.5 [72.6, 90.6][d]	83.8 [74.2, 90.2]		
	PL	y1: 725	79 [97]	10.9 [13.4]				
	RS-LAIV	y2: 658	22 [31]	3.3 [4.7]	89.0 [82.7, 93.3]	85.3 [78.3, 90.4]		
	PL	y2: 461	140 [148]	30.4 [32.1]				
Active-comparator studies								
Ashkenazi et al.[20][e]	RS-LAIV	1050	24[d] [29]	2.3 [2.8]			52.7 [21.6, 72.2]	52.4 [24.6, 70.5]
	TIV	1035	50[d] [60]	4.8 [5.8]				
Belshe et al.[19]	RS-LAIV	3916		1.4 [3.9*]			44.5 [22.4, 60.6][d,f]	54.9 [45.4, 62.9][f]
	TIV	3936		2.4 [8.6]				
Fleming et al.[21]	RS-LAIV	1109	46[d] [50]	4.1 [4.5]			34.7 [3.9, 56.0]	31.9 [1.1, 53.5]
	TIV	1102	70[d] [73]	6.4 [6.6]				
Coadministration study								
Lum et al.[22]	LAIV + MMR	765	9 [23]	1.2 [3.0]	78.4 [50.9, 91.3]	63.8 [36.2, 79.8]		
	PL + MMR	385	21 [32]	5.5 [8.3]				

a RS-LAIV + RS-LAIV vs RS-LAIV + PL.

b RS-LAIV + RS-LAIV/RS-LAIV vs RS-LAIV + PL/RS-LAIV.

c Y2 results given here are for the subgroup of subjects who received RS-LAIV or PL in both y1 and y2 of the study.

d Primary endpoint.

e In special populations; in children with asthma[21] or recurrent respiratory tract infections.[20]

f The statistical superiority of LAIV over TIV was established when the lower bound of the 95% CI was greater than the prespecified level of zero.

a/**m** = antigenically matched; **F-LAIV** = frozen LAIV; **MMR** = measles, mumps and rubella vaccine; **RS-LAIV** = refrigerator-stable LAIV; **y*x*** = year *x*. * $p < 0.001$ vs TIV.

90% CI 18.5, 100.0[21]) or B (68.0%; 90% CI 43.0, 82.9[20] and 36.3%; 90% CI 6.6, 56.8[21]) illness, but there was no significant between-group difference with influenza A/H3N2 illness.

Similar results were seen for culture-confirmed influenza caused by any viral strain (either antigenically matching or mismatching) [table IV].[20,21]

A subgroup analysis of the study in children with recurrent RTIs indicated that breakthrough disease may be less severe in LAIV than in TIV recipients.[26] A higher percentage of LAIV than TIV recipients with breakthrough influenza had afebrile disease (26% vs 5%, p = 0.005) and fewer days of school or daycare (1.6 vs 3.1 days; p = 0.025) were missed with LAIV versus TIV administration.[26] However, there was no between-group difference in these measures in the study in children and adolescents with asthma.[21]

2.1.3 Pooled Analyses

LAIV demonstrated efficacy in children aged ≥2 years (i.e. in children within the LAIV approved age range; n = 1048–4166), according to a subgroup analysis[27] of data from three studies[8,17,19] (see sections 2.1.1 and 2.1.2). In seasons where influenza was predominantly caused by influenza strains matching those contained in the vaccines, the efficacy of LAIV compared with placebo was 69.2% (95% CI 52.7, 80.4) and 94.6% (95% CI 88.6, 97.5). In a season where influenza was predominantly caused by mismatched strains of influenza virus, the absolute efficacy of LAIV compared with placebo was 87% (95% CI 77.0, 92.6), and during a late season epidemic, the absolute efficacy was 73.8% (95% CI 40.4, 89.4). Relative to TIV, influenza caused by matched or mismatched strains of influenza occurred in 52.5% (95% CI 26.7, 68.7) and 54.4% (95% CI 41.8, 64.5) fewer LAIV recipients.

An analysis[28] of data from the three active-comparator studies discussed in section 2.1.2[19-21] suggested that the relative efficacy of LAIV compared with TIV against antigenically similar strains of influenza virus may increase over time. Across the studies, the relative efficacy of LAIV compared with TIV ranged from 25% to 60% at 0–4 months post-vaccination, and from 49% to 89% at >4–8 months post-vaccination. However, the relative efficacy of LAIV compared with TIV against mismatched strains remained unchanged over time.

When data from four of the studies discussed in sections 2.1.1[17] and 2.1.2[19-21] were stratified according to patient age in a subgroup analysis,[29] the efficacy of LAIV against all influenza strains compared with placebo or TIV did not appear to be affected by age, as evidenced by relative or absolute efficacies that were similar across age groups within each study.

LAIV was associated with fewer influenza-associated complications in children aged 6–83 months than placebo or TIV, according to an analysis[30] of pooled data from eight randomized, double-blind, placebo-controlled[8,9,17,18,22,31] or active-comparator[19,20] trials. This was measured in terms of the incidence of influenza-associated acute otitis media, which occurred in numerically fewer LAIV recipients than placebo (0.4% vs 2.9%) or TIV (0.6% vs 1.2%) recipients, leading to an absolute and relative pooled LAIV efficacy of 85% (95% CI 78.3, 89.8) and 54% (95% CI 27.0, 71.7), respectively.

2.1.4 Coadministration with Other Vaccine

The efficacy of LAIV in young children did not appear to be affected by coadministration with the measles, mumps and rubella (MMR) vaccine, according to results of a noninferiority trial (see table III for trial design details and vaccine dosage regimens).[22] For example, culture-confirmed influenza caused by an influenza subtype that was antigenically similar to those contained in LAIV occurred in 1.2% of LAIV plus MMR recipients and 5.5% of placebo plus MMR recipients, and culture-confirmed influenza caused by any influenza subtype occurred in 3.0% of LAIV plus MMR recipients and 8.3% of placebo plus MMR recipients (see table IV for actual event numbers). Therefore, LAIV plus MMR was 78% more effective than placebo plus MMR in preventing culture-confirmed influenza caused by an influenza subtype antigenically similar to those contained in the LAIV vaccine, and 64% more effective in preventing culture-confirmed influenza caused by any influenza subtype (see table IV for 95% CIs).

Table V. Design of key live attenuated influenza vaccine (LAIV) efficacy studies conducted in healthy adults

Study	Subject age (season)	Dosage regimen	Key inclusion criteria	Key exclusion criteria	Primary endpoint
Monto et al.[33]	18–49 y (2007/2008)	1 dose of IN RS-LAIV, IM TIV or PL (either IN or IM)	In good health	Any medical condition for which routine vaccination with TIV is recommended	A case of symptomatic illness[a] that was confirmed as influenza A or B by isolation of the virus in cell culture or with real-time PCR assay
Nichol et al.[32]	18–64 y (1997/1998)	1 dose of IN F-LAIV or PL	In good health; worked outside of the home for ≥30 h/wk; had health insurance	Any medical condition for which routine vaccination with TIV is recommended; previously received TIV containing influenza viral strains for the 1997/1998 influenza season; working with high-risk people; acute febrile or respiratory tract illness in previous 72 h	The proportion of participants reporting ≥1 febrile illness[b] during peak outbreak periods

a Symptomatic influenza was defined as illness characterized by ≥1 respiratory symptom (cough or congestion) and by ≥1 constitutional symptom (fever, feverishness, chills or body aches).

b A febrile illness was defined as one in which symptoms were present for ≥2 consecutive days, with fever on ≥1 day, and ≥2 of the following symptoms on ≥1 day: fever, chills, headache, runny nose, sore throat, cough, muscle aches and/or tiredness/weakness.

F-LAIV = frozen LAIV; **IM** = intramuscular; **IN** = intranasal; **PCR** = polymerase chain reaction; **PL** = placebo; **RS-LAIV** = refrigerator-stable LAIV; **TIV** = trivalent inactivated influenza vaccine.

2.2 In Adults

The protective efficacy of LAIV in healthy adults has been investigated in two randomized, double-blind, multicentre trials (one placebo-controlled[32] and one placebo- and active-comparator-controlled;[33] see table V for key study design details).

2.2.1 Placebo-Controlled Study

During the peak outbreak period (median duration of 7 weeks), febrile illnesses (primary endpoint; table V) occurred in a similar proportion of LAIV as placebo recipients.[32] Overall, 373 of 2833 LAIV recipients and 207 of 1420 placebo recipients reported one or more febrile illnesses during the peak outbreak period (see table VI for actual event numbers), and this difference was not statistically significant.

However, LAIV was significantly more effective than placebo for other endpoints.[32] For example, compared with placebo, LAIV significantly reduced the number of febrile illnesses meeting criteria for febrile upper respiratory tract infections (URTIs) [24% reduction; 95% CI 12.7, 33.2; $p < 0.001$] or for severe febrile illnesses (19% reduction; 95% CI 7.4, 28.8; $p = 0.002$) during the peak outbreak period. According to the study investigators, these endpoints were expected to have a higher degree of specificity than the primary endpoint for true influenza illnesses (febrile URTIs) or for more severe illnesses (severe febrile illnesses).[32]

Furthermore, LAIV significantly ($p < 0.001$) reduced the overall number of days of febrile illness (days per 1000 persons per 7-week outbreak period: 1188 vs 1541 days), antibacterial use (196 vs 343 days) or over-the-counter medication use (577 vs 752 days) compared with placebo during the peak outbreak period.[32] There was no significant difference between the LAIV and placebo groups with regard to the number of days missed from work because of a febrile illness (days per 1000 persons per 7-week outbreak period: 173 vs 200 days) or the number of days with one or more visits to a healthcare provider (44 vs 52 days). However, when this analysis was performed using only those episodes of febrile illness that met the criteria for URTI, the between-group difference was significantly ($p < 0.001$ vs placebo) in favour of LAIV for both comparisons.

2.2.2 Placebo- and Active Comparator-Controlled Study

Symptomatic, laboratory-confirmed influenza occurred in 6.9% of LAIV recipients, 3.4% of TIV

recipients and 10.8% of placebo recipients in a placebo- and active comparator-controlled trial (primary endpoint; see tables V and VI for actual event numbers and endpoint definitions).[33] Relative to placebo, both vaccines significantly (positive value for lower limit of 95% CI) reduced the incidence of symptomatic, laboratory-confirmed influenza in the trial, with the absolute vaccine efficacy being 36% in the LAIV group and 68% in the TIV group (table VI). However, in terms of the relative vaccine efficacy, TIV was associated with a 50% greater reduction in the incidence of the primary endpoint than LAIV (table VI).

When stratified according to influenza type, TIV was associated with a 60% greater reduction in the incidence of influenza A than LAIV (95% CI 33, 77).[33] Although preliminary evidence suggested that neither vaccine was more effective than the other in preventing influenza B, too few episodes of influenza B occurred during the study to allow for an accurate analysis to be conducted.

