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EXPERT REVIEWS

Quadrivalent Ann Arbor strain live-attenuated influenza vaccine

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Influenza B is responsible for significant morbidity in children and adults worldwide. For more than 25 years, two antigenically distinct lineages of influenza B viruses, B/Yamagata and B/Victoria, have cocirculated globally. Current influenza vaccine formulations are trivalent and contain two influenza subtype A strains (A/H1N1 and A/H3N2) but only one B strain. In a half of recent influenza seasons, the predominant circulating influenza B lineage was different from that contained in trivalent influenza vaccines. A quadrivalent live-attenuated influenza vaccine (Q/LAIV) that contains two B strains, one from each lineage, has been developed to help provide broad protection against influenza B. Q/LAIV was recently approved for use in the USA in eligible individuals 2–49 years of age. This review summarizes clinical trial data in support of Q/LAIV.

Keywords: adults • children • clinical trials • immunogenicity • influenza B • intranasal • quadrivalent live-attenuated influenza vaccine • safety

Since the 1970s, seasonal influenza vaccines have been trivalent, composed of two influenza A strains (A/H1N1 and A/H3N2) and one type B strain [1]. The viral strains included in the vaccine are chosen annually by the WHO [101] and national authorities based on ongoing influenza epidemiology and surveillance. Since 1985, two antigenically distinct lineages of influenza B viruses have circulated globally (Yamagata and Victoria) [2], but only one B strain from one lineage is chosen for inclusion in trivalent vaccines. Owing to antigenic divergence, limited immunologic cross-reactivity exists between the B lineages such that immunization against one lineage does not provide optimal protection against the heterologous lineage [3,102]. Vaccine-induced protection against influenza B has been suboptimal owing to frequent mismatch between circulating and immunizing B lineages, with mismatches occurring in five out of ten influenza seasons in the USA from 2001 to 2011 and four out of eight influenza seasons in the EU from 2003 to 2011 (**Figure 1**) [4].

Influenza B is responsible for significant morbidity in children and adults worldwide. According to surveillance data from the USA and Europe, from 2001–2002 through 2010–2011 (excluding the 2009–2010 pandemic), on average 24 and 23% of influenza samples, respectively, were positive for influenza B [4]. Influenza B causes disease in all age groups, but older children and young adults tend to have higher rates of influenza B illness relative to influenza A [5,6]. Medically attended illnesses due to influenza A and B are generally similar with regard to symptoms, severity and rates of influenza-related complications [7–19]. Studies of severe influenza disease have demonstrated that influenza B infections also cause a significant proportion of influenza-attributable hospitalizations [20,21].

Vaccination is considered the best strategy for reducing influenza illness [22]. However, reduced efficacy resulting from mismatch between the lineage of the B strain included in trivalent influenza vaccines and that of the predominant circulating strain has resulted in suboptimal protection in recent years. Including influenza B viruses of both lineages in an annual formulation of seasonal influenza vaccines would eliminate potential lineage-level mismatch between immunizing and circulating B viruses and improve protection against influenza B. A recent analysis by the US CDC projected that between 2001 and 2009, the benefit of all trivalent vaccines being replaced by quadrivalent influenza vaccines would have been 2.74 million fewer cases

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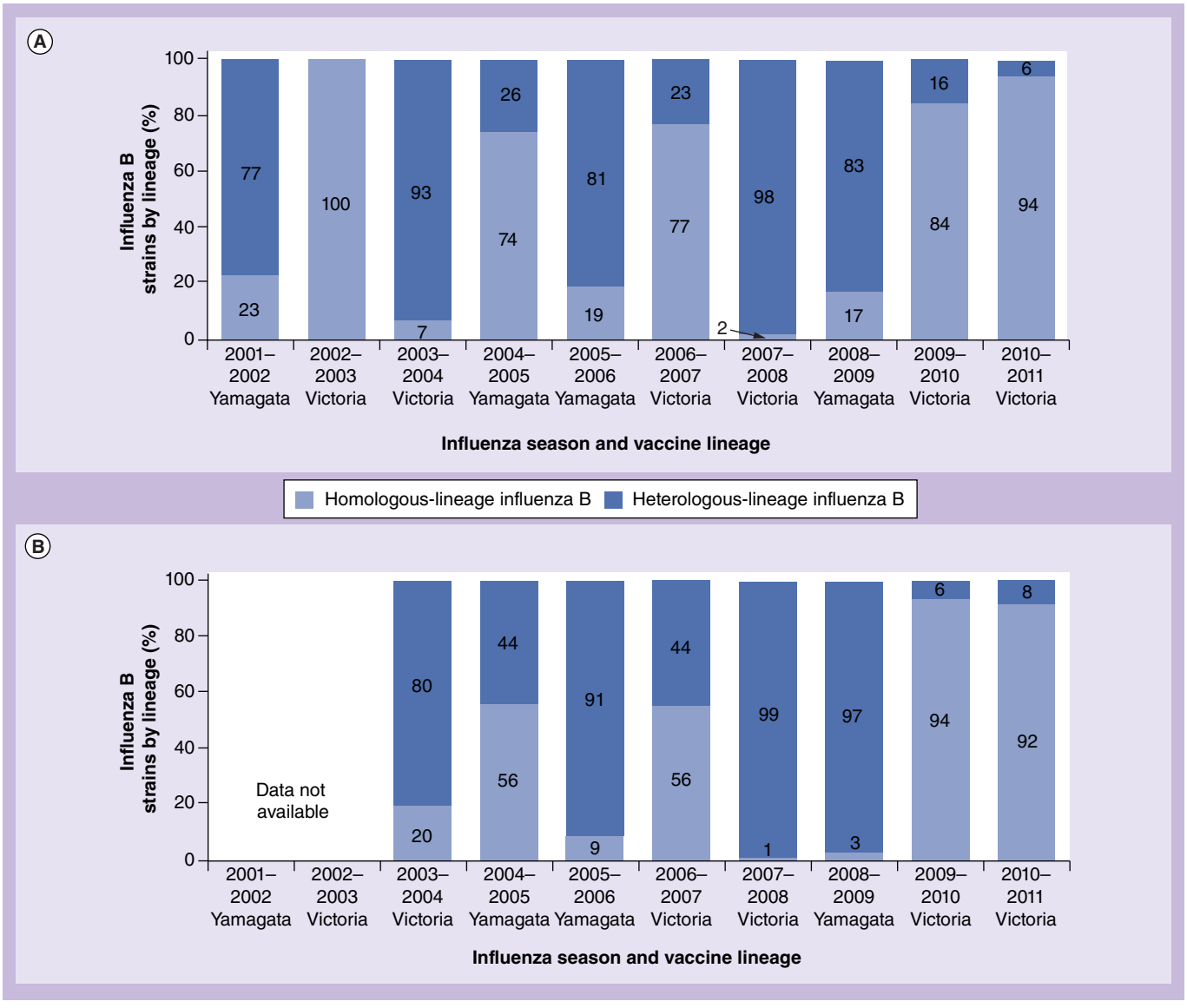

