An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)‡

Literature Review on Quadrivalent Influenza Vaccines

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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EXECUTIVE SUMMARY

The trivalent influenza vaccines currently used in Canada include two influenza A strains and one influenza B strain. Quadrivalent influenza vaccines include a second influenza B strain, from a different lineage than the first strain. The inclusion of a second lineage of influenza B is in response to the co-circulation of both lineages and/or the incorrect prediction of which lineage will circulate in a given season. Influenza B was responsible for 17% of laboratory-confirmed influenza cases in Canada over the past 12 seasons, with influenza A responsible for the remaining 83%. It is estimated that about 15-25% of hospital admissions and deaths are attributable to influenza B; a rate that varies dramatically from season to season. In general, children had higher rates of hospital admission and death than adults secondary to infection with influenza B.

To date, only one study has measured quadrivalent influenza vaccine efficacy. In that study, vaccine effectiveness was estimated at 59% in children 3-7 years of age, when comparing children that received hepatitis A vaccine and quadrivalent inactivated vaccine. No literature was found that conducted head to head efficacy or effectiveness studies directly comparing trivalent and quadrivalent formulations, for either inactivated or live attenuated formulations. With respect to immunogenicity, all reviewed studies reporting analyses for non-inferiority reported that both the inactivated (n=6) and live attenuated (n=3) quadrivalent influenza vaccines were non-inferior to their trivalent counterparts across all strains. Compared to the trivalent inactivated influenza vaccines, the quadrivalent vaccines provided superior seroprotection for the B strain not included in the trivalent vaccine, in both adults and children. In addition, the levels of seroprotection against the three shared influenza strains were similar to those provided by the trivalent formulas. The live attenuated vaccines had similar results, with superior protection against the missing B strain for quadrivalent recipients and no diminution of seroresponse noted with the addition of a fourth influenza strain.

There were no differences in the rate of reactions or occurrence of serious adverse events for children or adults receiving quadrivalent compared with trivalent influenza vaccines. The most frequently reported side effects for inactivated influenza vaccines were pain at the site of injection, myalgia, fatigue, and headache. Higher rates of pain following injection were reported by adults receiving IIV4 compared with IIV3 in two of the four studies that compared rates. Higher rates of arthralgia were reported by adults receiving IIV4 with adjuvant compared to those receiving IIV3 with adjuvant. In children, 2.3/10,000 experienced febrile seizure following immunization. Side effects attributed to receipt of live attenuated influenza vaccines included runny nose, headache, sore throat, and fatigue. Few serious adverse events were reported following the receipt of either LAIV4 or LAIV3 for adults or children.

I. INTRODUCTION

Seasonal trivalent influenza vaccines protect against three different influenza virus strains: two influenza A strains (H1N1and H3N2) and one B strain [1-5]. However, influenza B viruses have evolved into two genetically distinct lineages and viruses from both lineages have co-circulated and contributed variably to influenza illness since the 1980s [1-3, 6]. Predicting which lineage will predominate is imperfect and in some seasons the lineage chosen for the vaccine has differed from the predominant circulating lineage resulting in compromised protection against influenza

B [1, 6, 7]. Hence, quadrivalent influenza vaccines, which contain four strains of influenza virus: the same two influenza A strains available in the trivalent formulation (A/H1N1-like and A/H3N2-like), and two influenza B strains, one from each lineage (B/Victoria/02/1987-like and B/Yamagata/16/1988-like), may offer broader protection by having both B lineages in each season's formula [8, 9].

This systematic literature review was conducted to provide evidence to inform recommendations on immunization with quadrivalent vaccines against influenza infections, which are not yet authorized for use in Canada.

The nomenclature used in this review was adopted from the Centers for Disease Control and Prevention [10]. Inactivated influenza vaccines are denoted as IIV while live attenuated influenza vaccine acronym is LAIV. In each instance, a 3 follows the appropriate acronym for trivalent formulas (IIV3 or LAIV3) and a 4 follows for quadrivalent formulas (i.e., a quadrivalent inactivated vaccine would be IIV4 while a quadrivalent live attenuated would be LAIV4).

I.1 Epidemiology of influenza; focus on the epidemiology of influenza B

Human influenza infection is a contagious disease of the upper respiratory tract caused by seasonal circulating influenza viruses [11, 12]. There are two types of influenza virus that commonly infect humans and have epidemic potential: A and B [12, 13]. Influenza A virus strains infect humans and myriad other mammals and are thus susceptible to dramatic "shifts" in antigenic profile as the genetic segments are re-assorted between species [1]. Any major shift leaves humans susceptible to the new strain and can lead to epidemics and pandemics. The A viruses are also susceptible to the continual antigenic "drift" that results from the accumulation of minor genetic changes to the viral protein making them less recognizable to the immune system. Within the A strains, three subtypes of haemagglutinin (H1, H2 and H3) and two subtypes of neuraminidase (N1 and N2) are recognized as having caused seasonal illness [1, 12]. Influenza B strains, on the other hand, mainly infect humans and are prone to antigenic drift only. Influenza B viruses have evolved into two antigenically distinct lineages. The B/Yamagata/16/1988-like lineage predominated until the Victoria/2/1987-like lineage emerged in the 1980s. The B/Victoria lineage then predominated for a decade before the Yamagata lineage re-emerged and remained predominant until the early 2000s. Since then, both lineages have co-circulated with widely varying rates of infection caused by each lineage in each season [1,14, 15]. As a result of these drifts (influenza A and B) and the occasional shift (influenza A), strains are reassessed each year by the World Health Organization and the vaccines available in Canada are reformulated, as necessary, to match the strains that are anticipated to circulate during the next influenza season in the Northern hemisphere.

I.1.1 Epidemiology of influenza B

Canadian surveillance data from 2001-02 to 2012-13 (see Table 1) show that influenza A strains accounted for 83% of laboratory-confirmed tests for influenza while influenza B accounted for 17%. However, it varied by season, with influenza B accounting for <1% of laboratory tests in 2009-10 to as high as 50.6% in 2011-12 [18]. In keeping with these estimates, active surveillance for influenza virus carriage in Hutterite communities in Canada from January 2008 to December 2009 detected influenza B in 18% of all positive influenza tests [19].

Globally, seasonal influenza activity shows similar patterns to those seen in Canada. Surveillance data from 1976-77 through 1998-99 in the USA show that the main cause of seasonal epidemics was influenza A, with influenza B strains being responsible for about 25% of laboratory tests for influenza [median 15%, range 0.1 to 85.9%] [1, 20]. Since 1999-2000, influenza B strains have been responsible for between 0.4% (2009-10) and 43.6% (2002-03) of all laboratory-confirmed influenza infections reported to the CDC (21). Similarly, in Europe between 1.0% and 59.8% (2001-02 to 2010-11) of laboratory-confirmed cases of influenza were B strains [15], while in Australia they accounted for 0.8-63.3% of positive influenza tests between 2002 and 2011 [14].

The age-specific incidence of influenza associated with B strains specifically is as widely variable from season to season as influenza incidence itself. In a prospective study of Finish children 9 months to 3 years old, 5.2% of children were diagnosed with influenza B infection during the 2007-08 influenza season when the B lineage in the vaccine was not matched with the circulating strain of B virus [22]. In a second Finnish study, 16% of children younger than 13 years of age who tested positive for influenza were determined to be infected with a B strain in a prospective study conducted in 2000-01 and 2001-02 [23]. In a prospective cohort study of households with at least two children under 18 years of age, 3.1% of all participants developed influenza B during the 2010-11 influenza season in Michigan USA, a season when the vaccine and circulating B virus lineages matched [24]. In a vaccine effectiveness trial conducted in Michigan during the 2007-08 season, only 0.06% of adults acquired influenza B in a year of mismatch between the vaccine and the circulating B lineage [25]. Authors of a three-year study conducted Taiwan from 1997 through 1999 reported that 3.2% (range 0.4-6.7% per year) of children younger than 12 years of age who were tested in outpatient clinics were positive for influenza B [26].