2.3 Indirect (Herd) Immunity

LAIV appeared to provide indirect (herd) protection for the community, according to results of three large community-based studies[34-36] (see table VII for study design details).

In a study in which 44% of children from elementary schools in Carroll County (2005/2006) were vaccinated (see table VII), there was a reduction in the rise in absenteeism in elementary school children during that year compared with a control group of unvaccinated elementary school children from previous years (change from baseline of 0.61% vs 1.79%; p = 0.029; see table VIII for further details). Moreover, there appeared to be an indirect effect of immunizing elementary school children on high school children; the rise in high school absenteeism was 0.32% in the intervention group versus 1.80% in the control group (p = 0.028) [table VIII].[34]

In another study, significantly fewer episodes of fever or influenza-like illness were reported in children or adults during the peak influenza week in households with children attending intervention schools than in those with children attending comparison schools (table VIII).[36]

Scott and White Health Plan members within the intervention area were at a lower risk of medically attended acute respiratory illnesses than those in the comparison areas during the influenza epidemic and postepidemic periods in a third study (table VIII).[35]

3. Reactogenicity

LAIV was well tolerated in children and adolescents[8,18,19,23,24,37] and in healthy adults,[32,33] according to data from individual randomized clinical trials (see sections 2 and 4 for details of study design and vaccine dosage), a large safety analysis[38] and integrated multistudy analyses.[12,39] Most adverse events were of mild to moderate severity.

Table VI. Efficacy of live attenuated influenza vaccine (LAIV) [frozen formulation] in preventing influenza A or B in healthy adults. Results of two double-blind, multicentre phase III[32] or IV[33] trials. Subjects were randomized to receive a single intranasal (IN) dose of LAIV or placebo (PL),[32] or a single dose of IN LAIV, intramuscular (IM) trivalent inactivated influenza vaccine (TIV) or IN or IM PL.[33] Unless otherwise specified, analyses were conducted in the intent-to-treat population

Study	Vaccine (no. of subjects)	No. of subjects with influenza[a]	Attack rate[a] (%)	Vaccine efficacy (%) [95% CI]	
				Absolute (LAIV or TIV vs PL)	Relative (TIV vs LAIV)
Monto et al.[33]	LAIV (814)	56[b]	6.9	36 [0, 59]	50 [20, 69]
	TIV (813)	28[b]	3.4	68 [46, 81]	
	PL (325)	35[b]	10.8		
Nichol et al.[32]	LAIV (2833)	373	13.2[b]		
	PL (1420)	207	14.6[b]		

a No. (%) of subjects with culture-confirmed, symptomatic influenza during the 6-mo study period,[33] or the no. reporting ≥1 febrile illness during the peak outbreak period (median duration of 7 wk).[32]

b Primary endpoint.

Table VII. Design details of three open-label, community-based trials investigating the indirect (herd) immunity of live attenuated influenza vaccine (LAIV) in the US

Study	Intervention group (no. of subjects)	Comparison group (no. of subjects)	Intervention received	Data source(s)
Davis et al.[34]	Healthy students attending a school in Carroll County during the 2005/2006 school year (28 674)	Healthy students attending a public school between fall 2001 and spring 2005 (Carroll County; some elementary schools were excluded) or 2006 (Frederick County) [39 493]	5319 of 12 090 (44%) healthy elementary-school students in Carroll County received a single dose of F-LAIV during the 2005/2006 school year	Local medical centres, hospitals, school records and government websites
Glezen et al.[35]	SWHP members in the Temple-Belton area (50 665)	SWHP members in the Bryan-College Station and Waco areas (67 036)	5247 of 10 418 elementary-school students (aged 4–11 y) in the Temple-Belton area received RS-LAIV during the 2007/2008 influenza season	Medical records from SWHP and the Scott and White Memorial Hospital
King et al.[36]	Public elementary or parochial schools across four US states; 11 of the 28 participating schools were designated as intervention schools (5840)	Public elementary or parochial schools across four US states; 17 of the 28 participating schools were designated as comparison schools (9451)	Healthy children aged ≥5 y within the intervention schools were offered F-LAIV during the fall of 2004 (2004/2005 influenza season); children <9 y received 2 doses and older children received 1 dose	Household questionnaires, school and medical records

F = frozen; **RS** = refrigerator-stable; **SWHP** = Scott and White Health Plan.

3.1 In Children and Adolescents

3.1.1 Placebo-Controlled Studies

Runny nose (or nasal congestion) was the most common solicited reactogenicity event occurring in children and adolescents in individual placebo-controlled trials (see sections 2.1.1 and 4.2),[8,18,23,24] and in analyses of pooled tolerability data in children and/or adolescents aged 2–6 years (n = 876–1759)[12] or 2–17 years (n = 10 693)[39] who received LAIV.

The incidence of runny nose or nasal congestion and of other solicited reactogenicity events occurring at an incidence of ≥1% in LAIV recipients aged ≥2 years and at a higher frequency in LAIV than placebo recipients in the smaller pooled analysis of data obtained from two placebo-controlled, paediatric efficacy studies[8,12,23,24] are shown in figure 1.

The incidence and nature of solicited reactogenicity adverse events was similar in a larger pooled analysis of 14 placebo-controlled trials.[39] Runny nose/nasal congestion (rate difference 6.8%, $p < 0.01$), headache (rate difference 6.9%, $p = 0.02$) and tiredness/decreased activity (rate difference 2.1%, $p = 0.03$) all occurred at a significantly higher rate in LAIV than placebo recipients after the first vaccine dose. All other solicited reactogenicity events occurring after the first vaccine dose had between-group rate differences of <3%, and these differences were not statistically significant.

Solicited reactogenicity events occurring after the second vaccine dose in year 1 or after revaccination in year 2 were generally similar in nature to those occurring after the first vaccine dose in year 1.[12,39] However, the incidence appeared to be numerically lower after the second vaccine dose in year 1, or after revaccination in year 2, than after the first vaccine dose in year 1.[12,39] In the larger pooled analysis, decreased appetite was the only solicited adverse event to occur at a significantly different rate in LAIV versus placebo recipients after the second vaccine dose in year 1 (rate difference −2.9%, $p = 0.04$) and after revaccination in year 2 (rate difference 3.9%, $p = 0.03$).[39]

Unsolicited adverse events generally occurred at a similar incidence in LAIV and placebo recipients, with 29.7% of LAIV recipients and 27.6% of placebo recipients reporting at least one adverse event after the first vaccine dose, according to results of the larger pooled analysis.[39] General disorders occurred at a significantly higher incidence in LAIV than placebo recipients after the first vaccine dose (rate difference 2.2%, $p < 0.01$), and this was mostly attributed to the significantly higher incidence of pyrexia occurring in the LAIV group (rate difference 2.1%, $p < 0.01$).

The incidence of unsolicited adverse events generally occurred at a numerically lower incidence after the second vaccine dose in year 1, or revaccination in year 2, than after the first vaccine dose in year 1. For example, in the larger pooled analysis, the total number of adverse events occurring after the first and second vaccine doses in year 1, and after revaccination in year 2, was 1380, 893 and 955, respectively (statistical analyses not performed).[39] Ear disorders (rate difference 0.3%) and lower respiratory tract illnesses (rate difference 1.0%) both occurred in significantly ($p < 0.05$) fewer LAIV than placebo recipients after the second vaccine dose in year 1; no significant differences between the two treatment groups were seen after revaccination in year 2.

Serious adverse events were uncommon in LAIV recipients, with no significant differences between LAIV and placebo recipients in the larger pooled analysis.[39] The incidence of serious adverse events occurring up to 42 days after vaccination in year 1 or year 2 was 0.5% in LAIV recipients and 0.6% in placebo recipients.

3.1.2 Active-Comparator Studies

Reactogenicity events were common in recipients of LAIV (n = 4108; one dose) or TIV (n = 4118; one dose), according to an analysis of pooled tolerability data from six randomized, active-comparator studies in children or adolescents aged 2–17 years; individual trials not identified).[39] However, runny nose/nasal congestion occurred in significantly ($p < 0.01$) more LAIV than TIV recipients after either the first or second vaccine dose in year 1 (rate differences 11.8% and 4.1%), but muscle aches were less frequent in LAIV than TIV recipients after one dose ($p = 0.04$).

In the 10 days after vaccine administration, more LAIV than TIV recipients reported more than one unsolicited adverse event after the first dose (21% vs 18%; $p < 0.01$); however, there was no significant between-group difference after the second dose (16% vs 16%).[39] Significant rate differences ($p < 0.05$) in unsolicited adverse events in year 1 were reported for infections and infestations (rate difference 1.5% after one dose), respiratory, thoracic and mediastinal disorders (rate difference 1.5% after one dose; mainly attributable to nasal congestion and rhinorrhoea), nervous system disorders (0.6% after one dose; mainly attributable to headache) and surgical and medical procedures (rate difference –0.4% after the second dose). Serious adverse events were infrequent,

Table VIII. Indirect protective efficacy of intranasal live attenuated influenza vaccine. Results of open-label, community-based studies conducted in the US (see table VII for trial design details)

Study (season; hemisphere)	Primary (or key) endpoint	Primary (or key) endpoint result	
		intervention group	comparison group
Davis et al.[34] (2005/2006; NH)	Change from baseline in percentage of absenteeism during the peak influenza wk/total influenza outbreak period (%) [for elementary-/middle-/high-school students]	0.61*/0.61/0.32*; 0.05/–0.07/0.07	1.79/1.84/1.80; 2.31/2.56/2.32
Glezen et al.[35] (2007/2008; NH)	No. (rate per 1000 person/y) of MAARIs during influenza epidemic/postepidemic period	11 152 (18.3)/8090 (10.6)[a]	16 462 (20.5)/11 776 (11.7)
King et al.[36] (2004/2005; NH)	No. (%) of episodes of fever or influenza-like illness during peak influenza wk [children/adults]	1220 (40)**/979 (32)**	2874 (52)/2429 (44)

a The risk ratio for MAARI rates in the intervention vs comparison groups was 0.90 (95% CI 0.88, 0.92) for the epidemic period and 0.91 (95% CI 0.88, 0.93) for the postepidemic period.

MAARI(s) = medically attended acute respiratory illness(es); **NH** = northern hemisphere; * $p < 0.03$, ** $p < 0.001$ vs comparison group.