Figure 1. The percentage of circulating influenza B strains that were a lineage match (homologous lineage) or mismatch (heterologous lineage) with the B lineage included in the influenza vaccines by influenza season between 2001 and 2011 in the USA and Europe. Lineage match/mismatch **(A)** in the USA and **(B)** in Europe. The B lineage contained in the vaccine is indicated below each season.
Adapted with permission from [4].

of influenza illnesses and 21,440 fewer hospitalizations in the USA [23].

Overview of available influenza vaccines

Influenza vaccines in current use fall into two categories: trivalent inactivated influenza vaccines (TIVs) and trivalent live-attenuated influenza vaccines (LAIVs).

Trivalent inactivated vaccines

The majority of currently approved seasonal (nonpandemic) influenza vaccines are TIVs of one of the following two formulations: split-virion vaccines, which are derived by disrupting whole virus preparations, and subunit vaccines, which typically enrich for the surface antigens hemagglutinin (HA) and neuraminidase, although the only standardized component is HA. Beyond this difference, TIVs differ by whether or not they include an adjuvant or a preservative, the substrate in which the antigens are produced, the dose of antigen included and the route of administration. Because split-virion and subunit TIVs are generally only modestly immunogenic, some vaccine preparations incorporate adjuvants to increase immunogenicity [24]. Most influenza vaccines are produced in chicken eggs; however, several seasonal inactivated influenza vaccines manufactured using cell culture are approved for use in the EU. A high-dose TIV that uses 60 µg of HA per strain per dose was recently approved for use in individuals ≥65 years of age in the USA [1]. The majority of TIVs are administered as

intramuscular injections, but some are administered intradermally. Most TIVs are available in a preservative-free formulation, yet thimerosal is still a common preservative in multidose formulations. There are as yet no quadrivalent inactivated formulations approved for use, but several are being developed [103,104].

Trivalent LAIVs

Two trivalent LAIVs are in clinical use, one developed in the USA and one in Russia. LAIVs are composed of attenuated live influenza viruses that can replicate efficiently only within a limited range of conditions. Viral stocks used to produce LAIVs were generated by serial passage *in vitro* under suboptimal growth conditions to select for a set of favorable genetic characteristics. LAIV strains are attenuated in that they do not produce classic influenza-like illness, cold adapted to allow for efficient replication at cooler temperatures such as those found in the nasopharynx, and temperature sensitive such that replication is not supported in the warmer core temperatures of the lower respiratory tract where wild-type influenza viruses grow efficiently [25].

The genetic backbones of the current LAIVs are derived from master donor viruses (MDVs) that supply the cold-adapted, temperature-sensitive and attenuated phenotypes to each seasonal strain. The LAIV first approved for use in the USA in 2003 was generated from MDVs A/Ann Arbor/6/60 and B/Ann Arbor/1/66 [26]. A Russian LAIV is based on the MDVs A/Leningrad/134/17/57 (H2N2) and B/USSR/60/69 [27]. For each vaccine, the HA and neuraminidase for each strain selected for inclusion in an upcoming season's formulation are inserted into the MDV backbone, with the inserted antigens providing strain-specific immunogenicity and the MDV conferring the attenuation characteristics. LAIVs are administered intranasally. Ann Arbor strain LAIV is approved in several countries, including the USA, for use in eligible individuals 2–49 years of age, in Canada for use in individuals 2–59 years of age and in the EU for use in individuals 2–17 years of age. The Russian LAIV is approved for use in children and adults over 3 years of age in Russia [105].