The National Microbiology Laboratory characterization of influenza viruses circulating in Canada during the 2001-02 through 2012-13 seasons indicates that the B/Victoria lineage accounted for about 52% of the B strains tested; ranging from 2.6% in 2007-08 to over 95% in 2001-02, 2002-03, 2008-09, and 2010-11. As a point of comparison, about 55% of the A strains characterized over the same period were H3N2, ranging from about 1% in 2009-10 to over 95% in 2003-04 and 2004-05. Similarly, in the USA for 2007-08 through 2012-13, the B/Victoria lineage accounted for just over half of all B strains characterized, ranging from 2-94% annually. In Europe, the Victoria lineage accounted for 1-94% of B strains for 2001-02 through 2010-11 [15] while in Australia they accounted for 17-96% of influenza B strains characterized between 2002 and 2011 [14]. Over 12-years of influenza B surveillance in Brazil, B/Victoria lineage predominated in 5.5 years: 2003, 2004, 2007, 2010, 2011, and early in 2012 [27].

Table 1: Influenza B strains in Canada, 2001-02 to 2012-13

Influenza Season	B strains as % of all influenza tests[1]	B/Victoria as % of all B strains characterized[2]	B/Yamagata as % of all B strains characterized[2]	B lineage in influenza vaccine[3]	% paediatric influenza hospitalizations with B strains	% adults influenza hospitalizations with B strains
2001-02	12.9	96.7	3.3	Yamagata*		
2002-03	40.2	98.4	1.6	Victoria	NA	
2003-04	1.4	17.5	82.5	Victoria*	1.0	
2004-05	16.6	20.6	79.5	Yamagata	30.7	
2005-06	39.4	98.5	1.5	Yamagata*	38.1	
2006-07	12.8	10.1	89.9	Victoria*	15.3	
2007-08	42.5	2.5	97.5	Victoria*	36.9	
2008-09[a] 2008-09[b]	39.7[a] 0.3[b]	98.1	1.9	Yamagata*	46.9[a] 1.3[b]	
2009-10[b]	0.1[b]	85.7	14.3	Victoria	0	NA
2010-11	14.6	95.1	4.9	Victoria	32.8	9.3[4]
2011-12	50.6	47.7	52.3	Victoria*	58.3	54.1[4]
2012-13	16.1	22.9	77.1	Yamagata	29.6	7.7[5]

[1] FluWatch reports-surveillance from sentinel laboratories (18)

[2] FluWatch reports-samples characterized by the National Microbiology laboratory

[3] NACI statements on influenza vaccines

[4] CNISP, Canadian Nosocomial Infection Surveillance Program

[5] PCIRN-SOS, PHAC-CIHR Influenza Research Network - Serious Outcomes Surveillance

[a] Prior to A/H1N1 pandemic of 2009 ; [b] During the A/H1N1 pandemic of 2009

* Mismatch between circulating influenza B lineages and those in the seasonal influenza vaccine

NA: data not available

I.2 Vaccine effectiveness

Since the two lineages of influenza B virus have limited antigenic cross-reactivity, vaccine effectiveness may be compromised when the predominant circulating B strain differs from the vaccine strain (1). Skowronski et al. noted that virtually no antibody was produced in young immunologically naïve children, 6-23 months old, against the alternate (B/Victoria) lineage following vaccination with trivalent inactivated influenza vaccine (28). In the following two influenza seasons, B/Victoria lineage strains were included in the licensed vaccines and a number of the young children from this study were vaccinated both years and followed. In the follow-up study, Skowronski et al. noted that the children's seroresponse to the B/Victoria lineage included in the vaccines was dampened while the vaccines appeared to induce an immune response to the B/Yamagata strain included in their first year's vaccines (29). Although it remains to be studied, the authors question whether a quadrivalent influenza vaccine might not elicit the same response.

In Canadian population-based studies, the rate of influenza vaccine effectiveness (adjusted for age and chronic illness), as assessed by the Canadian Sentinel Surveillance Network, was 12% (CI95%; -134, 67) in 2006-07 when the lineage of the predominant B strain did not match the vaccine strain [30]. In comparison, the effectiveness was low, only 18% (-27, 47), in 2010-11 when the vaccine did match the predominantly circulating influenza B strain [31]. Higher rates of effectiveness were reported for the 2005-06 (48%; -21, 77) and 2007-08 (50%; 24, 67) seasons, when there was again a mismatch between the vaccine and the predominant circulating lineages [32, 33].

Meta-analyses, which combine data from numerous studies and seasons resulting in more stable and reliable results, describe decreasing effectiveness for influenza vaccines as the degree of match with the circulating strain declines [2, 34]. Tricco and all report that vaccine effectiveness when B strains matched the circulating strains was 77% (55, 88) compared with 62% (21, 81) when there was a drift mismatch and 43% (16, 66) when there was a lineage mismatch for live attenuated vaccines [34]. These authors report a similar result for inactivated vaccines, with effectiveness of 77% (25, 93) when B strains were well matched and 46% (27, 68) when mismatched. They noted the same pattern with influenza A strains, but with less difference in effectiveness estimates. In a meta-analysis of vaccine effectiveness of LAIV in children, effectiveness against influenza B was highest when the B strains in the vaccines were of the same lineage and closely matched with the circulating strain (86%), lower (55%) when the strain was antigenically drifted, and lowest (31%) when the strains were of the opposite lineage [2].

A review of B lineage antigens included in the Canadian influenza vaccines and the circulating strains each season indicates a match in 5 of the past 12 seasons, a moderate match (about 50% from each lineage) in 1 season, and a mismatch in remaining 6 influenza seasons (≥70% of the characterized B strains were of the opposite lineage to the antigen in that season's vaccine). Similarly in the USA, between 1999-2001 and 2012-13, 6 of the 14 seasons had a vaccine mismatch to the predominantly circulating B strain [1, 6]. Yet, influenza circulation differs across regions. In Europe for the 2002-03 to 2010-11 seasons, influenza vaccines matched the predominantly circulating strain of B virus well in only 2 of the 8 seasons, moderately in 2 seasons, and were not well matched in the remaining 4 seasons [15]. In the Southern hemispheric country of Australia, the vaccine strain matched the predominantly circulating B strain well in only 3 of the 10 seasons (2002-2011), moderately in 3, and were mismatched in the remaining 4 seasons [14]. Taiwan experienced mismatches of the B viruses in half (5/10) of the seasons from 2002-03 to 2011-12, with vaccine effectiveness estimated at 54% against influenza A subtypes but -66% for influenza B in the 2011-12 season [35]. Meanwhile, in Hong Kong, the vaccine antigen for the B strain matched the predominant circulating lineages in 3 of 10 years from 2000 through 2010, was moderately matched in 3 years, and was mismatched in 4 years [36].

I.2.1 Influenza B burden on the healthcare system

In Canada, an average of 12,000 hospital admissions per year were attributed to seasonal influenza for 1992-93 through 2008-09 with about 16,600 admissions during the 2009 pandemic. However, the number of admissions varies dramatically from season to season, ranging from 1,200-37,000 per year. Based on the proportion of influenza tests that tested positive for influenza B, the authors estimated that about 1,700 hospital admissions were due to a B strain of the viruses [37]. The rates of admission are highest for the very young and elderly. In children, it is estimated that there were 12-24 per 100,000 (mean 18) hospital admissions per

year for 1994-95 through 1999-2000 [38]. Rates of hospital admission for adults during the same period (1994-95 through 1999-2000) were significantly higher than for children, at 60-80 per 100,000 adults, with significantly higher rates for older adults. The estimated rate of hospital admission was 10-20 per 100,000 for adults 20-49 years old compared with 50-70 per 100,000 for 50-64 year olds, 100 per 100,000 for 65-69 year olds, and 650 per 100,000 adults 85 years and older [39].

Lower estimates were produced for people living in the USA for the 2005-06 through 2007-08 seasons, with rates of influenza-related hospital admission per 100,000 adults increasing with age from 4.5 in 18-49 year olds, 8.9 for 50-64 years, 23.7 for 65-74 year olds, and 68.0 for people 75 years and older [40]. In another study, rates of hospitalization for people 65 years and older ranged from 17.3-114.0 per 100,000 for 1990-91 through 2003-04 in the USA, with rates increasing "almost exponentially", with age [41].