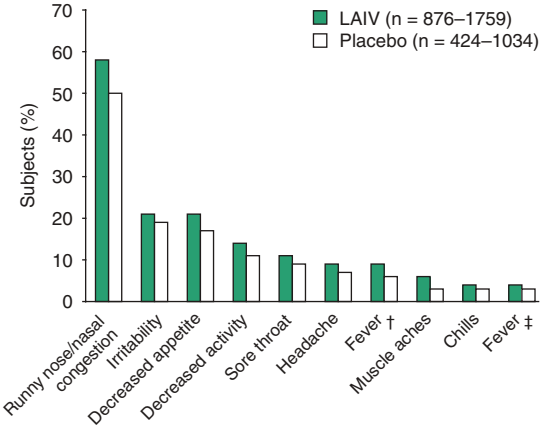

Fig. 1. Reactogenicity of live attenuated influenza vaccine (LAIV) in healthy young children. Solicited reactogenicity events occurring in ≥1% of LAIV recipients and at a higher rate in LAIV than in placebo (PL) recipients in two randomized, double-blind, multicentre trials conducted in children aged 12–36 months[8] or 15–71 months.[24] Results are from an analysis of pooled data from the subgroup of children in these trials who were within the approved age range for LAIV administration (i.e. ≥2 y) [available in the manufacturer's US prescribing information[12]]. Subjects received 1 or 2 doses of LAIV or PL in year 1 of each study, and a further single dose in year 2. Results presented here are those obtained within the first 10 d after the first vaccine dose in year 1. † indicates a fever of 100–101 °F (37.8–38.3 °C) obtained orally; ‡ indicates a fever of 101–102 °F (38.3–38.9 °C) obtained orally.

occurring in 0.75% of LAIV recipients and 1.01% of TIV recipients.

Results of a *post hoc* analysis of a large (n = 7852) active-comparator trial in children aged 6–59 months demonstrated that children aged 6–11 months who received LAIV had a significantly higher rate of hospitalization (for any cause) than those who received TIV (6.1% vs 2.6%; rate difference 3.5%; p = 0.002).[19] No significant between-group differences were demonstrated in children aged 12–23 months or ≥24 months. The majority of hospitalizations occurring during this period were as a result of gastrointestinal or respiratory tract infections, which generally occurred >6 weeks after vaccine administration.

3.1.3 Asthma or Wheezing

LAIV has been associated with an increased incidence of wheezing illness in young children.[12,19,38]

In a large (n = 9689) safety analysis, which enrolled healthy children aged 1–17 years, the risk of medically attended asthma events occurring was significantly higher in LAIV than placebo recipients aged 18–35 months (relative risk 4.06; 90% CI 1.29, 17.86).[38] On the basis of these results, an active-comparator trial was conducted to further evaluate the safety (and efficacy) of LAIV in children aged 6–59 months (see section 3.1.2 for further reactogenicity results).[19]

Overall (vaccine-naive and vaccine-experienced subjects in the 42-day period after one or two doses), the incidence of medically significant wheezing was not significantly different with LAIV or TIV. However, in vaccine-naive children (n = 6472), more episodes of medically significant wheezing occurred in the 42 days after vaccination with one dose of LAIV than TIV (adjusted rate difference 0.77%; 95% CI 0.12, 1.46).[19] Further analysis revealed that the between-group difference in the incidence of medically significant wheezing in vaccine-naive subjects over the 42-day post-vaccination period after one dose was primarily seen in children aged <24 months (3.2% of LAIV recipients vs 2.0% of TIV recipients; adjusted rate difference 1.18; 95% CI 0.13, 2.29) and, although not statistically significant, in those aged <12 months (3.8% of LAIV recipients vs 2.1% of TIV recipients; adjusted rate difference 1.6%; 95% CI –0.18, 3.53).[19] There was no significant difference demonstrated in the incidence of medically significant wheezing between vaccine-naive children aged ≥24 months who received LAIV and those who received TIV.

On review of hospital records for children aged <24 months who were hospitalized with medically significant wheezing in the first 42 days after the first dose of vaccine, there was no significant difference between LAIV and TIV recipients in the severity of medically significant wheezing, or in the duration of hospitalization, associated diagnoses or treatment received.[19] None of the episodes of medically significant wheezing occurring in this study required treatment in an intensive care unit or with mechanical ventilation, and no deaths occurred as a result of this adverse event.[19]

3.2 In Adults

3.2.1 Placebo-Controlled Studies

Runny nose was the most commonly reported solicited adverse event occurring in the total

population of LAIV recipients during the first 7 days after vaccine administration in a large (n = 4561) placebo-controlled trial in patients aged 18–64 years,[32] and in the subgroup of subjects in this trial who were within the approved age range (i.e. 18–49 years) for LAIV administration (figure 2).[12] Incidences of these and other solicited (or unsolicited) adverse events occurring in ≥1% of LAIV recipients in the subgroup analysis and at a higher rate than in placebo recipients are shown in figure 2.[32]

In the total patient population of this trial (i.e. not just in those in the approved age range), the incidences of runny nose (between-group difference 17.7%; 95% CI 14.7%, 20.7%) and sore throat (10.3%; 95% CI 7.7%, 12.9%) were significantly higher in LAIV than in placebo recipients.[32] This was confirmed when the upper limit of the 95% confidence interval for the difference in incidence rates between the LAIV and placebo groups exceeded the prespecified limit of 10%.[32] However, there was no between-group difference in the duration of the two adverse events, with both occurring for a median duration of 2 days in both groups.[32]

None of the serious adverse events or study withdrawals was considered to be related to the study vaccine.[32]

3.2.2 Active-Comparator Study

No significant differences were reported in the incidence of adverse events between LAIV or TIV and placebo in an active-comparator trial (n = 1952), except runny nose/nasal congestion, which was reported in significantly more LAIV than placebo recipients (52.3% vs 37.7%; p = 0.001), and arm soreness, which was reported in significantly more TIV than placebo recipients (52.6% vs 21.3%; p < 0.001).[33] Differences in the incidence of adverse events between LAIV and TIV were not reported.[33] None of the serious adverse events were considered to be vaccine related.

4. Immunogenicity

Immunogenicity was determined by assessing the level of haemagglutination-inhibiting (HI) antibodies against all three haemagglutinin antigen components (i.e. H1N1, H3N2 and B) of the vaccine in the serum of blood taken just before (pre-vaccination; day 0) and after (post-vaccination; day 21–42, depending on the study) administration of the vaccine.[16,18,23,24,37,40-45] In some studies, immunogenicity was also determined by assessing the level of influenza-specific IgA antibodies to vaccine haemagglutinins in pre- (day 0) and post-vaccination (days 1–28, depending on study) nasal wash specimens using kinetic enzyme-linked immunosorbent spot assay (ELISA).[37,46]

Key immunogenicity endpoints and terms are shown in table IX.

Immunogenicity criteria have not been established for seasonal LAIVs and those set for seasonal, inactivated influenza vaccines do not apply to seasonal LAIVs.[47] Therefore, immunogenicity results in this section were unable to be reviewed in light of any pre-set criteria.

4.1 Comparative Immunogenicity of Frozen and Refrigerator-Stable Intranasal Live Attenuated Influenza Vaccine

Refrigerator-stable LAIV was as immunogenic as frozen LAIV in healthy volunteers participating

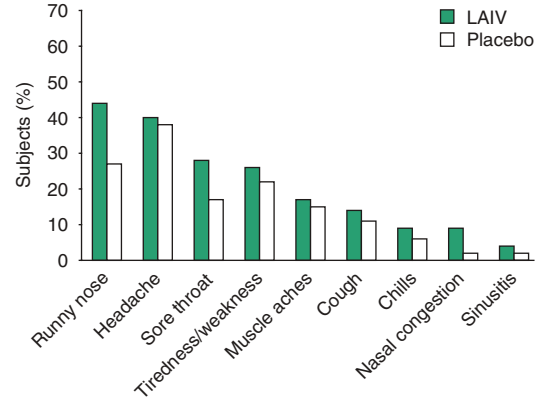

Fig. 2. Reactogenicity of live attenuated influenza vaccine (LAIV) in healthy, working adult subjects. Solicited and unsolicited (nasal congestion and sinusitis) adverse events occurring in ≥1% of LAIV recipients and at a higher rate in LAIV than in placebo (PL) recipients in a randomized, double-blind, multicentre trial (n = 4561).[32] Although the trial enrolled subjects aged 18–64 years, incidences given here are for the group of adults who are within the approved age range for LAIV administration (i.e. 18–49 years) [available in the manufacturer's US prescribing information[12]]; the number of subjects in this subgroup was not specified. All subjects received a single intranasal dose of LAIV or PL, and filled out a reactogenicity symptom card for 7 days following vaccination.

Table IX. Immunogenicity endpoints and terms

Term	Definition
Endpoints	
GMT of HI antibodies	Geometric mean titre (GMT) of haemagglutination-inhibiting (HI) antibodies
GMT ratio	Between-group ratio of post-vaccination HI antibody GMTs
Mucosal (nasal) IgA response	See text (sections 4.2[46] and 4.3[37]) for definition in each study
Seroconversion rate	The proportion of subjects with a ≥4-fold increase from baseline in post-vaccination serum HI antibody titre[8,16,18,44-46] or a rise in serum HI antibody titre from ≤1 : 4 at baseline to 1 : 8 post-vaccination[46]
Seroprotection rate	The proportion of subjects with a post-vaccination HI titre of ≥1 : 40
Seroresponse rate	The proportion of subjects with a ≥4-fold increase from baseline in post-vaccination serum HI antibody titre
Other terms	
Seronegative	A baseline serum HI antibody titre of ≤1 : 4[8,16,18,24,43-45][a]
Seropositive	A baseline[16,43,46] or post-vaccination[23,40] serum HI antibody titre of >1 : 4[16,46] or ≥1 : 8[23,40,43]
Serosusceptible	A baseline serum HI antibody titre of ≤1 : 8[16,37,41,43][a]

a In general, the term 'seronegative' was used for young children (aged ≤8 y) and 'serosusceptible' was used for older children (aged ≥9 y) and adults, in whom previous natural exposure to the three major human influenza subtypes was likely.

in a phase III equivalency trial (see table X for trial design details and vaccine dosage regimens).[16] The immunogenicities of the two vaccine formulations were shown to be equivalent with respect to the ratio of the adjusted post-vaccination HI antibody geometric mean titres (GMTs) against each of the LAIV viral strains in subjects receiving refrigerator-stable LAIV compared with those receiving frozen LAIV (primary endpoint) [see table XI for quantitative data and equivalency criteria].[16]

The seroconversion or seroresponse rates for each of the three vaccine viruses were similar in both age groups after administration of both LAIV formulations.[16] Seroconversion/seroresponse rates were 11–62% in subjects aged 5–8 years and 10–15% in those aged 9–49 years (values estimated from a graph), indicating that young children may potentially have a more robust immunological response to both vaccine formulations than older children and adults (statistical analyses not performed).

In addition, subjects with strain-specific seronegativity at baseline appeared to have a numerically higher immunological response to either vaccine formulation than those who did not.[16] In subjects aged 5–8 years, the seroconversion rate was 4–32% in seropositive subjects and 39–100% in seronegative subjects, and in subjects aged 9–49 years, the seroconversion rate was 1–4% in seropositive subjects and 12–55% in seronegative subjects (values estimated from a graph; statistical analyses not performed). For both LAIV formulations, the highest seroconversion rates were seen for HI antibodies to H3N2 virus in subjects who were seronegative for these antibodies at baseline.