Ann Arbor strain LAIV

The trivalent formulation of the Ann Arbor strain LAIV (trivalent LAIV [T/LAIV]) is the foundation for the recently developed quadrivalent LAIV (Q/LAIV). Since the licensure of T/LAIV in 2003 in the USA, more than 50 million doses have been distributed for use, with the majority of use occurring in children, adult healthcare workers and US military personnel. Safety and efficacy have been rigorously assessed in more than 70 clinical studies that examined more than 50,000 individuals aged 6 weeks to >90 years. In addition, more than 100,000 doses have been administered in postmarketing safety studies [28–30]. T/LAIV is safe and effective against influenza illness in both children and adults 2–49 years of age who are eligible for the vaccine [31–34]. In the USA, T/LAIV is not approved for use in individuals 50 years of age and older because in a study of T/LAIV conducted in adults 18–64 years of age, effectiveness was not demonstrated in the subgroup of adults 50–64 years of age [35]. In addition, LAIV use is restricted to those 24 months of age and older owing to an increased rate of medically attended wheezing following vaccination in children 6–23 months of age [36]. In clinical studies, adverse reactions occurring in ≥10% of T/LAIV recipients and at a rate at least 5% greater than in placebo recipients included runny nose/nasal congestion in all ages, sore throat in adults and fever >100°F in children 2–6 years of age [37].

T/LAIV efficacy has been best characterized in children. In a meta-analysis of eight studies that evaluated T/LAIV efficacy against culture-confirmed influenza in children 2–17 years of age, the efficacy of two doses of T/LAIV in previously unvaccinated children in year 1 was 83% (95% CI: 78–87%) against antigenically similar strains and 79% (95% CI: 73–83%) against all strains regardless of antigenic match to the vaccine [33]. The decreased efficacy against all strains regardless of antigenic match is in part driven by suboptimal protection against heterologous lineage influenza B strains not covered by the trivalent formulation [3]. In children of all ages, B strain efficacy has been estimated at 86% for antigenically similar influenza B strains but falls to 31% against heterologous lineage influenza B strains [3].

To provide broad influenza vaccine coverage and decrease the potential for B virus lineage mismatch, a quadrivalent formulation of Ann Arbor LAIV (MedImmune, LLC) has been developed. Q/LAIV uses the same attenuated vaccine strains at the same doses ($10^{7.0 \pm 0.5}$ fluorescent focus units of each viral strain per 0.2-ml dose) as T/LAIV. Q/LAIV and T/LAIV are produced using identical processes, share the same refrigerated formulation without adjuvant and are delivered as a 0.2-ml nasal spray divided between two nostrils. All excipients are the same. The only difference between Q/LAIV and T/LAIV is that a fourth strain is incorporated in Q/LAIV: A/H1N1, A/H3N2 and both B lineages, B/Yamagata and B/Victoria.

Preclinical studies of LAIV containing two influenza B viruses

Initial studies of Ann Arbor strain LAIV containing two influenza B strains were performed in ferrets, which are the standard animal model for influenza because they are easily infected, support virus replication in the lungs, manifest illness and produce a vigorous homologous antibody response [3,38]. Several ferret studies of bivalent, trivalent and quadrivalent formulations of LAIV that contained B strains from both lineages were conducted. In studies where animals were challenged with wild-type influenza viruses from both B-lineage viruses, animals vaccinated against both B lineages demonstrated protection against influenza illness caused by both B lineages, whereas controls vaccinated against a single lineage demonstrated only lineage-specific protection [3,39]. Cross-reactive antibodies to the heterologous lineage virus were not detected, which is consistent with previous studies that found poor cross-protection between B lineages in naive hosts [3]. These studies also concluded that the inclusion of a second B lineage virus did not diminish HA inhibition (HAI) antibody production to the other vaccine strains, indicating a lack of interference between vaccine strains [39].

Clinical studies of Q/LAIV

Based on the similarities between Q/LAIV and T/LAIV, and in accordance with the principles outlined in guidance documents from regulatory agencies for the approval or licensure

of influenza vaccines [106–108], a bridging strategy was pursued for the clinical development of Q/LAIV. Safety and immunogenicity data for Q/LAIV were collected in children and adults in two large randomized controlled studies that compared Q/LAIV and T/LAIV. Both studies were designed to confirm that inclusion of a second B strain did not meaningfully interfere with the immune response against any of the other three vaccine strains or result in any important changes in the safety profile of the vaccine. Owing to the fact that Q/LAIV contains a B strain from the Victoria lineage and a B strain from the Yamagata lineage, Q/LAIV was compared with two separate T/LAIV formulations that contained either a B/Victoria lineage strain (T/LAIV-B/Victoria) or a B/Yamagata lineage strain (T/LAIV-B/Yamagata), along with the same two A strains included in Q/LAIV [40,41].

Immunogenicity of Q/LAIV

Immune responses in the clinical studies of Q/LAIV were evaluated using the HAI assay to evaluate strain-specific antibody. Functional serum antibody titers as measured by HAI are generally regarded as a correlate of protection for inactivated influenza vaccines. However, studies have demonstrated that LAIV can induce protection from influenza illness in the absence of robust serum antibody responses, as measured by fourfold rises in HAI [42–45]. Mucosal [46] and cell-mediated immune responses [47] are important contributors to LAIV-induced immunity; however, these responses are difficult to measure, and there are no standard or widely accepted assays. Although HAI responses are not an absolute correlate of protection for LAIVs, they are an indicator of a functional immune response to vaccination [48–50]. In studies of LAIV-induced immune responses, adults demonstrate limited seroresponse (fourfold rise) by HAI [51], but young children, particularly those without pre-existing antibodies to influenza, can exhibit higher seroresponse rates [47,48,50,52–56]. Postvaccination HAI geometric mean titers and seroresponse rates have been used previously as biomarkers of T/LAIV-induced immunogenicity to demonstrate comparability between the frozen and refrigerated formulations of T/LAIV, for manufacturing and lot consistency, and for evaluating the concomitant administration of T/LAIV with other live virus vaccines [53,55,57–59].