Rates of influenza B-related hospital admission are modelled using the proportion of laboratory tests for each strain of influenza, which may or may not accurately reflect the actual distribution of cases hospitalized by strain of influenza. In Colorado, USA for the 2004-05 through 2007-08 seasons, 18.5% (3.3-34.2% per year) of patients who tested positive for influenza were laboratory-confirmed as influenza B [42]. Similarly, 24% [i] of people hospitalized between 2000 and 2010 at one hospital in Hong Kong were diagnosed with influenza B, ranging from 10.5-33% per year, except in 2009 when only 1.1% of cases were influenza B [36].

As shown in Table 1, Canadian hospitals participating in IMPACT reported that <1% (2009-10) to 58.3% (2011-12) of influenza-related paediatric hospital admissions was attributed to the B strains of influenza. Further analysis of the IMPACT data revealed that between 2004-05 and 2012-13, 34% of influenza-related paediatric hospital admissions were associated with influenza B; of these, 14% of children had an underlying condition for which influenza vaccination is recommended by NACI [43]. In the Toronto/Peel region in the 2004-05 season, 46% (85 of 184) of paediatric hospital admissions for influenza were for B strains – in a year when 16.6% of influenza tests were positive for B strains [44]. In Hong Kong, between 2000 and 2010, influenza B accounted for 24% of all influenza-associated admissions, with children 5-19 years old having the highest proportion of admissions with influenza B, at 41.9% [36]. Children also had higher rates of influenza B-related hospital admission than adults in the Colorado surveillance study for 2004-05 through 2007-08, with age-specific rates of influenza B being the highest in children under 2 years of age in three of the four seasons; only in 2007-08 were rates higher for adults 60 years and older [42].

Canadian hospitals participating in CNISP and PCIRN's Serious Outcome Surveillance reported that 7.7-54% of influenza-related hospital admissions for 2010-11 through 2012-13 were associated with B strains and that 1-16% of adults had an underlying medical condition for which influenza vaccination is recommended by NACI, see Table 1 [43]. In adults admitted to six Toronto-area intensive care units with laboratory-confirmed influenza, 45.7%, 37%, and 0% were positive for influenza B in the 2007-08 and 2008-09 seasons, and during the second wave of the 2009 pandemic, respectively [45], which mirrors the percentage of influenza-positive tests that were of a B lineage: 42.5%, 39.7%, and 0.1% (Table 1).

In Australia during the 2010 and 2011 influenza seasons, 10% of Australian adults 65 years and older who were hospitalized with laboratory confirmed influenza infection carried a B strain [46] in years when 12.7% and 31.2% of circulating strains were of a B lineage and there was a good

[i] Excluding 2009

match between the circulating and vaccine B strains [14]. In Hong Kong, over a 10-year period of surveillance (2000-2010), the median annual rates of admission for older adults (65 years and older) was 6.7 times higher for influenza A than influenza B [36].

Surveillance of acute respiratory illness in children younger than 15 years in France determined that 5.4% and 5.9% of children in 2000-01 and 2001-02, respectively, with a fever (≥38°C) and at least one symptom of a respiratory illness tested positive for influenza, with influenza B accounting for 31.6% of positive tests [47]. In another study in France, during the 4-week peak influenza period (>20% increase in influenza-like illness and >10% increase in positive influenza positive cultures in region) in the 2001-02 influenza season, 49% of febrile children younger than 3 years old tested positive for influenza; 11% with influenza B [48]. Seventy percent of children with influenza had an average of 2.1 additional medical visits, 34% received an antibiotic that the authors deemed potentially inappropriate, and 10% were hospitalized as a result of their infection or a complication of the infection (9% of those with influenza A and 13% with influenza B). This review did not identify additional information on the outpatient burden of influenza B, such as emergency department or physician visits.

I.2.2 Mortality associated with influenza

In Canada, it was estimated that about 3,500 deaths annually were related to influenza between 1992-93 and 2009, ranging from a few hundred to 6,700 per year. The authors estimate that about 390 deaths every year were due to influenza B [37]. Over 90% of the influenza-related mortality was among adults 65 years or older [49]. In another study, an estimated 256 Ontario residents' deaths per year were attributed to influenza from 2005 through 2007 [50].

In the USA, for 1976-77 through 1998-99, 25% of all influenza-related deaths were attributed to influenza B viruses [51]. In children, 830 paediatric influenza-related deaths were reported for 2004-05 through 2011-12 in the USA, with 20% (ranging from 1-38% annually) associated with influenza B infections [52]. In Canadian children, 9 of 18 or 50% (CI95%; 28, 72) of influenza-related paediatric deaths in Canada, as reported by hospitals participating in IMPACT for 2006-07 to 2012-13, were linked to influenza B while only 5% of deaths in adults (2010-11 and 2012-13 seasons only) were linked to influenza B [18].

II. LITERATURE REVIEW METHODS

II.1 Search strategy

The literature search was conducted using three electronic databases – Web of Science, Medline and EMBASE – for primary studies using applicable Medical Subject Headings (MeSH) and key words. The general search strategy was (influenza vaccine) OR (influenza virus AND vaccine) AND (quadrivalent formulations) limited to humans without any date restrictions (see Appendix B). The search strategy was applied to all three databases on August 19, 2012 and yielded 825 citations. Seven more citations were identified through registered drug trials on ClinicalTrials.gov. A second search was completed October 15, 2013 using the same strategy. Two independent reviewers also hand searched reference lists of relevant review articles, but did not identify further citations (see Appendix B).

II.2 Eligibility screening

Two reviewers independently screened all titles and/or abstracts for relevance based on the eligibility criteria established *a priori.* There were no age restrictions and results include those with underlying health conditions. When available, the areas of review are provided specifically for children (6 months to 19 years), adults (19-64 years), and seniors (65 years and older). Due to the novelty of this vaccine, the review includes both licensed and unlicensed experimental vaccines, but with explicit identification of the license status. Included studies were limited to clinical trials and observational studies with a comparison group. Case reports, case series, and opinion papers were excluded. Records were excluded if it was clear from their title and abstract that the study failed to meet the criteria for population (humans), intervention (quadrivalent influenza vaccine) and comparators (placebo or trivalent vaccine). Records were also excluded if the outcomes did not include either lab-confirmed [PCR/culture/ELISA] or clinical diagnosis of influenza infection, applicable immunogenicity results, or reactogenicity information including adverse events.

Nineteen articles were retrieved for first full-text review. Two articles were retrieved on the follow-up search; one article in-press and one trial from ClinicalTrials.gov. Articles were only excluded if they were assessed as ineligible by two independent reviewers. Any disagreements were resolved through discussion and/or by consulting a third reviewer. Articles were designated as ineligible by reviewers if the intervention did not include two influenza B strain components in the quadrivalent formulations. Any model-based studies or studies using animal subjects as well as secondary research articles were excluded.

II.2.1 Quality assessment of studies

Each of the articles retained for review were critically appraised independently by two reviewers using a criteria for grading the internal validity of individual studies [53] (Appendix D). Studies that were rated fair or better were included in the review. Any disagreements were resolved through consensus between both reviewers. No studies were excluded due to poor quality.

II.2.2 Data extraction

Two reviewers independently extracted data from unmasked manuscripts using a common abstraction form designed to capture data for each of the outcomes of interest. The data was abstracted into the forms as reported by the original authors with applicable fields calculated using data presented within the article. All data abstracted was assessed for quality and the results were compiled into evidence tables for this review. Any disagreements or discrepancies between abstractors were resolved by discussion or by consulting a third reviewer.