4.2 In Children

The immunogenicity of LAIV (refrigerator-stable[8,18] or frozen[23,24] formulation) in healthy young children was investigated in three clinical trials, each of 2 years in duration (see tables III and X for study design details and vaccine dosage regimens).[8,18,23,24]

In general, LAIV was associated with numerically or significantly higher seroconversion rates than placebo for all three viral strains in all trials (US,[24] South American and South African,[18] and Asian[8]) and, where reported, in both study years[8,18] (table XII). Where investigated, these between-group differences occurred in both the total immunogenicity population and in the subgroups of patients who were seronegative to a specific LAIV viral strain at baseline.[8,18] In general, serum HI antibodies to the H3N2 or B antigens in year 1 of the US study were observed after one vaccine dose, whereas two vaccine doses were required to induce serum HI antibodies to the H1N1 antigen.[24] Of interest, in year 2 of the Asian study, the subgroups of subjects who received LAIV in the second study year generally had numerically higher rates of seroconversion than those who received placebo in the second study year, irrespective of serological status and whether they had received LAIV or placebo in year 1 of the study (table XII).[8]

Table X. Key trial design details and vaccine regimens for the key trials reviewed in the immunogenicity section. The primary objective of some of the trials was to assess the protective efficacy of live attenuated influenza vaccine (LAIV);[8,18,23,24,37] hence, immunogenicity was assessed in a subgroup of study participants in some of these trials[8,18,23,24]

Trial	Design	Subject age	Country (season[s]; hemisphere)	Vaccine dosage regimen[a]
Comparative trial				
Block et al.[16]	r, db, mc	5–49 y	US (2003/2004; NH)	If aged 5–8 y: 2 doses of RS-LAIV or F-LAIV, 46–60 d apart; if aged 9–49 y: 1 dose of RS-LAIV or F-LAIV
Adults				
Treanor et al.[37]	r, db, tc	18–45 y	US (1995/1996; NH)	Vaccination: 1 dose of LAIV + IM PL, TIV + IN PL or IM PL + IN PL; IN challenge (28 d after last vaccination): wild-type influenza vaccine strain to which subject was serosusceptible at baseline
Children				
Belshe et al.[23,24]	r, db, mc	15–71 mo	US (1996/1997, 1997/1998; NH)	y1: 1 or 2 doses of F-LAIV or PL, 60 ± 14 d apart; y2: 1 dose of F-LAIV or PL
Bracco Neto et al.[18]	r, db, mc	6 to <36 mo	South Africa and South America (2001, 2002; SH)	y1: 2 doses of RS-LAIV, 1 dose of RS-LAIV + PL_S or 2 doses of PL_E or PL_S; y2: 1 dose of RS-LAIV or PL_S
Tam et al.[8]	r, db, mc	12 to <36 mo	Asia (2000/2001, 2001/2002; NH)	y1: 2 doses of RS-LAIV or PL, ≥28 d apart; y2: 1 dose of RS-LAIV or PL[b]
Patients with HIV infection				
King et al.[41]	r, db, tc	18–58 y	US (1997/1998; NH)	1 dose of F-LAIV or PL
Levin et al.[42]	r, ac	5 to <18 y	US (2004/2005; NH)	1 dose of F-LAIV or TIV
Viral shedding studies				
Block et al.[43]	nc, mc	5–49 y	US (2003/2004; NH)	1 dose of F-LAIV
Belshe et al.[48]	challenge after r, db trial[24]	34–91 mo	US (1997/1998; NH)	Vaccination: see regimen for Belshe et al.;[23,24] IN challenge (6–8 mo after last vaccine dose): monovalent, cold-adapted, influenza A/H1N1 vaccine containing same H1N1 viral strain as used in LAIV during y2 of previous trial[24]
Transmission study				
Vesikari et al.[49]	r, db	9–36 mo	Finland (1998/1999; NH)	1 dose of F-LAIV or PL
Coadministration studies				
Nolan et al.[44]	r, pb,[c] mc	12–15 mo	US (May-Oct 2001 and 2002; NH) and Australia (Nov 2000–May 2001, Nov 2001–May 2002; SH)	One of three regimens: (i) d0: LAIV + MRR + VAR, d42: LAIV, d72: IN PL (LAIV + MMR + VAR arm); (ii) d0: LAIV, d42: LAIV, d72: MMR + VAR (LAIV alone arm); or (iii) d0: MMR + VAR + IN PL, d42 and d72: LAIV (MMR + VAR + IN PL arm)
Breiman et al.[45]	r, pb,[d] mc	6–36 mo	Asia and South America (2002; SH)	d0: LAIV + OPV, LAIV alone or OPV + IN PL; d28–42: LAIV recipients received a second dose of LAIV

a Unless otherwise specified, all LAIV or PL vaccines were administered intranasally and, in the studies of 2-y duration, subjects received the same vaccine in y2 as they did in y1. TIV was administered intramuscularly, MMR and VAR subcutaneously and OPV orally. TIV was administered at a dose of 0.5 mL in adults and children aged ≥36 mo at a dose of 0.25 mL in children aged 6–35 mo. Each dose of TIV contained 15 μg of haemagglutinin from each of the three influenza virus strains recommended by the WHO for that season and hemisphere [i.e. the same strains used in the LAIV vaccine in each study].

b Subjects were rerandomized to treatment in y2 of this study.

c The study was db in terms of whether the child was receiving LAIV or IN PL in the LAIV + MMR + VAR and MMR + VAR + IN PL arms; otherwise study vaccines were administered in an open-label manner, because no subcutaneous PL was used in the trial.

d The study was db in terms of whether the child was receiving LAIV or IN PL in the LAIV + OPV or OPV + IN PL arms; otherwise study vaccines were administered in an open-label manner, as no oral PL was used in the trial.

ac = active-comparator; **db** = double-blind; **d*x*** = day *x*; **F** = frozen; **IM** = intramuscular; **IN** = intranasal; **mc** = multicentre; **MMR** = measles, mumps and rubella vaccine; **nc** = noncomparative; **NH** = northern hemisphere; **OPV** = oral poliovirus vaccine; **pb** = partially-blind; **PL** = placebo; **PL_E** = excipient PL; **PL_S** = saline PL; **r** = randomized; **RS** = refrigerator-stable; **SH** = southern hemisphere; **tc** = two-centre; **TIV** = trivalent inactivated influenza vaccine; **VAR** = varicella vaccine; **y*x*** = year *x*.

Table XI. Immunogenicity of the refrigerator-stable (RS) and frozen (F) formulations of live attenuated influenza vaccine (LAIV). Geometric mean titre (GMT) ratios in healthy subjects who received RS-LAIV or F-LAIV in an equivalency trial (see table X for trial design details and vaccine dosage regimens).[16] Both vaccine formulations met the WHO recommendations for the preparation of the influenza vaccine for the 2003/2004 influenza season in the Northern Hemisphere (table I)

Age group	No. of subjects	GMT ratio (95% CI)[a]		
		H1N1	H3N2	B
5–8 y	332	1.24 (1.02, 1.49)	1.02 (0.88, 1.19)	1.00 (0.81, 1.24)
9–49 y	546	1.14 (0.94, 1.36)	1.12 (0.95, 1.32)	0.96 (0.83, 1.10)

a RS-LAIV and F-LAIV were considered to have equivalent immunogenicity because the 95% CIs for all of these GMT ratios were within prespecified limits (>0.5 but <2.0). GMTs were determined in serum samples collected 28–35 d after the last vaccine dose: GMTs were adjusted for baseline serostatus.

Although year-2 seroconversion rates were not reported in the US study, significantly ($p < 0.01$) more LAIV than placebo recipients were seropositive for GMT antibody titres against H1N1 (82% vs 20% of subjects), H3N2 (100% vs 65%) or B (100% vs 46%) antigen, according to year-2 results.[23]

In general, post-vaccination GMTs were numerically[18,24] or significantly (p-value not stated)[23] higher in LAIV recipients than in placebo recipients, irrespective of baseline serostatus, in both study years of the US[23,24] and South African/South American studies.[18] In the South African/South American study (year 1), GMTs of HI antibodies to the three vaccine antigens were 21.7–73.1 in recipients of two LAIV doses, 11.5–20.6 in recipients of one LAIV dose plus placebo and 4.7–9.2 in the recipients of placebo, indicating that subjects who received two doses of LAIV (i.e. the recommended dose [section 5]) may potentially have a more robust immunological response than those who received only one dose (between-group statistical analyses not performed).[18]

In the Asian study, the geometric mean fold rise (GMFR) in HI antibody GMTs showed significant ($p < 0.05$) increases from pre- to post-vaccination in all LAIV recipients in year 1.[8] However, in year 2, GMFRs reflecting significantly ($p < 0.05$) higher HI antibody GMTs were seen only in subjects who received LAIV in year 2 of the study, regardless of whether they had received LAIV or placebo in year 1.

According to results of a 2-year extension (see table XIII for trial design details and vaccine dosage regimens) of the US study, a response to LAIV was maintained over 4 years.[40] Serum samples taken post-vaccination in year 4 demonstrated that at least 79% of LAIV recipients were seropositive for HI antibodies against H1N1, H3N2 or B viral strains in both groups (i.e. yearly and first-time) [table XIII]. However, post-vaccination HI antibody GMTs to H3N2 and B antigen were significantly higher in the group of control children who had received LAIV vaccination for the first time in year 4 of the study than in the group of children who had received LAIV for 4 years consecutively (table XIII).[40]

In a subgroup analysis ($n = 19$) of the US trial, a mucosal influenza-specific IgA response to H1N1, H3N2 or B antigen was demonstrated in 62%, 69% and 85% of LAIV recipients, and 33%, 0% and 17% of placebo recipients.[46] The between-group differences in mucosal IgA response to H3N2 and B were significantly ($p = 0.01$) in favour of LAIV. An influenza-specific mucosal IgA response was defined as a ≥4-fold rise in corrected values of the ratio of mean influenza-specific IgA : total secretory IgA, or as an influenza-specific IgA value of <5 milli optical density units (mOD)/min pre-vaccination and ≥5 mOD/min post-vaccination. Overall, subjects who were seropositive at baseline were 4.5 times more likely to develop a mucosal immune response than a seroresponse ($p = 0.015$), indicating that mucosal immune response may be the only indication of a vaccine take in seropositive children. No correlation between mucosal immune response and seroresponse was shown in this study.