Q/LAIV was first studied in 1800 adults 18–49 years of age who were healthy or had stable underlying chronic disease. Subjects were randomized 4:1:1 to receive Q/LAIV or T/LAIV containing matching A strains and only one of the two matching B strains (T/LAIV-B/Yamagata and T/LAIV-B/Victoria) [40]. Subsequently, a similar pediatric study enrolled 2312 children aged 2–17 years who were randomized 3:1:1 as above [41]. The majority of children in this study were 2–8 years of age (n = 1808) and were to receive two doses of vaccine; a smaller number of children aged 9–17 years (n = 504) received one dose. Baseline HAI antibody titers were assessed prior to dosing in all subjects. Postvaccination titers were assessed at a single time point for each subject depending on their age and prior vaccination history. For adults, children 9–17 years of age and children 2–8 years of age who had previously been vaccinated against seasonal influenza, postdose samples were collected for HAI antibody analysis approximately 1 month after the first dose of Q/LAIV; for children 2–8 years of age who had never previously been vaccinated, samples were collected 1 month after the second dose of Q/LAIV. Vaccine virus strains used in both studies are listed in Table 1.

The adult and pediatric studies provided evidence that Q/LAIV was immunologically noninferior to T/LAIV and that the addition of the second B strain did not result in meaningful immune interference with other strains included in the vaccine [37,40,41]. Geometric mean titers (GMTs) of HAI antibody to each of the strains in the Q/LAIV formulation were compared with those in the T/LAIV formulations. The ratio of these antibody responses was determined by dividing the value in the T/LAIV arm by the value in the Q/LAIV arm. Thus, a ratio of 1 would indicate that the immunogenicity of Q/LAIV and of the T/LAIV comparator were identical. The immune response produced by Q/LAIV was noninferior to T/LAIV because the upper bounds of the two-sided 95% CI for the strain-specific HAI antibody GMT ratios were ≤1.5, the prespecified limit for noninferiority (see Figure 2A). In addition to GMT ratios, the geometric mean fold rise from baseline in HAI antibodies was evaluated because it accounts for differences in GMTs at baseline. Results for geometric mean fold rise ratios were similar to those for GMT ratios (Figure 2B).

Post hoc analyses were performed to determine whether the immune response to a B lineage strain contained in Q/LAIV was higher than the immune response to that strain in the T/LAIV comparator that did not contain it. In children and adults, the proportion of subjects achieving a fourfold rise in HAI antibody titer from baseline in those receiving Q/LAIV and the T/LAIV containing the B lineage being assessed was statistically significantly higher than the responses observed for those receiving the T/LAIV formulation that did not include it (Figure 3). Overall, the data confirmed the noninferiority of the immune response to

Table 1. Vaccine strains contained in the quadrivalent live-attenuated influenza vaccine, trivalent live-attenuated influenza vaccine B/Yamagata and trivalent live-attenuated influenza vaccine B/Victoria vaccine formulations used in the adult and pediatric quadrivalent live-attenuated influenza vaccine studies.

Strain	Q/LAIV	T/LAIV-B/Yamagata	T/LAIV-B/Victoria
A/H1N1	A/South Dakota/6/2007	A/South Dakota/6/2007	A/South Dakota/6/2007
A/H3N2	A/Uruguay/716/2007	A/Uruguay/716/2007	A/Uruguay/716/2007
B/Yamagata	B/Florida/4/2006	B/Florida/4/2006	
B/Victoria	B/Malaysia/2506/2004		B/Malaysia/2506/2004

Q/LAIV: Quadrivalent live-attenuated influenza vaccine; T/LAIV: Trivalent live-attenuated influenza vaccine.

Q/LAIV to that of T/LAIV, justifying the application of the extensive efficacy data for T/LAIV to Q/LAIV.

Safety & tolerability of Q/LAIV

Safety and tolerability were assessed similarly in both studies of Q/LAIV. Solicited symptoms were queried and temperatures were taken daily during days 0–14 after any dose. Children who, in the judgment of the investigator, were too young to voice a complaint of sore throat, headache or muscle aches were not included in the denominator for those solicited symptoms. The studies did not include placebo arms, and since solicited symptoms are events that occur commonly even in the absence of vaccination, the rate differences between Q/LAIV and T/LAIV recipients are more relevant than the absolute rates of occurrence of these events. Adverse events (AEs) were collected during days 0–28 after any dose. Serious AEs (SAEs) and new onset chronic diseases were collected from 0–180 days after the last dose of study vaccine.

Solicited symptoms

In the adult study, solicited symptoms occurred at similar rates in Q/LAIV and T/LAIV recipients, and no statistically significant differences between treatments were observed (Figure 4A). Runny/stuffy nose was the most commonly reported solicited symptom and it accounted for the largest rate difference: it was reported in 4.1% more Q/LAIV than T/LAIV recipients. No other solicited symptom occurred with a rate difference >1.1%.

In the pediatric study, solicited symptoms also occurred at similar rates in Q/LAIV and T/LAIV subjects. No significant difference in rates of fever ≥38°C (100.4°F) were observed between the two groups (Q/LAIV: 5.7%; T/LAIV: 3.9%; p > 0.05, Figure 4B). However, a small (2.4%) but statistically significant increase in fever ≥38°C (100.4°F) after the first dose of Q/LAIV occurred in the subset of children who were 2–8 years of age (Q/LAIV: 6.6%; T/LAIV: 4.2%; p = 0.04). Rates of fever were not increased after dose 2 of Q/LAIV compared with T/LAIV. Overall, high fever in children 2–8 years of age was uncommon (Table 2), the median duration of fever was 1 day and no febrile seizures were observed.