The search strategy identified 15 eligible studies: 13 randomized controlled trials and 2 non-randomized controlled trials. Most, but not all studies, compared a quadrivalent vaccine with trivalent influenza vaccine(s). Of the 15 studies, one included a vaccine with adjuvant for adult participants [54], 11 used an inactivated formulation without adjuvant – three with child participants [55-58] and eight with adults [54, 59-65] – while three studies compared LAIV formulations: one with children [66] and two with adults [67, 68]. Only one study assessed the efficacy of the quadrivalent vaccine (in children) [69]; all others assessed immunogenicity and safety in a variety of age groups.

III. RESULTS

Given the recent introduction of the quadrivalent influenza vaccine, there is limited data on its efficacy, safety, and immunogenicity. However, the quadrivalent influenza vaccines are manufactured using the same process and have overlapping compositions with the trivalent vaccines which have well-defined safety and efficacy profiles such that these profiles can be expected to be extended to their quadrivalent counterparts [70-73].

III.1 Efficacy or effectiveness

Studies of absolute vaccine efficacy compare the frequency of influenza illness (attack rates) in people who receive the vaccine with those who do not when participating in randomized controlled trials. Vaccine efficacy estimates the percent reduction in attack rates between groups or populations. Relative vaccine efficacy is a measure of the reduction in attack rates in people vaccinated with different formulations of vaccine (e.g., quadrivalent compared to trivalent). The search of the literature did not identify any controlled studies that compared the efficacy or effectiveness of quadrivalent versus trivalent vaccines for either IIV or LAIV.

One study conducted in 2011, reported the efficacy of a quadrivalent inactivated influenza vaccine (IIV4), manufactured by GSK, compared to a hepatitis A vaccine in healthy children 3 to 8 years old as 59% [69]. The attack rates for influenza in children receiving IIV4 were 2.4% compared with 5.7% for those receiving the hepatitis A vaccine, as evidenced by nasal and throat swabs tested by polymerase chain reaction (PCR) for all children with an influenza-like illness. The authors report vaccine effectiveness of 73% for moderate-to-severe influenza (defined as fever>39^{o}C and otitis media, lower respiratory tract illness, or extrapulmonary complications) in this study. Vaccine effectiveness was good for both of the A strains (56% and 58%, for H1N1 and H3N2, respectively) and for both of the B strains (47% and 100%, for Victoria and Yamagata lineages, respectively) in the IIV4. The children enrolled in this study were from 13 different countries (Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Phillipines, Turkey, and Thailand) in three world regions and should be generalizable to healthy children across the world.

III.2 Immunogenicity

Immunogenicity is a surrogate marker for vaccine efficacy and refers to the ability of a vaccine to induce an immune response. A common measure of immunogenicity is to assess the level of serum antibodies to antigens included in the vaccine through a laboratory test called a hemagglutination inhibition (HI) assay. Seroconversion is measured as the proportion of participants with a minimum of a four-fold increase in pre- and post-immunization titres (≤1:10 to ≥1:40 or at least 4-fold). Seroprotection is a measure of the proportion of participants with a HI titre of ≥1:40 (or ≥1:32 in some studies) post-vaccination and is generally accepted as being correlated with a 50% reduction in the risk of influenza.

When comparing two vaccines, there are two commonly used assessments of non-inferiority: 1) the geometric mean titre ratio (GMTR), which uses the ratio of the geometric mean titre of antibody response of people receiving each vaccine, and 2) the difference in the proportion of people who seroconvert in each group [74].

Since data used in this review include both published and unpublished, tests of non-inferiority are not available for all studies. In this review, we also present the geometric mean folder rise (GMFR), rates of seroprotection, and rates of seroconversion, basing evaluation of the vaccines on the European Agency for the Evaluation of Medicinal Products' Committee for Medicinal Products for Human Use (CHMP) criteria for assessing annual influenza vaccines. The CHMP require that each antigen meet at least one of three serological indicators: 1) mean geometric titre increases of at least 2.5-fold and 2.0-fold in adults 18-59 and 60 years and older, respectively; 2) at least 70% and 60% are seroprotected, respectively by age group, or 3) at least 40% and 30% seroconvert or have a significant increase in titres, respectively by age group [(75)].

Similarly, the US Department of Health and Human Services' Center for Biologics Evaluation and Research state that expedited approval may be considered for influenza vaccines for which the lower bound of the two-sided 95% CI meets or exceeds: 1) 30% and 40% for rates of seroconversion in adults 65 years and older and for people younger than 65 years, respectively and 2) 60% and 70% for rates of seroprotection for adults 65 years and older and people younger than 65 years, respectively [(74)].

III.3 Immunogenicity of inactivated influenza vaccines

Seven studies investigated the immunogenicity of IIV4 compared with IIV3 in adults. One study evaluated immunogenicity in adults younger than 60 years of age [(54)] while four others stratified results for younger and older adults [(59, 60, 64, 65)], one studied adults 65 years and older only [(62)], and one presented aggregated data for adults 18 years and older [(61)]. Four of the trials of inactivated influenza vaccines provided information about non-inferiority to the IIV3s [(54, 59, 61, 64)] while the other three were unpublished at the time of this review and as such, had no non-inferiority analyses available [(60, 62, 65)]. All four of the trials, including three studies of adults 18 years and older and one study of adults 18-59 years of age, reported that the IIV4 vaccines were non-inferior to the IIV3 vaccines [(54, 59, 61, 64)].

III.3.1 Adults younger than 61 years

Three of five studies of healthy adults younger than 61 years report that the quadrivalent inactivated influenza vaccines used in their trials met all three of the CHMP criteria [(54, 60, 64)]. In one of the other two studies, the IIV4 met CHMP requirements for seroprotection and GMTR, but failed to meet the requirement for seroconversion (40%), with only 34% and 36% of participants in this small open-label trial seroconverting to the B/Victoria and B/Yamagata strains, respectively [(65)]. In the other study that failed to meet all three CHMP requirements, only 60% of the 94 people receiving the IIV4 were seroprotected following immunization – which was similar to that reported for people receiving the IIV3 (55%) containing the same (B/Yamagata) lineage strain [(59)], but failing to meet the 70% requirement.

Four studies compared IIV4 to IIV3. Two studies, Beran et al. [(54)] and Greenberg et al. [(59)] reported that, compared to participants receiving the IIV3, a significantly higher percentage of people receiving the IIV4 seroconverted, were seroprotected, and had higher GMFR for the B strain(s) missing from the IIV3.Two other studies by GlaxoSmithKline [(60)] and Pépin et al. [(64)] report that people receiving the IIV4 had higher rates of seroconversion and higher GMFR, but similar rates of seroprotection for the B strains not included in the respective IIV3. In all four

studies, the rates of seroconversion, seroprotection, and the GMFR for IIV4 and IIV3 recipients were similar for both A strains and the common B strain, suggesting no interference caused by the addition of a fourth strain to the vaccine.

One study compared IIV3 and IIV4 lower dose formulations with an adjuvant (AS03) in 18-59 year old adults [54]. Both vaccines met all CHMP criteria for the three shared virus strains while the IIV4 vaccine also met all criteria for the second B strain. People receiving the IIV4 had significantly higher rates of seroconversion, seroprotection, and higher GMFR than people receiving the IIV3, for the B strain missing from the IIV3. No differences were reported for seroresponse of people receiving the IIV4 compared with the IIV3 for the shared influenza strains.

III.3.2 Adults 61 years and older

Four studies reported immunogenicity data for adults 60 years and older [59, 60, 62, 64]. Three of the four studies report that the IIV4 met all CHMP criteria for all strains [59, 60, 64] for adults 60 years and older. The one study restricted to adults 65 years and older reported that the IIV4 failed to meet the seroconversion criteria: 28.6% of recipients seroconverted to the B/Victoria lineage strain in the IIV4 [62], just below the 30% requirement of the CHMP. Of note, the percentage of IIV3 recipients receiving the vaccine that included the B/Victoria lineage strain who seroconverted was also low (18.7%), but significantly higher than for those who received the IIV3 without the B/Victoria strain (8.6%).