4.3 In Adults

The immunogenicity of trivalent LAIV in healthy adults was investigated in a challenge study in

which the efficacy of LAIV (frozen formulation) was compared with that of TIV (see table X for study design details and vaccine dosage regimens).[37]

No statistically significant differences were demonstrated in the LAIV group versus the placebo group with respect to GMTs of HI antibodies to vaccine viral strains or seroresponse rates determined post-vaccination (table XIV).[37] However, post-vaccination GMTs and seroresponse rates to the viral strains were significantly higher in the TIV group than in the placebo group (p-values not stated; table XIV). The seroresponse to H1N1 and H3N2 observed in the placebo group meant that interpretation of results was difficult, and it was thought the placebo responses may have occurred because of the presence of asymptomatic intercurrent influenza infection with an influenza A virus and/or variability in antibody assays.

Although mucosal (nasal), strain-specific IgA antibody responses (defined as a ≥2-fold increase in ELISA signal between pre- and post-vaccination samples) to H1N1, H3N2 or B viruses appeared to be more frequent in the LAIV-containing (14.3%, 32.1% and 17.9%) and TIV-containing (23.3%, 16.7% and 16.7%) groups than in the placebo group (12.9%. 9.7% and 3.2%), these between-group differences were not significant.[37] The nasal antibody responses seen in the placebo group occurred mainly in those individuals who also had serum antibody responses, further indicating that some participants may have had asymptomatic exposure to circulating wild-type viruses.

In the 92 of 103 randomized subjects who were eligible for challenge, rates of seroresponse to challenge with the wild-type H1N1, H3N2 or B viruses contained in the vaccines were not significantly

Table XII. Immunogenicity of live attenuated influenza vaccine (LAIV) [refrigerator-stable[8,18] or frozen[24] formulation] in healthy young children in 2-y clinical studies (see tables III and X for study design details and vaccine dosage regimens).[8,18,24] The antigenic composition of LAIV met the WHO recommendations for the preparation of the influenza vaccine for the 1996/1997 and 1997/1998 influenza seasons[24] or the 2000/2001 and 2001/2002 influenza seasons[8] in the northern hemisphere, or for the 2001 and 2002 influenza seasons in the southern hemisphere[18] (table I)

Study (location)	Vaccine [y1/y2]	Seroconversion rates after 1 y (2 y) [% of subjects][a]							
		all subjects				seronegative subjects			
		no.	H1N1	H3N2	B	no.	H1N1	H3N2	B
Belshe et al.[23,24] (US)	LAIV					56–78	61	96	96
	PL					27–40	2	11	3
Bracco Neto et al.[18] (South Africa and South America)	LAIV + LAIV	113	56	80***	69***	NS	74***	92***	89***
	LAIV + PL_S	112	26	56***	55***	NS	32***	60***	75***
	PL + PL	109	4	9	11	NS	7	8	16
	LAIV + LAIV/LAIV	133	(28)	(14*)	(10***)	NS	(66***)	(36***)	(20***)
	LAIV + PL_S/LAIV	265	(33)	(17***)	(8**)	NS	54***	(45***)	(14***)
	PL + PL/PL_S	126	(2)	(3)	(1)	NS	(2)	(5)	(1)
Tam et al.[8] (Asia)	LAIV	111	60	61	57	61–82	85	95	74
	PL	75	11	4	4	47–63	14	2	5
	LAIV/LAIV	50	(28)	(32)	(26)	4–21	(82)	(75)	(52)
	PL/LAIV	45	(20)	(38)	(31)	16–32	(32)	(75)	(41)
	LAIV/PL	50	(4)	(0)	(2)	6–24	(9)	(0)	(4)
	PL/PL	26	(4)	(12)	(12)	11–21	(7)	(18)	(10)

a Where specified, post-vaccination serum samples were collected 4 wk[24] or 35 ± 7 d[18] after the last vaccination in each year. In children who received only one vaccine dose in y1, post-vaccination serum was collected on day 35–49 post-vaccination.

NS = not stated; **PL** = placebo; **PL_S** = saline PL; **y*x*** = year *x*; * p = 0.003, ** p = 0.002, *** p ≤ 0.001 vs PL + PL (y1) or PL + PL/PL (y2).

Table XIII. Immunogenicity of live attenuated influenza vaccine (LAIV) [frozen formulation] in healthy children aged 15–71 mo. Results of an open-label extension[40] of a double-blind trial[23,24] (see table X for details of the design of the original study) in which subjects received a single intranasal dose of LAIV each year for 2 y (yearly). As a control, a cohort of vaccine-naive children (aged 3–10 y) were randomized to receive two doses of LAIV or placebo (PL) in the final study year (first time). The antigenic composition of LAIV met the WHO recommendations for the preparation of the influenza vaccine for the 1998/1999 and 1999/2000 influenza seasons in the northern hemisphere (table I). Analyses were conducted in subjects who had received at least one dose of LAIV in each of 4 study years (yearly) or in the final study year (first time)

Endpoint[a]	Vaccine group	No. of children	Antigen		
			H1N1	H3N2	B
GMT pre-/post-vaccination	First time	151–156	4.7/17.7	55.5/137.8*	12.3/34.9*
	Yearly	107–109	7.8†/13.6	44.5/66.1	22.6†/27.4
Seropositive pre-/post-vaccination (% of subjects)	First time	151–156	34.2/79.5	90.3/100	74.8/99.3
	Yearly	107–109	60.6†/79.4	98.2†/100	100†/100

a Post-vaccination serum samples were collected ≈30 d (in the first-time vaccine group) or ≈4–6 wk (in the yearly vaccine group) after the last vaccine dose.

GMT = geometric mean titre. * $p < 0.05$ vs yearly vaccine group for post-vaccination values; † $p < 0.05$ vs first time vaccine group for pre-vaccination values.

different in subjects who had received an LAIV-containing regimen (20% [2 of 10 subjects], 22% [2 of 9] and 20% [2 of 10]) compared with those who had received placebo (50% [5 of 12], 50% [4 of 8] and 36% [4 of 11]). None of the subjects who received a TIV-containing regimen had a seroresponse to virus challenge, and the difference between the TIV-containing and placebo groups in seroresponse rates to H1N1 or H3N2 challenge was statistically significant ($p < 0.05$) and in favour of the placebo group.[37]

4.4 In Patients with HIV Infection

4.4.1 Children with HIV Infection

In contrast to the low number of adults with HIV infection who achieved a seroresponse to intranasal LAIV (section 4.4.2), 32% and 22% of previously vaccinated children (n = 243) with HIV infection (plasma HIV RNA <60 000 copies/mL) who received LAIV (frozen formulation) had a seroresponse to H1N1 antigen at 4 and 24 weeks after vaccination (see table X for study design details and vaccine dosage regimens).[42] This did not differ significantly from the percentage of TIV recipients showing a response at these same timepoints (33% and 16%). However, significantly ($p < 0.05$) fewer LAIV than TIV recipients achieved a seroresponse to H3N2 antigen at 4 weeks (14% vs 44%), and to B antigen at 4 (11% vs 34%) or 24 (11% vs 22%) weeks; rate of seroresponse to H3N2 at week 24 did not differ significantly between the two vaccines (29% vs 34%).

Post-vaccination HI antibody GMTs at 4 and 24 weeks were significantly ($p < 0.05$) lower in LAIV than in TIV recipients for H3N2 and B antigens, and seroprotection rates at 4 and 24 weeks were significantly ($p < 0.05$) lower in LAIV than in TIV recipients for the B antigen.[42] Of note, a significant ($p < 0.05$) between-group difference in favour of TIV was observed for the percentage of patients with seroprotective titres against the H3N2 and B antigens at baseline.

GMTs of anti-influenza neutralizing antibodies against all viral vaccine strains increased significantly ($p \leq 0.02$) from baseline to 4 and 24 weeks after vaccination in both treatment groups; however, GMTs were significantly ($p \leq 0.002$) higher in TIV than LAIV recipients at 4 weeks after vaccination for all three vaccine viral strains.[50] Despite this, a similar proportion of children in each treatment group achieved protective levels (i.e. ≥1 : 40) of anti-influenza neutralizing antibodies at both timepoints.

Neither LAIV nor TIV affected HIV replication, as demonstrated by the absence of significant differences in mean (or median) plasma HIV RNA levels between baseline and study follow-up. The median percentage of CD4+ cells contained in the total lymphocyte pool also remained stable throughout the study period.[42]

4.4.2 Adults with HIV Infection

LAIV (frozen formulation) did not appear to be immunogenic in terms of the number of patients achieving seroresponse (≤8% of HIV- and nonHIV-infected subjects) in adults with (n = 57) or without (n = 54) asympomatic or mildly symptomatic HIV infection (plasma HIV RNA <10 000 copies/mL; CDC class A1-2; >200 CD4 cells/mm^3) [see table X for study design details and vaccine dosage regimens].[41] This possibly reflected the low percentage of patients who were serosusceptible to the H1N1 (4% of patients with HIV infection and 11% of patients without HIV infection), H3N2 (4% and 4%) or B (31% and 11%) antigens at baseline.

Overall, administration of the vaccine to these otherwise healthy adults was not associated with an increase in HIV replication in terms of plasma HIV RNA levels or CD4 cell counts.[41] However, two LAIV recipients and one placebo recipient had a ≥10-fold rise in HIV RNA levels from baseline to one of the post-vaccination follow-ups; levels returned to baseline (or near baseline) by the next follow-up visit in both of the LAIV recipients, but not in the placebo recipient. Of note, these episodes occurred in patients with HIV infection who were (as opposed to those who were not) receiving antiretroviral therapy during the study.

4.5 Studies on Viral Shedding

Infectious vaccine viruses may be cultured from nasal secretions after vaccination with LAIV, and this is known as viral shedding.[12,43] Various studies have investigated LAIV virus shedding in specific groups of subjects, including children,[24,48,49] adults[51] and subjects with or without HIV infection.[41,42] Where reported, the rate of viral shedding in these studies ranged from 1.8% (1 of 55 subjects) in HIV-infected adult subjects at the day 3–5 follow-up visit[41] to 80% (78 of 98 subjects) in young children aged 9–36 months at some stage over the 21-day follow-up period (see section 4.6 for further results of the latter study).[49]

In a large phase IV study in healthy subjects (see table X for trial design details and vaccine dosage regimens), viral shedding occurred in 99 of 343 subjects (28.9%) overall.[43] Peak titres of nasal LAIV virus occurred on days 2–3 post-vaccination and coincided with peak shedding frequency, which occurred on day 2. Levels of shed virus decreased to undetectable levels after day 10 in children aged 5–8 years and after day 6 in those aged 9–17 or 18–49 years. Mean titres of shed virus were <3 $\log_{10}$ $TCID_{50}$/mL in all groups. A/H1N1, A/H3N2 and B vaccine strains were shed by 13%, 5% and 12% of participants in this trial;[43] however, it should be noted that the B vaccine virus was the predominant virus (72% of subjects vs 31% and 12% of subjects who shed H1N1 or H3N2 viruses) to be shed in young children aged 9–36 months in another trial.[49] The incidence of viral shedding was shown to be associated with a number of factors, including patient age and baseline serostatus.[43]

Similar findings were seen in a challenge study, in which H1N1 virus shedding was shown to be associated with post-vaccination (but pre-challenge)

Table XIV. Immunogenicity of live attenuated influenza vaccine (LAIV) [frozen formulation] in healthy adults. Results of a challenge study (see table X for trial design details and vaccine dosage regimens) in which the antigenic composition of LAIV and trivalent inactivated influenza vaccine (TIV) met the WHO recommendations for the preparation of the influenza vaccine for the 1995/1996 influenza season in the northern hemisphere (table I).[37] Analyses are for results determined post-vaccination but pre-challenge

Vaccine	No. of adults	GMT pre-/post-vaccination			Seroresponse rates[a] [%] (no. of subjects)		
		H1N1	H3N2	B	H1N1	H3N2	B
LAIV + IM PL	29–30	4.8/9.8	6.1/14.3	18.8/19.4	7 (23)	10 (33)	1 (3)
TIV + IN PL	33	4.9/199.0*	11.0/99.5*	17.4/133.5*	30 (91)*	25 (76)*	25 (76)*
IM PL + IN PL	32–33	5.8/11.8	9.3/11.9	15.3/15.3	5 (16)	2 (6)	0 (0)

a Serum samples were collected 28 d post-vaccination.