In children and adults, the number and types of AEs were generally similar among Q/LAIV and T/LAIV recipients. The only events occurring at a statistically increased rate among Q/LAIV recipients were pyrexia (Q/LAIV: 1.7%; T/LAIV: 0.7%; p = 0.04), headache (Q/LAIV: 0.9%; T/LAIV: 0.2%; p = 0.04) and oropharyngeal pain (the term used for sore throat in the coding dictionary; Q/LAIV: 0.6%; T/LAIV: 0%; p = 0.03) in children 2–17 years of age after dose 1. No treatment-related SAEs or new onset chronic diseases were associated with Q/LAIV in either study. The rates of SAEs were comparable between Q/LAIV and T/LAIV in both studies. No increase in asthma or wheezing events was associated with Q/LAIV in either study [109]. In these two studies, the safety and tolerability of Q/LAIV were similar to that of T/LAIV, supporting the applicability of the extensive safety database for T/LAIV to Q/LAIV.

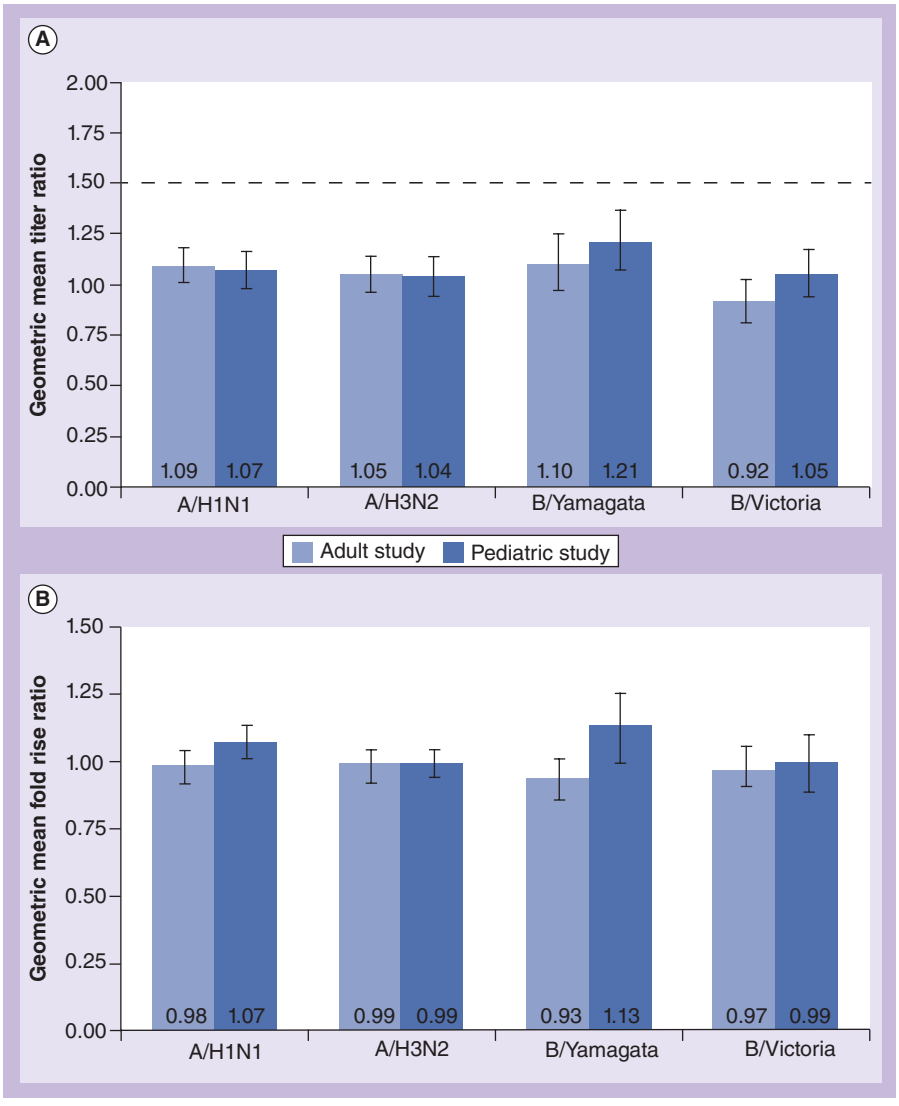

Figure 2. Comparative immunogenicity of quadrivalent live-attenuated influenza vaccine to trivalent live-attenuated influenza vaccine in children and adults.
(A) Geometric mean titer ratios (T/LAIV ÷ Q/LAIV) after vaccination by strain with two-sided 95% CI. Noninferiority was prespecified as an upper bound of the 95% CI of the ratio ≤1.5 (noninferiority margin, indicated by dotted line). **(B)** Geometric mean fold rise ratios (T/LAIV ÷ Q/LAIV) after vaccination by strain with two-sided 95% CI.
Q/LAIV: Quadrivalent live-attenuated influenza vaccine; T/LAIV: Trivalent live-attenuated influenza vaccine.
(A) Data taken from [40] and **(B)** data taken from [41].