Two of the four studies reported that, compared to participants receiving the IIV3, a significantly higher percentage of people receiving the IIV4 seroconverted, were seroprotected, and had higher GMFR for the B strain(s) missing from the IIV3 [59, 62].Similar to the studies of younger adults, the other two studies in the review report that people receiving the IIV4 had higher rates of seroconversion and higher GMFR, but similar rates of seroprotection for the B strains not included in the respective IIV3 [57, 64]. Also in keeping with the results from younger adults, there was no significant difference in seroresponse for the shared strains in people receiving the IIV4 compared with those receiving the IIV3.

III.3.3 Adults 18 years and older

One large study of healthy adults 18-92 years old (median 64), who received IIV4 or one of two IIV3 formulations reported that the IIV4 met all CHMP requirements for annual influenza vaccine approval for adults 60 years and younger [61]. The IIV4 was non-inferior to the IIV3 for all four strains in the vaccine(s), further supporting the contention that the addition of the fourth strain did not interfere with seroresponses.

An early, small trial of tetravalent influenza vaccine, conducted in 1991-92, compared seroresponses of healthy adults to those of people infected with the human immunodeficiency virus. Although CHMP criteria were not reported, the IIV4 (Solvay-Duphar) induced similar responses in both groups of people, with a higher response to the B/Victoria lineage than to the other three antigens in the vaccine [63].

III.4 Safety of IIV in adults

The reactogenicity (expected reactions) and safety of vaccines in Canada are evaluated prior to authorization and continually throughout their use by means of post-marketing surveillance of

adverse events by the Public Health Agency of Canada, using the Adverse Event following Immunization Surveillance System (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php). Data regarding safety and reactogenicity results provided in each study are available in the Appendices.

In adults, no published study included in this review reported a serious adverse event that was determined to be related to an IIV4 or IIV3. Common complaints following receipt of the injected influenza vaccine include pain at the injection site, myalgia, fatigue, and headache. The percentage of adults receiving IIV4 compared with IIV3 who reported pain at the site was 32.6-73.2% and 23.1-52.1%, respectively, with two studies reporting significantly higher rates of pain following injection with the IIV4 [54, 60] of the four studies comparing the rates. Myalgia was reported by 10.7-37.5% and 3.8-25.3% of people receiving IIV4 and IIV3, respectively, with one study reporting a higher rate following receipt of IIV4 compared with people receiving IIV3 [54]. No significant differences in rates of arthralgia (5.4-12.5% vs. 7.5-10.5%), headache (8.9-22.9% vs. 11.6-21.9%), or fatigue (10.5-30.5% vs.12.1-31.4%) were reported for adults receiving IIV4 and IIV3, respectively [54, 59, 60, 62, 65]. For participants receiving inactivated vaccines with an adjuvant, a higher percentage (24.0 vs. 12.4%) reported arthralgia following receipt of the IIV4 compared with IIV3, while no significant differences were reported for injection site pain (76.0 vs. 70.5%), myalgia (38.5 vs.31.4%), headache (31.7 vs. 24.8%), or fatigue (45.2 vs. 34.3%) for IIV4 versus IIV3, respectively [54].

The manufacturer's information sheets produced for the market in the USA for Fluzone quadrivalent®, Fluarix quadrivalent®, and Flulaval quadrivalent® influenza vaccines state that they should not be given to anyone with a history of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine [71-73].

III.5 IIV in children

Four studies investigated the immunogenicity of IIV4 in children. Two studies used IIV3 as the comparator for children 3-17 years old while also studying the IIV4 alone in children 6-35 months old [55, 56]. In these studies, the IIV4 was considered non-inferior to the IIV3 on both GMTR and seroconversion. Although 29.6-41.3% of children *did* seroconvert to the B lineage missing from the IIV3, the rates of seroconversion were significantly higher (70.0-75.2%) in children receiving the IIV4. As shown in the Appendix F, rates of seroconversion to the B lineages were similar for children receiving the IIV4 and the IIV3 (68.5-73.4%) formulations. Similarly, there was no apparent diminution in responses to the A strains in the IIV4 vaccines compared to the IIV3 formulations.

Children 6-35 months of age received the IIV4 in open-label subsets in these two trials [55, 56]. All adult CHMP criteria were met for those receiving two doses of the IIV4, with rates of seroconversion of 68.5-84.9% to the influenza A strains and 68.1-93.8% to the B strains in the IIV4 vaccines. Rates of seroprotection for these young children ranged from 72.2-89.6% for A strains and 71.4-96.5% for B strains. However, three of eight comparisons of seroprotection failed to meet the US Department of Health and Human Services requirements for expedited approval of influenza vaccines: both A/H3N2 and one B/Victoria strain failed to meet the 70% lower CI boundary.

Authors of a study comparing IIV4 with IIV3 in children 6 months to 8 years of age reported that the IIV4 was non-inferior for both A strains and superior to the IIV3 not containing the same B lineage strain, for both B strains in the quadrivalent vaccine [58]. In an as yet unpublished randomized controlled trial of IIV4 compared to IIV3 conducted with children 6-35 months of

age, GlaxoSmithKline reports superior performance of the IIV4 for the B/Victoria lineage included only in the IIV4 and somewhat higher rates of seroconversion and seroprotection against the A/H1N1 and A/H3N2 strains in children receiving the IIV4 (personal communication, R. Sharma). The higher rates of seroresponse to the IIV4 were not noted in other published data for children or adults.

One study compared IIV4 with Havrix®, a hepatitis A vaccine, in 3-8 year old children [(69)]. Children in both arms of the study received two doses of vaccine/placebo if they had not previously been vaccinated against influenza, but only one dose if they had. The IIV4 met all adult criteria for influenza vaccines and seroresponse was significantly better for all antigens compared with children receiving the hepatitis A vaccine [(69)].

III.6 Safety of IIV in children

Of 3094 vaccinated children in one study, four events in three children that were possibly related to the vaccine were reported. One child who received an IIV3 had two events angioedema and acute conjunctivitis. In young children (<3 years) receiving the IIV4, one child had a generalized seizure and another had a febrile seizure [(55)]**.** A second study of 2584 children reported one serious adverse event (bronchitis) following receipt of IIV4 that was considered possibly related to immunization [(69)]. The third study of 2738 children receiving IIV4 or IIV3 reported no serious adverse events [(56)] while the authors of a fourth study, including 4363 children 3 months to 8 years old, reported three possibly related events: one following immunization with IIV4 (croup) and two following immunization with IIV3 (2 incidents of febrile seizure) [(58)].

In children receiving IIV4, 27.0-47.7% had pain at the site of injection, 15.6% had myalgia, 8.7% arthralgia, 14.7% headache, 11.1-23.8% fatigue or drowsiness, and 5.1-20% had a fever [(55, 56, 58, 69)].

III.7 Conclusions for inactivated influenza vaccines

The quadrivalent formulas of the inactivated influenza vaccines were non-inferior to the trivalent vaccines for matching antigens in all studies of children and adults except one. That study was of adults 65 years and older and the rate of seroconversion to the A/H1N1 antigen for those with IIV4 was inferior to that of people receiving the IIV3. However, this data is preliminary, as reported on clinicaltrials.gov [(62)]. In all other studies, the seroresponses to the IIV4 were similar to the IIV3 for the shared influenza strains, supporting the contention that the addition of the fourth strain did not impair the response to the other strains. In each comparison, for both adults and children, the seroresponses to the IIV4 were higher than to the IIV3 for the unmatched B strain lineage, although there was some apparent boosting of the opposite B lineage. Antibody responses to inactivated quadrivalent vaccines were generally higher in children than younger adults (<61 years old) and lowest in older adults.

The safety profile of the IIV4 is similar to that of the IIV3, with pain at the injection site being the most common complaint for both adults and children followed by myalgia, fatigue and headache. Arthralgia is also a common complaint in adults, but is less frequently reported in studies of children. Three, of over 12,700 vaccinated children, experienced febrile seizure following receipt of either IIV4 or IIV3.