GMT = geometric mean titre; **IM** = intramuscular; **IN** = intranasal; **PL** = placebo. * indicates a statistically significant difference vs IM PL + IN PL (p-value not available).

serum HI antibody levels in young children (n = 222) [see table X for trial design details and vaccine dosage regimens].[48] Regardless of whether subjects had received LAIV or placebo, children who were seropositive for HI antibodies to H1N1 post-vaccination but pre-challenge appeared to be protected from the H1N1 challenge virus, as demonstrated by the low rate of H1N1 virus shedding seen in seropositive LAIV or placebo recipients (2% and 0% of subjects).[48] However, the rate of H1N1 virus shedding was significantly lower in LAIV than placebo recipients (9% vs 37%; p = 0.001) who were seronegative for H1N1 antibodies pre-challenge, suggesting that H1N1 HI antibodies were not the only factors protecting against H1N1 virus challenge in LAIV recipients.

Pre-challenge levels of IgA antibody to H1N1 in nasal wash specimens were also associated with protection against H1N1 virus challenge with regard to viral shedding rates.[48] In children with nasal wash IgA antibody present pre-challenge, 1% of LAIV recipients and 13% of placebo recipients shed H1N1 challenge virus. In contrast, in children without nasal wash IgA antibody present pre-challenge, H1N1 challenge virus was shed in 12% and 36% of LAIV or placebo recipients ($p < 0.01$ vs placebo).

4.6 Transmission Study

The rate and probability of LAIV virus transmission was assessed in healthy young children in a double-blind trial (see table X).[49] All children were required to attend daycare for at least 3 days per week for at least 4 hours per day and to be in contact with at least four other study participants, including at least one subject who received LAIV.

Despite the high rate of viral shedding occurring in this study (section 4.5), the rate of viral transmission was low.[49] There was one confirmed episode of LAIV virus transmission (a type B vaccine strain) to a placebo recipient during the 21-day follow-up period, and two other episodes which were regarded as possible but unconfirmed transmissions. Thus, the rate of transmission (calculated using the one confirmed case) was 1.01% in the all-available transmission population (n = 99) and 1.75% in the all-evaluable population (n = 57). Importantly, the one confirmed case of transmission did not lead to disease, and the clinical signs and symptoms occurring in this child were similar to those seen in other study children, regardless of whether they had received LAIV or placebo.

According to results of a *post hoc* exploratory analysis using the Reed-Frost model, and assuming a single confirmed transmission, the probability of LAIV virus transmission was calculated to be 0.58%, 1.16%, 1.73%, 2.3% and 2.87% in placebo recipients who were in regular contact with one, two, three, four or five LAIV-vaccinated children, respectively.[49]

Of note, the phenotypic characteristics of the LAIV virus strains (i.e. cold adaptation and temperature sensitivity) were preserved in all shed viruses, indicating the phenotypic stability of the vaccine.[49]

4.7 Cell-Mediated Immunity

LAIV (refrigerator-stable formulation, where specified[31]) increased cell-mediated immunity (CMI), according to data from several trials.[31,52,53]

For example, LAIV (refrigerator-stable formulation) at a recommended dose (i.e. $10^{7.0 \pm 0.5}$ FFUs) elicited a CMI response in young children (n = 162) participating in an exploratory immunogenicity study in the northern hemisphere (see table XV).[31] The median number of interferon-γ-secreting peripheral blood mononuclear cells in post-vaccination serum samples after *in vitro* stimulation with inactivated monovalent H1N1, H3N2 or B influenza virus antigens increased by up to 130-fold in all children and 213-fold in seronegative children who received LAIV at a dosage of 10^7 FFUs of live attenuated influenza virus reassortants (table XV). In contrast, no response was seen in samples from subjects who received LAIV at a lower-than-recommended dose (i.e. $10^{5.0 \pm 0.5}$ FFUs) [section 5] or placebo, and the response to TIV was minimal.

A large (n = 2172) field study conducted on the basis of these results indicated that, unlike TIV, which only elicited CMI responses in children

Table XV. Effect of live attenuated influenza vaccine (LAIV) [refrigerator-stable formulation] on cell-mediated immunity in an exploratory immunogenicity trial. Children aged 6 to <36 months received a single dose of LAIV containing 10^7 fluorescent focus units (FFUs) or $<10^5$ FFUs of live attenuated influenza virus reassortants, trivalent inactivated influenza vaccine (TIV) or placebo (PL).[a] The antigenic composition of LAIV met the WHO recommendations for preparation of the influenza vaccine for the 2001/2002 influenza season in the northern hemisphere (table I)

Vaccine (no. of children)	Median number of IFNα-secreting PBMCs (SFC per 10^6)[b]					
	all subjects			seronegative subjects		
	H1N1	H3N2	B	N1N1	H3N2	B
LAIV 10^7 FFUs (3–5)	55	67	130	55	104	213
LAIV $<10^5$ FFUs (3–11)	1	1	1	1	1	1
TIV (3–9)	3	3	1	1	1	1
PL (2–9)	1	1	1	1	1	1

a The median number of IFNγ-secreting PBMCs in pre-vaccination serum samples after *in vitro* stimulation with inactivated monovalent H1N1, H3N2 or B influenza virus antigens was 1 SFC per 10^6 PBMCs in all treatment groups for all antigens, regardless of baseline serostatus.

b Assessed using enzyme-linked immunosorbent spot assay in post-vaccination serum samples (day 13).

IFN = interferon; **PBMCs** = peripheral blood mononuclear cells; **SFC** = spot-forming cells.

with detectable levels of pre-existing antibody against influenza virus, LAIV at the recommended dose elicited CMI responses in children with no detectable antibody at baseline and in whom the risk of acquiring influenza infection is potentially the highest.[31] CMI played a significant role in protection against community-acquired influenza infection, with further analyses indicating that the majority of children with ≥100 spot-forming cells (SFCs)/10^6 peripheral blood mononuclear cells (PBMCs) could be considered seroprotected against influenza infection.

CMI response to LAIV (2004/2005 northern hemisphere) was also seen in another study, which reported a significantly ($p \leq 0.0056$) higher adjusted geometric mean percentage (aGMP) of influenza A virus-reactive interferon (IFN)γ-secreting CD4+ T cells and CD8 T cells (determined in PBMC cultures that had been stimulated with a live wild-type H3N2 influenza virus of the same strain as that contained in the vaccines) at day 10 and 28 post-vaccination than at baseline in children aged 5–9 years but not in recipients aged 22–49 years.[52] Furthermore, the T-cell response elicited by LAIV appeared to be higher in children than in adults, as demonstrated by a significantly ($p \leq 0.0363$) higher fold change in the aGMP of influenza A virus-reactive IFNγ-secreting CD4+ T cells and CD8 T cells in children than in adults at day 10 or 28.

In this same study, LAIV was associated with a greater CMI response than TIV in children, with the fold change in the aGMP of influenza A virus-reactive IFNγ-secreting CD4+ T cells and CD8 T cells being significantly ($p \leq 0.0226$) higher in children receiving LAIV than in those receiving TIV at day 10 and 28.[52] CMI response to LAIV and TIV did not differ significantly in the adult population.

Further analysis revealed that CMI response (defined as the fold change from baseline to day 10 in the aGMP of influenza A virus-reactive IFNγ-secreting CD4 T cells, CD8 T cells, $CD56^{bright}$ natural killer [NK] cells and $CD56^{dim}$ NK cells) was significantly ($p < 0.05$) and inversely correlated with pre-vaccination GMPs of these cells in adults, and that the correlation appeared to be stronger in LAIV than TIV recipients.[52] Although inverse correlations with baseline GMPs were also seen in children, not as many reached significance compared with the comparisons in adults.[52]

LAIV (2004/2005 northern hemisphere) was also shown to induce effector B-cell responses 7–12 days post-vaccination in children aged 5–9 years and adults aged 21–48 years, and these responses were similar in magnitude to those seen with TIV.[53] However, in contrast to TIV, which increased the percentage of circulating memory B cells 1 month post-vaccination, LAIV did not.

4.8 Cross Immunogenicity

The cross immunogenicity of LAIV has not been formally assessed. However, in one of the key immunogenicity studies conducted in young children discussed in section 4.2 (see tables X and XII for study design details and immunogenicity results), LAIV (frozen formulation) elicited an HI antibody response to the H3N2 viral strain contained in the vaccine for the second study season (1997/1998), as well as to the antigenically distinct H3N2 influenza strain, A/Sydney/5/97, that became a major cause of influenza in 1997.[23] Cross-reactive antibodies to this variant strain were seen in 98% of children receiving LAIV and 60% of those receiving placebo. In addition, GMTs of HI antibody to this variant strain were significantly ($p < 0.01$) higher in LAIV than placebo recipients (68 vs 12).

4.9 Coadministration with Other Vaccines

The immune response against LAIV (frozen formulation) in young, healthy children aged 12–15 months was equivalent to the response against LAIV when coadministered with the MMR and varicella vaccines in terms of seroconversion rates and post-vaccination GMTs for HI antibodies (see tables X and XVI for study design details, immunogenicity results and equivalence criteria).[44] The immune response was also similar in baseline seronegative patients against MMR and varicella vaccines with, and without, concomitant LAIV administration.