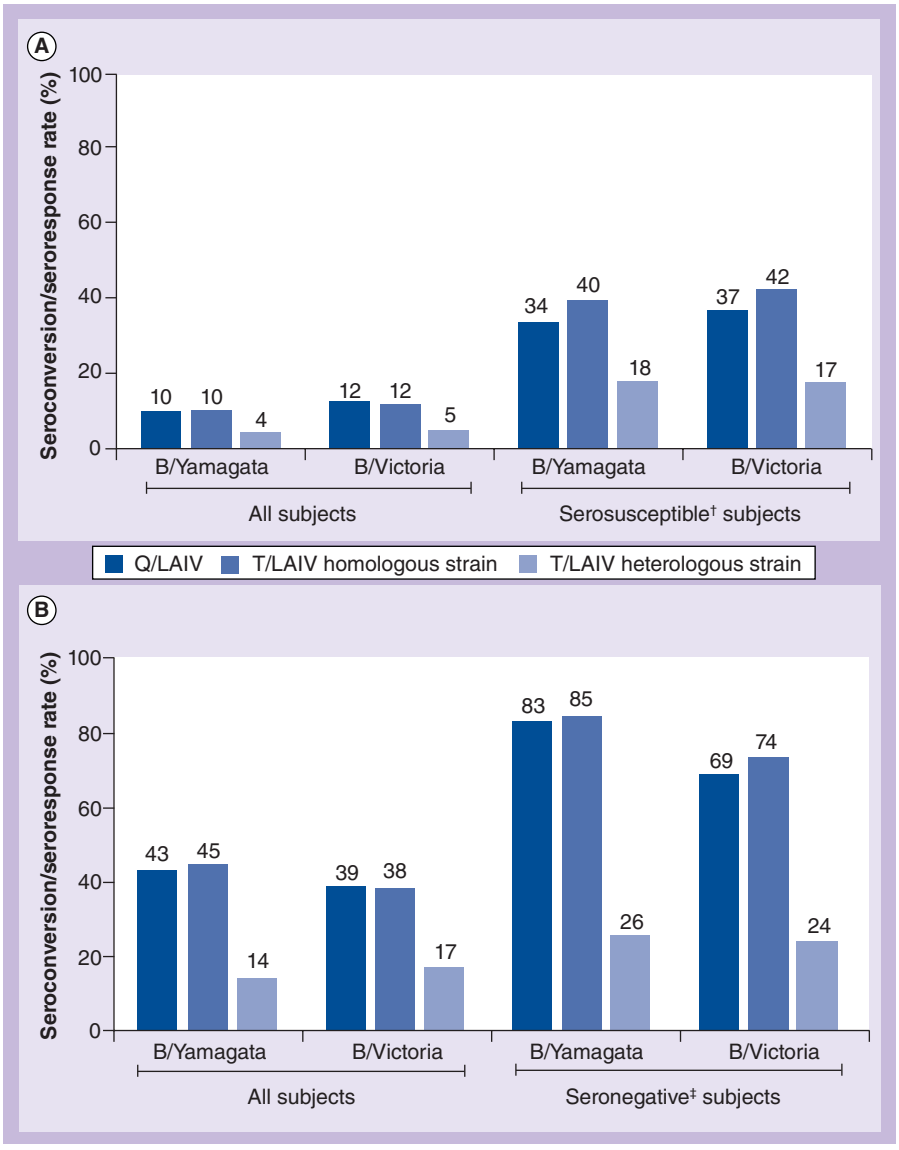

Figure 3. Seroconversion/seroresponse to homologous and heterologous lineage B strains in adults and children. (A) Response in adults and **(B)** in children. In all subjects and in the subset of subjects that included baseline serosusceptible adults or seronegative children, the proportion of subjects achieving a fourfold rise in hemagglutination inhibition (HAI) antibody titer from baseline in those receiving Q/LAIV and the T/LAIV containing the B lineage being assessed (homologous responses) was statistically significantly higher than the responses observed for those receiving T/LAIV that did not include the B lineage (heterologous responses).
†Serosusceptible = baseline HAI titer ≤8.
‡Seronegative = baseline HAI titer ≤4.
Q/LAIV: Quadrivalent live-attenuated influenza vaccine; T/LAIV: Trivalent live-attenuated influenza vaccine.
(A) Data taken from [40] and **(B)** data taken from [41].

Licensure of Q/LAIV in the USA

In the US approval, Q/LAIV has the same age indication, warnings and precautions as T/LAIV. Q/LAIV will contain the viral strains recommended annually by the WHO and the US FDA. In fact, the WHO began identifying candidate vaccine strains from both influenza B lineages starting with recommendations for the 2011–2012 northern hemisphere seasonal influenza vaccine formulation [101]. Q/LAIV is contraindicated in individuals who have had a severe allergic reaction to any component of the vaccine including egg proteins, gentamicin, gelatin and arginine, those who have had a serious reaction to any previous influenza vaccine, and in children and adolescents receiving concomitant aspirin or aspirin-containing therapy. Information concerning additional warnings and precautions regarding use of Q/LAIV are available in its package insert. Q/LAIV will be available commercially in the USA for the 2013–2014 influenza season.

Conclusion

Influenza B is responsible for significant morbidity in children and adults worldwide. Current trivalent influenza vaccines provide limited protection against B viruses of a different lineage than the one included in the vaccine. Vaccination with a quadrivalent influenza vaccine containing strains from both B lineages should provide broad protection against both influenza A and B. In two clinical studies conducted in adults 18–49 years and children 2–17 years of age, the addition of a second B strain did not result in immune interference with other strains included in the vaccine, and the safety and tolerability profiles of Q/LAIV and T/LAIV were similar. Seasonal vaccination with Q/LAIV has the potential to augment the protection provided by T/LAIV by providing protection against both lineages of influenza B.