III.8 Immunogenicity of live attenuated influenza vaccines

Live attenuated influenza vaccines were first authorized for use in Canada in 2010. These vaccines are administered intranasally and stimulate a mucosal response as well as a systemic immune response. The Canadian National Advisory Committee on Immunization (NACI) recommends LAIV for use with healthy children 2-17 years old without contraindications. There is some evidence that LAIV3 may be more effective than IIV3 in preventing influenza infection in children [76]. In adults under 60 years old, there is contradictory evidence, with LAIV3 being equally or less effective than IIV3 [77, 78]. Effectiveness has not been studied in older adults, pregnant or breastfeeding women, or children under 2 years old [70]. Although seroresponses to LAIV are not directly comparable to injected vaccines, they are used as one of the surrogates of efficacy.

Two studies in this review compared serological responses between LAIV4 and LAIV3 (FluMist®, MedImmune) in 18-49 year old adults. Non-inferiority assessment, based on GMTR, determined that the LAIV4 vaccines were non-inferior to the LAIV3 comparators for adult participants [67, 68]. In both studies, there were no significant differences when comparing the participants' seroresponses to each antigen contained in the vaccines.

One study compared LAIV4 and LAIV3 (FluMist®, MedImmune) in children 2-17 years of age. Based on GMTR, the LAIV4 formulation was non-inferior to the LAIV3 for all antigens in the vaccines. The rates of seroconversion for each B strain in the LAIV4, compared with the corresponding B strain *not* in the LAIV3, were higher for children receiving the LAIV4 [66].

III.9 Safety of LAIV

In adults, the most commonly reported events following receipt of LAIV4 are runny nose (31.3-43.6%), headache (23.8-28.2%), sore throat (17.3-19.0%), and fatigue (16.2-17.6%) [67, 68], with no differences between people receiving the LAIV4 or LAIV3. Similar to symptoms reported by adults, the most common complaints following LAIV4 administration in children 2-17 years old were runny nose (31.6%), headache (8.4%), sore throat (7.2%), and fatigue (8.5%). In this study, a higher proportion of children 2.8 years old experienced a fever following receipt of the LAIV4 (5.1%) than the LAIV3 after the first dose of vaccine only (3.1%). The frequency of other events, including the overall frequency of fever for all ages and after each dose, was similar between the two formulations of vaccine [66].

One serious adverse event was reported that investigators considered related to receipt of an LAIV (not stated whether it was LAIV4 or LAIV3); one adult sought care for bronchospasm two days after vaccination [67]. Although serious adverse events were reported during the conduct of the second trial with adults, the details regarding whether they were considered related to vaccination were not available from the clinicaltrials.gov database [68]. No vaccine-related serious adverse events were reported following receipt of a LAIV in the study with children [66].

According to prescribing information published for the United States by MedImmune, FluMist quadrivalent® should not be administered to anyone who has had a severe allergic reaction to any component of the vaccine or after a previous dose of any influenza vaccine. Also, FluMist should not be administered to any child under 18 years old who is receiving aspirin therapy, any child under 5 years of age with recurrent wheezing, or immunocompromised people of any age (70). The National Advisory Committee on Immunization recommends that LAIV can be used in

children 24 months and older but that it "should not be used in those with severe asthma (defined as currently on oral or high dose inhaled glucocorticosteriods or active wheezing) and those with medically attended wheezing in the seven days prior to vaccination" [77].

III.10 Conclusions for live attenuated influenza vaccines

The LAIV4 was shown to be non-inferior to LAIV3 in studies including adults younger than 50 years of age and in children 2-17 years old. The safety profile of the LAIV4 vaccines were substantially similar to the profile of the LAIV3 formulations with the most common complaints following vaccine administration being runny nose, headache, sore throat, and fatigue.

IV. CONCOMITANT ADMINISTRATION OF OTHER VACCINES

No studies reviewed concomitant administration of IIV4 or LAIV4 with other vaccines. For products licensed in the USA, the manufacturer's information sheet for Fluzone quadrivalent®, Fluarix quadrivalent®, and Flulaval quadrivalent® influenza vaccines state that they should not be mixed in the same syringe with another vaccine [71-73]. GlaxoSmithKline also states that there is insufficient data to assess the concurrent administration of Fluarix or Flulaval with other vaccines but advise that if required, the vaccines should be administered at different sites [71, 72].

V. EVIDENCE GAPS

The most notable gap is the limited evidence on vaccine efficacy and effectiveness. Only one trial reported on the efficacy of IIV4 in children, with all others focused on investigating the immunogenicity and safety of the quadrivalent vaccines. Also, the studies reviewed were conducted with healthy populations thus limiting the ability to generalize the results. Although there is good evidence for the effectiveness and safety of IIV3 formulations for pregnant women and nursing mothers as well as people with immune compromising conditions, there is a lack of evidence for IIV4 formulations. Safety and effectiveness of LAIV has not been established in pregnant women, nursing mothers, geriatric adults, or children less than 2 years of age.

VI. DISCUSSION/SUMMARY

The studies we reviewed found that the seroresponses elicited with the addition of a fourth antigen did not reduce the body's response to the other three antigens, as evidence by similar responses to the quadrivalent and trivalent vaccines on shared antigens. In addition, people receiving the fourth antigen had significantly increased levels of seroprotection and seroconversion for the second B lineage. This finding was consistent across age groups and different types of vaccine: IIV and LAIV, alike. The safety profile of the quadrivalent vaccines is comparable to that of the trivalent vaccines, with similar proportions of people reporting adverse events after vaccination.

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(72) GlaxoSmithKline. Highlights of prescribing information - FluLaval quadrivalent (influenza virus vaccine), 2013-14 formula. (Research Triangle Park, NC, 2013).

(73) Sanofi Pasteur. Highlights of prescribing information - Fluzone Quadrivalent (influenza virus vaccine) 2013-14 formula. (Sanofi Pasteur, Pennsylvania, USA, 2013).

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APPENDIX A: SEARCH TERMS

Table A-1. Quadrivalent Influenza Vaccine systematic literature review search terms

	Database	Medline (n=146)	Embase (n=205)	Web of Science (n=474)
KEYWORDS AND LIMITS	**1. Influenza vaccine**	exp Influenza Vaccines/ or influenza vaccin*.mp.	exp influenza vaccine/ or exp influenza vaccination/	
	2. Influenza	influenza.mp. or exp Influenza, Human/ or "influenza".m_titl.	exp Influenza virus B/ or exp influenza A/ or exp Influenza virus/ or exp Influenza virus A/ or exp Influenza virus A H3N2/ or exp influenza B/ or influenza.mp. or exp influenza/ or exp seasonal influenza/ or exp "influenza A (H2N2)"/ or exp Influenza virus A H1N1/ or exp "influenza A (H1N1)"/ or exp "influenza A (H3N2)"/ or exp Asian influenza/ or influenza.m_titl.	((TS=(influenza) OR TI=(influenza))
	3. Vaccine	exp Vaccines/ or vaccin*.mp. or exp Viral Vaccines/ or exp Mass Vaccination/ or exp Immunization Programs/ or immuni*.mp. or "immuni*".m_titl. or "vaccin*".m_titl.	exp vaccine/ or vaccin*.mp. or exp vaccination/ or "vaccin*".m_titl. or exp immunity/ or exp vaccination/ or exp immunization/ or immuni*.mp. or "immuni*".m_titl.	(TS=(vaccin* OR immuni*) OR TI=(vaccin* OR immuni*))
	4. Quadrivalent	quadrivalent.mp. OR quadrivalent.m_titl. OR multivalent.mp. OR multivalent.m_titl. OR tetravalent.mp. OR tetravalent.titl. OR polyvalent.mp. OR polyvalent.titl. OR four strain$.mp	quadrivalent.mp. OR quadrivalent.m_titl. OR multivalent.mp. OR multivalent.m_titl. OR tetravalent.mp. OR tetravalent.m_titl. OR polyvalent.mp. OR polyvalent.m_titl. OR four strain$.mp.	(TS=(quadrivalent OR multivalent OR tetravalent OR polyvalent OR four strain) OR TI=(quadrivalent OR multivalent OR tetravalent OR polyvalent OR four strain)
	5. Population	Humans	Human	
	6. Dates	No restrictions to DATE of search	No restrictions to DATE of search	No restrictions to most recent
	7. Boolean terms	([1 OR (2 AND 3)] AND 4) limited to 5	([1 OR (2 AND 3)] AND 4) limited to 5	(2 AND 3 AND 4)