In healthy children aged 6–36 months, the immunogenicity of LAIV (refrigerator-stable formulation) when coadministered with the oral poliovirus vaccine (OPV) was noninferior to that of LAIV alone (table XVII), and the immunogenicity of OPV when coadministered with LAIV was noninferior to that of OPV plus intranasal placebo (data not shown), supporting the combined use of the two vaccines (see tables X and XVII for study design details and noninferiority criteria).[45] Of interest, seroconversion rates to the H1N1 component of LAIV ($p = 0.002$ after one dose of LAIV and $p = 0.015$ after two doses) and GMTs for this component (p-values not available) were significantly higher in the group of patients receiving LAIV plus OPV than in the group receiving LAIV alone (table XVII).

5. Dosage and Administration

Each dose of LAIV has been formulated to contain $10^{6.5–7.5}$ FFUs of each of three live attenuated virus reassortants that the WHO expects to be circulating in the community in the upcoming winter.[12] The refrigerator-stable formulation of LAIV is used in preference to the frozen formulation because of improved storage convenience.

Table XVI. Immunogenicity of intranasal live attenuated influenza vaccine (LAIV) [frozen formulation] when coadministered with subcutaneous measles, mumps and rubella vaccine (MMR) and subcutaneous varicella vaccine (VAR).[44] Although there were three treatment arms in this study (see table X for study design details and vaccine dosage regimens), seroconversion rates and GMTs for influenza vaccine strains are only available for two of the treatment arms. The antigenic composition of LAIV met the WHO recommendations for the preparation of the influenza vaccine for the 2000/2001 influenza season in the northern hemisphere (table I)

	Vaccine regimen	No. of children	Influenza strain		
			H1N1	H3N2	B
Seroconversion rate (% of pts)	LAIV + MMR + VAR	286–319	42.6	97.9	95.6
	LAIV alone	299–328	43.7	98.3	92.1
BGD in seroconversion rates [95% CI][a]			–1.0 [–8.7, 6.7]	–0.4 [–3.0, 2.0]	3.6 [–0.2, 7.5]
GMT post-vaccination	LAIV + MMR + VAR	334	5.7	102.9	20.5
	LAIV alone	338–339	5.7	112.3	17.7
GMT ratio[a] [95% CI]			0.98 [0.85, 1.13]	0.92 [0.81, 1.04]	1.16 [1.03, 1.30]

a The immunogenicity of LAIV administered alone or in conjunction with MMR + VAR was considered equivalent when the lower limit of the 95% CI for the difference in seroconversion rates for the LAIV + MMR + VAR group minus the LAIV alone group was more than –10% for all vaccine influenza virus strains, and when the lower limit of the 95% CI for the ratio of HI antibody GMTs in the LAIV + MMR + VAR group compared with the LAIV alone group was more than 0.5 for all strains.

BGD = between-group difference; **GMT** = geometric mean titre.

Table XVII. Immunogenicity of intranasal live attenuated influenza vaccine (LAIV) [refrigerator-stable formulation], when coadministered with oral poliovirus vaccine (OPV) [see table X for study design details and vaccine dosage regimens].[45] The antigenic composition of LAIV met the WHO recommendations for the preparation of the influenza vaccine for the 2002 influenza season in the southern hemisphere (see table I). Because OPV was obtained from a variety of sources, according to regional preferences and vaccine availability, the antigenic composition of OPV varied across study sites

Vaccine regimen	No. of children	Seroconversion rate[a,b] (% of children)			GMT pre-/post-vaccination[b]		
		H1N1	H3N2	B	H1N1	H3N2	B
LAIV + OPV	707–713	58.2*	60.4	25.2	7.6/32.8	7.9/49.0	2.9/4.8
LAIV	724	51.7	58.7	22.9	6.1/20.6	7.3/40.7	2.9/4.7
OPV + PL	713–722	2.2	4.1	3.5	6.9/6.9	7.8/8.3	2.9/3.0

a The immunogenicity of LAIV when coadministered with OPV was considered noninferior to that of LAIV alone because the lower limit of the 90% CI for the difference between the two treatment arms (LAIV + OPV minus LAIV) in seroconversion rates was greater than −10% (quantitative data not available). Seroconversion rates were defined as the proportion of subjects with a ≥4-fold increase from pre- to post-vaccination in HI antibody levels.

b At day 35 ± 7 after second LAIV dose.

GMT = geometric mean titre; **PL** = placebo; * $p = 0.015$ vs LAIV.

In the US, LAIV is indicated for active immunization in individuals aged 2–49 years for the prevention of disease caused by the influenza virus subtypes A and B contained in the vaccine.[12] The recommended dosage of LAIV in children aged 2–8 years who have not previously received influenza vaccination is two 0.2 mL doses of the refrigerator-stable formulation administered intranasally at least 1 month apart. Only one annual dose of LAIV is recommended in children aged 2–8 years who have previously received influenza vaccination, and in children, adolescents or adults aged 9–49 years.

Concomitant use of LAIV with aspirin (or aspirin-containing drugs) is contraindicated in children and adolescents aged 2–17 years, because of the association between aspirin and Reye's syndrome (a serious, acute encephalopathy that is associated with liver dysfunction[54]) in the setting of febrile illnesses, such as wild-type influenza infection.[12] Administration of LAIV to individuals with known systemic hypersensitivity reactions to egg proteins (a vaccine component), gentamicin, gelatin or arginine, or those who have previously had a life-threatening reaction to influenza vaccination, is also contraindicated.[12]

LAIV should not be administered to children aged <24 months or, in the US, to individuals with asthma or children aged <5 years with recurrent wheezing, unless the benefits of treatment are shown to outweigh the risks (section 3).[12] Because of lack of reactogenicity data in individuals with severe asthma or active wheezing, LAIV should not be administered to individuals with these conditions.

Careful consideration of the benefits and risks of LAIV treatment is also recommended in individuals who have previously developed Guillain-Barré syndrome within 6 weeks of influenza vaccine administration, immunocompromised patients and patients with medical conditions that may predispose them to complications following wild-type influenza infection.[12]

Only limited data are available regarding the use of LAIV in pregnant women. Although animal studies do not indicate direct or indirect harmful effects during pregnancy, the use of the LAIV vaccine is not recommended in pregnant women.[12]

Local prescribing information should be consulted for other specific details of indications, warnings, contraindications and precautions.

6. Place of Intranasal Live Attenuated Influenza Vaccine in the Prevention of Seasonal Influenza

Vaccination remains the most effective means of preventing seasonal influenza,[2,55,56] and the CDC recommends routine, annual vaccination of all individuals aged ≥6 months.[2] However, the focus should still be on individuals who are at higher risk of influenza-related complications than others, particularly in times when vaccine is in short supply. Individuals at higher risk than others include (but are not limited to) children

aged 6 months to 4 years, adults aged ≥50 years, those with chronic diseases or immunosuppression, those living in chronic-care facilities, pregnant women and anyone who is in regular contact with such individuals.[2]

In 2009, the CDC recommendations for routine influenza vaccination were predominantly for individuals who were at higher risk or in contact with individuals at higher risk of influenza-related complications, although recommendations were also extended to children aged 5–18 years for the first time that year.[57] Therefore, the only group of individuals for whom routine vaccination was not specifically recommended at this time were healthy non-pregnant adults aged 19–49 years who had no known risk factors for influenza-related complications or were not in contact with any high-risk individuals.[57] However, it was noted that influenza-related complications still occurred in the latter group of individuals, and that perhaps a proportion of them might actually have medical conditions or age-related risks for which they were unaware that routine influenza vaccination was recommended.[2] Furthermore, the possibility of continued circulation of 2009 pandemic influenza A/H1N1-like viruses in the upcoming influenza season(s) was particularly concerning with regard to this group because the incidence of influenza-related complications was much higher in these individuals during the 2009 influenza pandemic than during normal influenza seasons. For these reasons, the CDC recommendations for routine influenza vaccination were expanded to include healthy non-pregnant adults aged 19–49 years who had no risk factors for complications or were not in regular contact with people who did.[2]

The 2010/2011 season represents the first season that the expanded CDC recommendations took effect. Overall, in the US, the seasonal influenza vaccination coverage was estimated to be 43%, according to interim data obtained from the Behavioral Risk Factor Surveillance System and National Immunization Survey.[58] In particular, the vaccination coverage in children aged 6 months to 17 years was estimated to be 49%, a moderate increase (6.75%) on the previous season. The highest overall estimated vaccination rates were in children aged 6 months to 4 years (61%) and in adults aged ≥65 years (69%).[58] Of note, there was no significant increase in the rate of vaccination for adults aged 18–49 years for this season from the previous 2009/2010 season (30.2% vs 30.3%).

Thus, even in the 2010/2011 influenza season, influenza vaccination coverage rates remained below the 80% (in children aged 6 months to 17 years, noninstitutionalized adults aged 18–64 years and pregnant women) and 90% (in noninstitutionalized high-risk adults aged 18–64 years, noninstitutionalized adults aged >65 years, institutionalized adults aged >18 years and health-care workers) targets set out in the US-based Healthy People 2020 national objectives.[59]

Barriers to routine seasonal influenza vaccination are most likely similar to those that have been identified as barriers to pandemic influenza vaccination.[60] These include the perception that the vaccine is not needed, because the risk of influenza infection or associated complications is perceived to be low, and concerns regarding adverse events and/or the effectiveness of the vaccine.[60] The same questions and concerns are shared by the general public and healthcare workers alike, and are related to a lack of knowledge regarding influenza illness.[60] In order to convince the public that seasonal influenza vaccination is important, it is likely that they must first be convinced that influenza can be serious and that vaccination is effective in preventing the illness.[60] One way in which rates of vaccination may be increased is by educating healthcare workers and encouraging them to receive routine seasonal influenza vaccination themselves.[60] Not only would this prevent transmission of influenza virus to patients and other colleagues but, at the recommendation of a trusted healthcare worker, the general public is more likely to accept vaccination also.[60]

A number of influenza vaccines are available for the prevention of seasonal influenza, including LAIV and numerous TIVs. According to the CDC recommendations, neither LAIV nor TIV is recommended over the other for seasonal influenza protection in healthy non-pregnant individuals aged 2–49 years.[2] However, because LAIV is not approved for use in children <2 years (because of the increased risk of hospitalization

or wheezing[12] [section 3]) or in adults aged 50–64 years (because vaccine efficacy was not demonstrated in this population[12]) or ≥65 years (reason not stated), TIV vaccines are recommended for use in these individuals.[2] TIV vaccines are also recommended in the US for use in patients with chronic medical conditions who are at high risk of influenza-related complications, because the efficacy and safety of LAIV has not been established in these individuals.[2]

LAIV offers a number of advantages over TIV and, because of these, the WHO is focusing efforts on expanding the production of LAIV as part of the global pandemic influenza action plan (GAP) to increase global pandemic influenza preparedness.[61] A live influenza A/H1N1 monovalent vaccine was among the first vaccines to be approved for the prevention of influenza caused by the 2009 pandemic influenza A/H1N1 virus.[62,63] The advantages of LAIV, as identified by the WHO, include the needle-free mode of administration, which could potentially ''facilitate mass immunization and be safer'', the intranasal mode of delivery, which is ''expected to elicit a similar immune response to natural infection'' and the administration of a live replicating vaccine which ''might induce a broader immune response''.[11] Other advantages identified were the speed at which LAIV could be produced (within 1 year vs 1–2 years for TIV), the higher number of doses which could be obtained per egg (30–50 times more than TIV) and the straightforward technology.[11] In addition, the average capital investment cost required to create the capacity to produce one dose of seasonal influenza vaccine per year was lowest ($US0.20) for LAIV compared with other egg-based or cell-culture based vaccines, including cell culture-based LAIV,[64] which is currently being investigated in a proof-of-concept trial.[65] These advantages were all thought to be particularly attractive for resource-poor countries.[11] Although the WHO GAP focused on the advantages of the production and use of LAIV in a pandemic influenza setting, the majority of benefits associated with its use in this setting also apply in the seasonal influenza setting.