Expert commentary

Influenza B accounts for approximately a quarter of all influenza infections and affects all age groups. The severity of disease and propensity toward complications is similar for influenza A and B, but as a recent CDC publication stated: "the public health impact of influenza B virus has been overshadowed by the magnitude of disease caused by influenza A viruses" [15]. An editorial associated with this article called for additional studies to increase our understanding of influenza B and its outcomes [13]. Medical and scientific opinion concerning influenza B may still be influenced by early studies that concluded that influenza B resulted in less of a disease burden than influenza A did [60,61]. Perhaps the severity and historical significance of influenza A pandemics has also influenced the underestimation of the significance of influenza B infection. The approval of the

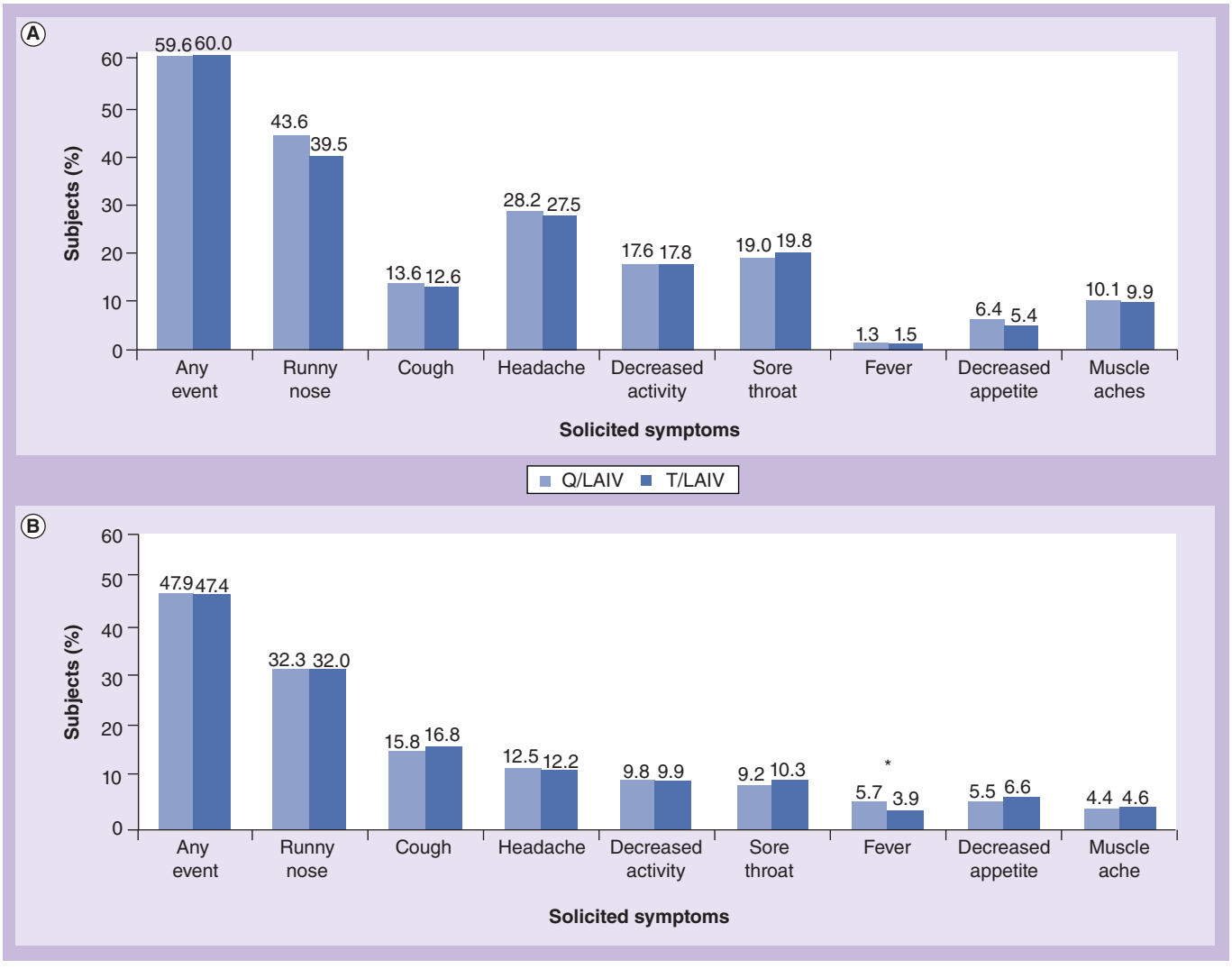

Figure 4. Percentage of subjects reporting solicited symptoms 0–14 days after the first dose of study vaccine by symptom in adults and children. (A) Percentage of subjects reporting solicited symptoms in adults and **(B)** percentage of subjects reporting solicited symptoms in children. Fever was defined as a temperature ≥38°C (100.4°F).
*p = 0.04 (Q/LAIV vs T/LAIV).
Q/LAIV: Quadrivalent live-attenuated influenza vaccine; T/LAIV: Trivalent live-attenuated influenza vaccine.
(A) Adapted with permission from [40] and **(B)** adapted with permission from [41].

first quadrivalent influenza vaccine may help highlight the importance of influenza B and prompt additional research to further characterize disease caused by influenza B.