:

APPENDIX B: SEARCH STRATEGY

Table B-1. Quadrivalent Influenza Vaccine systematic literature review search strategies

Medline

#	Searches	Results
1	exp Influenza Vaccines/ or influenza vaccin*.mp.	18669
2	influenza.mp. or exp Influenza, Human/ or "influenza".m_titl.	77813
3	exp Vaccines/ or vaccin*.mp. or exp Viral Vaccines/ or exp Mass Vaccination/ or exp Immunization Programs/ or immuni*.mp. or "immuni*".ti. or "vaccin*".ti.	504847
4	quadrivalent.mp. or quadrivalent.ti. or multivalent.mp. or multivalent.ti. or tetravalent.mp. or tetravalent.ti. or polyvalent.mp. or polyvalent.ti. or four strain$.mp.	15216
5	1 or (2 and 3)	28215
6	4 and 5	225
7	limit 6 to humans	**146**

EMBASE

#	Searches	Results
1	exp influenza vaccine/ or exp influenza vaccination/	27155
2	exp Influenza virus B/ or exp influenza A/ or exp Influenza virus/ or exp Influenza virus A/ or exp Influenza virus A H3N2/ or exp influenza B/ or influenza.mp. or exp influenza/ or exp seasonal influenza/ or exp "influenza A (H2N2)"/ or exp Influenza virus A H1N1/ or exp "influenza A (H1N1)"/ or exp "influenza A (H3N2)"/ or exp Asian influenza/ or influenza.ti.	100908
3	exp vaccine/ or vaccin*.mp. or exp vaccination/ or "vaccin*".ti. or exp immunity/ or exp vaccination/ or exp immunization/ or immuni*.mp. or "immuni*".ti.	1947971
4	quadrivalent.mp. or quadrivalent.ti. or multivalent.mp. or multivalent.ti. or tetravalent.mp. or tetravalent.ti. or polyvalent.mp. or polyvalent.ti. or four strain$.mp.	17048
5	1 or (2 and 3)	50085
6	4 and 5	343
7	limit 6 to human	**205**

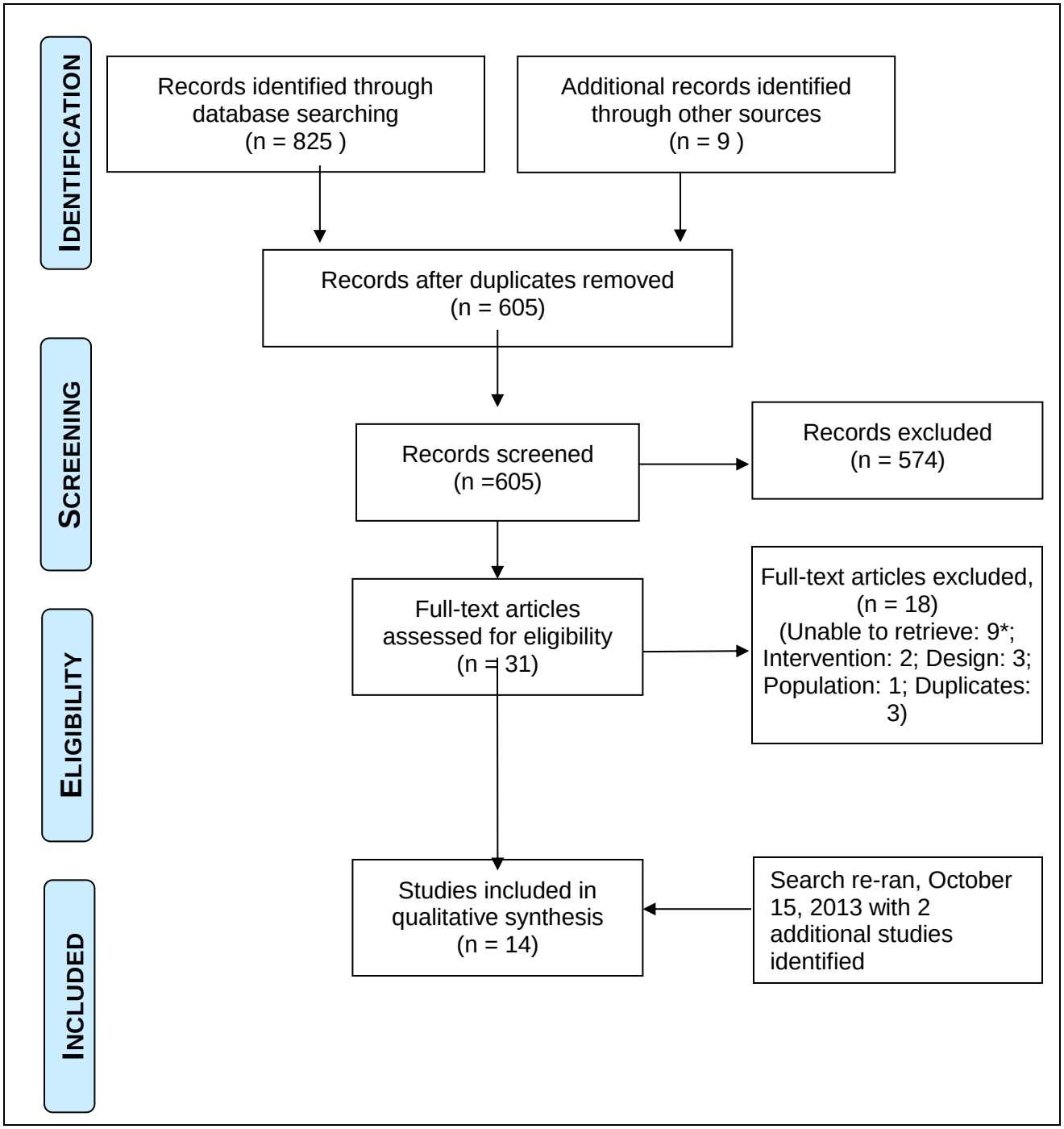
Web of Science

#	Searches	Results
# 1	(TS=(influenza)) OR (TI=(influenza)) *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*	69,880
# 2	(TS=(vaccin* OR immuni*)) OR (TI=(vaccin* OR immuni*)) *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*	391,888
# 3	(TS=(quadrivalent OR multivalent OR tetravalent OR polyvalent OR four strain)) OR (TI=(quadrivalent OR multivalent OR tetravalent OR polyvalent OR four strain)) *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*	73,645
# 4	#3 AND #2 AND #1 *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*	**474**

ALSO: Searched clinicals.gov using the phrase “quàdrivalent influenza” (n=21)

APPENDIX C: ATTRITION FLOW DIAGRAM

Figure C-1 Study Attrition Flow
Quadrivalent vaccine efficacy, immunogenicity and safety in children and adults



APPENDIX D: DEFINITION FOR TABLES OF EFFICACY, IMMUNOGENICITY, AND SAFETY

Table D1: Definition of overall study quality

Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

VIII.LIST OF ABBREVIATIONS

Abbreviation	***Term***
ARI	acute respiratory illness
B/Vic	influenza B, Victoria lineage
B/Yam	Influenza B, Yamagata lineage
GMFR	geometric mean fold rise - post-vaccine GMT/pre-vaccine GMT (also seroconversion factor)
GMT (geometric mean titre)	measure of serological antibody level
GMTR	geometric mean titre ratio (e.g., quadrivalent GMT/trivalent GMT)
GP	general practitioner
Hemagglutination inhibition (HI) titres	serological test measuring serological antibody levels to each influenza antigen (strain)
ID	intradermal
IIV3	inactivated influenza vaccine, trivalent (formerly referred to as TIV)
IIV4	inactivated influenza vaccine, quadrivalent (also referred to as QIV)
ILI	influenza-like illness
IM	intramuscular
LAIV3	live attenuated influenza vaccine, trivalent (also referred to as LAIV)
LAIV4	live attenuated influenza vaccine, quadrivalent (also referred to as Q-LAIV)
MAE	medically attended adverse event
NR	not reported
SAE	serious adverse events
Seroconversion	Proportion of participants with negative (≤1:10) pre-vaccination and ≥1:40 post-vaccination titre OR a significant (four-fold) HI titre increase from pre- to post-vaccination