LAIV is an intranasally administered seasonal influenza vaccine that contains three live, genetic reassorted viruses.[6] Originally approved in a formulation that required freezing, it has now been replaced by a refrigerator-stable formulation (section 1).[16] In phase III trials, LAIV was not always associated with high rates of seroconversion, particularly in older children and adults, and in subjects who were seropositive for a particular influenza strain at baseline (section 4). Despite the low (or inconsistent) rates of seroconversion seen in most of the trials reviewed in section 4, LAIV demonstrated efficacy in protecting against seasonal influenza infection in various clinical trials (section 2).

One of the most likely reasons for LAIV efficacy in the absence of a serum antibody response is the CMI response elicited by the vaccine.[48] In an exploratory immunogenicity study conducted in young children aged 6 to <36 months, seroconversion rates ranged from 20% to 70%, depending on influenza viral strain. However, strong CMI responses were seen in LAIV recipients in this study and, unlike TIV, which generally only elicited CMI responses in subjects with detectable levels of pre-existing antibody against influenza virus,[31] LAIV, at the recommended dose, generated responses in young children with no detectable HI assay titres at baseline (section 4.7).

Furthermore, in a field efficacy study conducted on the basis of these results, it was shown that CMI played a significant role in protection against community-acquired influenza infection, and further analysis indicated that the majority of children with ≥100 SFCs/10^6 PBMCs could be considered seroprotected against clinical influenza (section 4.7).[31] Because of this, it was proposed that this may represent a target for protection in future influenza vaccine development. However, further investigation is required.

Mucosal (nasal) response was also proposed to be involved in the mechanism of action of LAIV. In a subgroup of young children participating in one of the key immunogenicity studies, seropositive LAIV recipients were 4.5 times more likely to develop a mucosal immune response than a seroresponse, indicating that mucosal immune response may be the only indication of a vaccine take in seropositive children (section 4.2). Of

interest, results of a challenge study demonstrated that the presence of post-vaccination serum HI antibody or nasal wash IgA antibody to H1N1 antigen in young children was correlated with significant protection from H1N1 challenge, as indicated by lower rates of viral shedding in these children than in those with no post-vaccination serum HI antibody or nasal wash IgA antibody detected (section 4.5).

Further immunogenicity studies indicated that the rate of viral shedding after LAIV administration may decrease with increasing age, and that it might be higher in subjects who were seronegative/serosusceptible to a particular influenza viral strain at baseline than in those who were seropositive for that strain (section 4.5). Viral shedding is the process by which infectious vaccine viruses may be cultured from nasal secretions after vaccine administration, meaning that there is a theoretical possibility that infectious viruses may be transmitted to non-vaccinated individuals.[43] However, despite the high rate of viral shedding (80%) seen in young children aged 9–36 months who attended daycare in a double-blind, randomized trial (section 4.5), the rate (1.01–1.75%) and probability (0.58–2.87%, depending on the number of LAIV-vaccinated children in the group) of viral transmission to other daycare attendees who received placebo was low (section 4.6). Of note, the one case of confirmed transmission observed in this study did not lead to influenza illness (section 4.6). Results of another viral shedding study discussed in section 4.5 confirmed that there was a theoretical risk of LAIV virus transmission from children to adults or other children, or from adults to children.[43] This conclusion was based on a comparison of shed virus titres observed in the study. However, the risk of transmission was thought to be highly unlikely after 5–7 days post-vaccination, and the actual amount of transferred virus (i.e. picked up from droplets on counter surfaces, etc.) was expected to be lower than the quantity actually recovered from the mucosa.[43] These results support the current CDC recommendation for LAIV recipients to avoid contact with severely (but not less severely) immunosuppressed patients for at least 7 days after vaccination.[2,43]

Although the cross immunogenicity of LAIV has not been formally assessed, an HI antibody response was elicited to an H3N2 viral strain that was antigenically different to the one contained in the vaccine (and became the major cause of influenza that season) after LAIV administration in one of the key immunogenicity studies conducted in young children (section 4.8). In this study, cross-reactive antibodies to the variant H3N2 strain were seen in 98% of LAIV recipients.

Seroresponse rates elicited by LAIV did not significantly differ from those elicited by TIV in children with HIV infection (section 4.4.1). In contrast, LAIV did not appear to be immunogenic in adults with HIV infection in terms of seroresponse rates (section 4.4.2). In addition, results of these studies demonstrated that LAIV did not affect HIV replication in HIV-infected subjects in terms of changes in plasma HIV RNA levels or CD4 cell counts. However, because of the potential risks associated with administration of a live vaccine to immuncompromised patients, the manufacturer's US prescribing information recommends careful consideration of the risks and benefits before deciding to use LAIV in such patients.[12]

Other immunogenicity studies showed that the immunogenic response to LAIV in young healthy children was not affected by concomitant administration with the MMR and varicella vaccines or OPV, and that the immunogenic response to the MMR and varicella vaccines or OPV was not affected by concomitant administration with LAIV (section 4.9).

The efficacy of LAIV in adults was investigated in two randomized, double-blind, multicentre studies (section 2.2). In a placebo-controlled study conducted in healthy working adults, there was no significant difference between LAIV and placebo in the incidence of febrile illnesses occurring during the peak influenza outbreak period (primary endpoint) [section 2.2.1].[32] However, LAIV was significantly more effective than placebo in terms of other endpoints, including the number of febrile illnesses meeting the criteria for URTIs or severe febrile illnesses, which were thought to be have more specificity for true influenza illnesses.[32] LAIV was also associated with a

reduction in work absenteeism and healthcare provider use (section 2.2.1).[32] Moreover, the duration of illness was shorter in the LAIV population than in the placebo population and there was less antibacterial or over-the-counter drug use in LAIV recipients with febrile illness (primary endpoint) or febrile upper respiratory tract illness.[32] Given that antibacterials are not effective against viral illnesses, the lower antibacterial use in LAIV recipients indicates that LAIV vaccination may actually help to control the emergence of antimicrobial resistance.[32]

In a placebo- and active-comparator study, conducted in adults in a 'real-world' setting, LAIV significantly reduced the incidence of symptomatic, laboratory-confirmed influenza compared with placebo (primary endpoint) [section 2.2.2].[33] However, TIV was associated with a 50% greater reduction in the primary endpoint than LAIV in this study.[33] Because LAIV must 'infect to protect',[10] it is possible that the difference in vaccine efficacy demonstrated in this study was related to an inability of LAIV to infect, potentially because of HI antibodies which may be present because of prior exposure to similar viral influenza strains.[33]

However, this does not appear to be a limitation in young children, who are less likely than adults (or older children) to have had previous exposure to influenza viruses.[10] In randomized, double-blind, multicentre studies conducted in children aged ≤71 months, LAIV was effective in preventing culture-confirmed influenza caused by viral strains that antigenically matched those in the vaccine and/or in preventing culture-confirmed influenza caused by any viral strain (each a primary endpoint in two trials) [section 2.1.1]. In addition, the absolute efficacy of LAIV in preventing culture-confirmed influenza caused by antigenically matching viral strains was up to 89% (primary endpoint in one trial). The vaccine was effective in both study years of each of the trials, even in years when the circulating strains of H3N2 virus did not match those contained in seasonal vaccines, including those contained in LAIV.

LAIV also demonstrated statistical superiority over TIV in protecting against antigenically-matching vaccine influenza strains (primary endpoint), or against any influenza viral strain in healthy young children aged 6–59 months participating in a randomized, double-blind, multinational study (section 2.1.3). Furthermore, LAIV was statistically more effective than TIV in preventing against culture-confirmed influenza illness caused by antigenically matching (primary endpoint of both trials) and/or mismatching viral strains in children with recurrent RTIs, and in children or adolescents with asthma (section 2.1.3). Although it appeared that the relative efficacy of LAIV compared with TIV might be higher in older compared with younger children with recurrent RTIs,[20] the discrepancy was thought to be caused by a difference between the two age groups in the incidence of influenza A/H3N2 versus A/H1N1 and B, and no such difference was shown when data were analyzed by strain in each age group.[29]

Not only did LAIV provide direct immunity in clinical trials, but the vaccine also appeared to provide indirect (herd) protection to the community, as demonstrated by the lower rates of school absenteeism, medically attended acute respiratory illness and fever or influenza-like illness seen in intervention areas than in comparison areas in three large community-based studies (section 2.3).

LAIV was generally well tolerated in clinical trials, with most adverse events being mild to moderate in severity (section 3). Runny nose/nasal congestion was the most commonly occurring LAIV-associated adverse event in all age groups. Study discontinuations due to adverse events were infrequent, and vaccine-related serious adverse events were not seen in most age groups.

However, LAIV was associated with an increased incidence of medically attended asthma events in children aged 18–35 months in a large safety analysis,[38] and an active-comparator trial conducted on the basis of these results demonstrated a higher incidence of medically significant wheezing in children aged <24 months receiving LAIV than in those receiving TIV (section 3.1.3).[19] In addition, more children aged 6–11 months with a history of wheezing were hospitalized in the LAIV than in the TIV group in the active-comparator study.[19] In addition, it was noted

that LAIV recipients aged 6–11 months had a significantly higher rate of hospitalization from any cause than TIV recipients (section 3.1.2). Based on these results, LAIV is not approved for use in children <2 years of age.[12] In addition, the manufacturer's US prescribing information states that LAIV should not be used in asthmatic subjects or children aged <5 years with recurrent wheezing unless the benefits outweigh the risks.[12] In addition, use in subjects with severe asthma or active wheezing is not recommended (section 5).[12]

In conclusion, LAIV is a trivalent, seasonal influenza vaccine that is nasally administered and is effective and well tolerated in children, adolescents and adults. LAIV was more effective than TIV in children, although this advantage was not seen in studies in adults. In the US, LAIV is indicated for the active immunization of healthy subjects aged 2–49 years against influenza disease caused by virus subtypes A and type B contained in the vaccine.

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