There are many benefits to including both influenza B lineages in an influenza vaccine. The most obvious is to provide a direct benefit to vaccine recipients, particularly when a large number of circulating influenza B viruses do not match the lineage chosen for the trivalent influenza vaccine. This clinical benefit would occur whenever a B strain from the incorrect lineage is chosen for the trivalent vaccine or when both lineages are cocirculating to a significant degree. The efficacy of the current trivalent LAIV has been shown to decrease from 86% versus matched B strains to 31% versus heterologous B strains [3]. Moreover, in seasons in which influenza B circulation is minimal or B viruses are well matched to the trivalent vaccine strain, vaccination with a quadrivalent influenza vaccine would still provide benefit to the individual by priming the immune response to both lineages of influenza B so that subjects will enter future influenza seasons with antibodies to strains from both B lineages.

An underappreciated benefit of quadrivalent vaccines is the potential, from a public health perspective, to improve the public's confidence and acceptance of influenza vaccination [23]. Each influenza season in which the trivalent influenza vaccine does not match circulating strains allows for the possibility of breakthrough influenza infections, and the resultant widely read news stories concerning the poor efficacy of the vaccine erode the public perception of the value of influenza vaccination. Quadrivalent vaccines may obviate the contribution of an incorrectly chosen influenza B lineage in this scenario. Increased acceptance of influenza vaccination would help further the trends toward higher rates of vaccination that have been apparent over the last several

Table 2. Fever, days 0–14 after dose 1 in subjects 2–8 years of age.

Fever	Q/LAIV (%) n = 1078	T/LAIV (%) n = 716	Rate difference (%)
≥38.0 to <38.5°C	2.6	2.0	0.6
≥38.5 to <39.0°C	2.3	1.4	0.9
≥39.0 to <39.5°C	1.3	0.6	0.7
≥39.5 to <40.0°C	0.3	0.3	0.0
≥40.0°C	0.1	0.0	0.1

Q/LAIV: Quadrivalent live-attenuated influenza vaccine; T/LAIV: Trivalent live-attenuated influenza vaccine.

years. This, along with the efficacy and safety profile of Q/LAIV, is predicted to reduce the morbidity associated with influenza.

Five-year view

Other quadrivalent influenza vaccines in development

The inclusion of a fourth B strain in influenza vaccines has been discussed by public health authorities for a number of years; however, manufacturing limitations that could have resulted in insufficient vaccine supply were a significant concern, given that the addition of a fourth strain would require additional capacity and extend manufacturing timelines. Currently, manufacturing capacity exceeds usage and, because inactivated quadrivalent influenza vaccines are projected to be available soon from several manufacturers, it seems probable that the supply of a quadrivalent vaccine will be sufficient for projected demand [62]. Manufacturers are also likely to extend their current practice of manufacturing seasonal strains 'at risk' – prior to final selection by the WHO and local authorities – to meet the timelines needed to have a quadrivalent vaccine available early, in time to vaccinate a large number of people prior to widespread circulation of influenza in the community.

An inactivated quadrivalent influenza vaccine by GlaxoSmithKline has completed Phase III development and has been submitted for regulatory review in the USA and EU [103]. Similarly, a quadrivalent inactivated influenza vaccine based on the approved trivalent Fluzone® is in Phase III development by Sanofi Pasteur (ClinicalTrials.gov identifiers: NCT01218646, NCT01481454 and NCT01240746 [104]). Similar to Q/LAIV, these quadrivalent vaccines contain two influenza A strains (A/H1N1 and A/H3N2) and two B strains (B/Yamagata and B/Victoria). Limited published study results are available for these novel quadrivalent vaccines. Other manufacturers also report that quadrivalent formulations are in development [63].

Trends in influenza vaccination

For many years, influenza vaccination was targeted to older adults and individuals with high-risk medical conditions. However, there has been increasing recognition of the burden of influenza in children and younger adults, and several countries have recommended annual influenza vaccination for healthy children; some countries, including the USA, have recommended universal influenza vaccination of all individuals 6 months of age and older. The benefits of influenza vaccination should be enhanced by the advent of quadrivalent influenza vaccines that provide broad protection against influenza A and B. Policymakers will need to determine whether quadrivalent influenza vaccines should become the new standard of care for all or for specific populations, much as was determined when trivalent vaccines replaced bivalent vaccines containing A/H3N2 and one B strain in the 1970s.

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Key issues

- In a half of recent influenza seasons, the predominant circulating influenza B lineage was different from that contained in trivalent influenza vaccines. This frequent lineage mismatch between the circulating influenza B virus and the lineage contained in the seasonal influenza vaccine has reduced overall influenza vaccine effectiveness.
- An intranasally administered Ann Arbor strain quadrivalent live-attenuated influenza vaccine (Q/LAIV) composed of two influenza A viruses and two influenza B viruses, one each from the Yamagata and Victoria lineages, has been developed for the prevention of seasonal influenza. It has been approved for use in the USA.
- Q/LAIV shares the same core characteristics of trivalent live-attenuated influenza vaccine (T/LAIV; manufacturing process, excipients, master donor viruses, strain dosage and delivery system) and builds on the safety and efficacy profile already established for T/LAIV.
- Two studies conducted in adults and children provide evidence that the addition of the second B strain does not result in meaningful immune interference between strains included in the vaccine. The safety profiles of Q/LAIV and T/LAIV are similar.
- Shifting from trivalent to quadrivalent influenza vaccines is expected to increase protection against influenza by providing coverage against circulating viruses from both B lineages.

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