Seroprotection	Proportion of participants with an HI titre of ≥1:40 post-vaccination
UAE	unsolicited adverse events
Vs	versus

SEROLOGICAL CRITERIA FOR ASSESSMENT OF INFLUENZA VACCINES

A) Committee for Proprietary Medicinal Products (Europe)

Meets at least one of following three measures should be met, for each strain in the vaccine, according to the guidance for influenza vaccines (Committee for Proprietary Medicinal Products, 1997)

18-60 years old:
1) Seroconversion or significant increase in antibody titres of >40% of participants, OR
2) Mean geometric increase of >2.5, OR
3) Seroprotection of >70% of participants

60 years & older:
1) Seroconversion or significant increase in antibody titres of >30% of participants, OR
2) Mean geometric increase of >2.0, OR
3) Seroprotection of >60% of participants

Children <18 years:
No similar criteria exist
Note: These criteria cannot be used to assess immunogenicity of LAIV

B) US Department of Health and Human Services (Centre for Biologics Evaluation & Research)

< 65 years old and the paediatric population:
1) The lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%
2) The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%.

≥ 65 years old:
1) The lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30%
2) The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60%.

Non-inferiority of vaccine immunogenicity

US Department of Health and Human Services
(Centre for Biologics Evaluation & Research)
To assess the non-inferiority of a new vaccine when comparing it to a licensed vaccine: (Center for Biologics Evaluation and Research, 2007)

1) Ratio of post-vaccine GMT (trivalent/ quadrivalent) has an upper-bound of 2-sided 95% confidence interval (CI) of <1.5 [OR quadrivalent/trivalent has a lower bound of >0.67], AND
2) Difference in seroconversion rates (trivalent – quadrivalent) has an upper bound of 2-sided 95% CI of <10 percentage points.

APPENDIX E: SUMMARY OF EVIDENCE RELATED TO EFFICACY/EFFECTIVENESS OF QUADRIVALENT INFLUENZA VACCINES

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
Inactivated Influenza Vaccine - Children					
Jain VK, Rivera L, Zaman K, et al. Vaccine for prevention of mild and moderate-to-severe influenza in children. *NEJM* 2013*; 369(26)*:2481-2491. *ClinicalTrials.gov*. (NCT01218308)	**Name:** Quadrivalent influenza vaccine GSK2282512A **Manufacturer:** GlaxoSmithKline **Dose:** 15 µg, 0.5 mL (primed: 1; unprimed: 2) **Admin:** IM **Details:** inactive split-virion ; A/H1N1/ California/7/09 A/H3N2/ Victoria/210/09 B/Vic/ Brisbane/60/08 B/Yam/ Florida/4/06 **Season:** Dec 2010-Oct 2011 **Other vaccine:** Havrix (Hepatitis A vaccine), 0.5 mL/dose	RCT, phase III, double-blind, multicentre	**Age:** 3-8 years; mean(SD): 5.4 (1.65) **Sex:** 51.7% male **Country:** Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Phillipines, Turkey, and Thailand **Setting:** multicentre **Number of participants** **Vaccine:** 2584 **Hepatitis A:** 2584 **Inclusion criteria**: healthy children	**Follow-up:** active, 6 months (day 14 to 180) **Influenza-like illness** (37.8^{o}C+ and 1+ of: cough, sore throat, runny nose, or nasal congestion) (Influenza Vaccine (QIV) vs Havrix (Hep A)) 422 (16.3%) vs 507 (19.6%); NS **rt-PCR confirmed influenza A or B** (nasal & throat swabs with influenza-like illness); (QIV vs Hep A) Attack rate: 62 (2.4%) vs 148 (5.7%) RR: 0.42 Vaccine effectiveness (overall): 59.3% (45.2, 69.7) **Vaccine effectiveness, by strain** (per protocol) A/H1N1 55.6 (21.3, 74.9) A/H3N2 57.6 (28.5, 74.9) B/Vic 47.2 (12.4, 68.2) B/Yam 100 (~ , 100)	**Rank: I** **Quality:** Good

AR: attack rate; RR: relative risk; VE: vaccine effectiveness; ILI: influenza-like illness; IM: intramuscular; LAIV: live attenuated influenza virus; IIV4: quadrivalent inactivated (influenza) vaccine; PCR: polymerase chain reaction; RCT: randomized controlled trial; HIV: Human Immunodeficiency Virus

APPENDIX F: SUMMARY OF EVIDENCE RELATED TO IMMUNOGENICITY OF QUADRIVALENT INFLUENZA VACCINES

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
Inactivated Influenza Vaccines – Adults					
Beran J, Peeters M, Dewe W, et al. Immunogenicity and safety of quadrivalent versus trivalent inactivated influenza vaccine: a randomized, controlled trial in adults. *BMC Infect Dis,* 2013; 13:224-234. (NCT00714285)	**Name:** Quadrivalent Influenza Vaccine (IIV4) **Manufacturer(s):** GlaxoSmithKline **Dose:** 0.5 mL **Admin:** IM **Details:** non-adjuvant, inactive split-virion, 15µg HA of: A/H1N1/Solomon Islands/03/2006 A/H3N2/ Wisconsin/67/2005 B/Vic/ Malaysia/2506/2004 B/Yam/ Jiangsu/10/2003 **Season:** 2007-2008 **Other vaccine:** IIV3 **Manufacturer(s):** GlaxoSmithKline **Details:** without B/Yam	RCT, phase I/II, single-centre, single-blind	**Age:** 18-59 years mean(SD): 37.6(12.3) **Sex:** 40% male **Country:** Czech Republic No adjuvant **Number of participants:** IIV4: 104 IIV3: 105	**Follow-up:** 21 days **Seroconversion** (4-fold increase) - IIV4 vs IIV3-B/Vic A/H1N1 56.7 (46.7, 66.4) vs 60.0 (50.0, 69.4) A/H3N2 60.6 (50.5, 70.0) vs 59.0 (49.0, 68.5) B/Vic 57.7 (47.6, 67.3) vs 59.0 (49.0, 68.5) B/Yam 76.0 (66.6, 83.8) vs 19.0 (12.0, 27.9)* **Seroprotection** (≥1:40) A/H1N1 92.3 (85.4, 96.6) vs 90.5 (83.2, 95.3) A/H3N2 97.1 (91.8, 99.4) vs 96.2 (90.5, 99.0) B/Vic 97.1 (91.8, 99.4) vs 93.3 (86.7, 97.3) B/Yam 98.1 (93.2, 99.8) vs 63.8 (53.9, 73.0)* **GMFR** (95% CI) A/H1N1 6.1 (4.6, 8.0) vs 7.3 (5.3, 9.9) A/H3N2 5.5 (4.4, 6.9) vs 5.4 (4.1, 7.0) B/Vic 6.0 (4.7, 7.7) vs 6.9 (5.2, 9.3) B/Yam 9.1 (7.2, 11.5) vs 2.3 (1.9, 2.6)* **Non-inferiority -** Details not reported, but not inferior by text	**Rank: I** **Quality:** Good
	Name: Low Dose Quadrivalent Influenza Vaccine (LD IIV4-AS) **Manufacturer(s):** GlaxoSmithKline **Dose:** 0.5 mL **Admin:** IM **Details:** adjuvant, inactive split-virion, 5µg HA, with AS03 A/H1N1/Solomon Islands/03/2006 A/H3N2/ Wisconsin/67/2005 B/Vic/ Malaysia/2506/2004 B/Yam/ Jiangsu/10/2003 **Season:** 2007-2008 **Comparator vaccine:** Low Dose IIV3 with adjuvant AS-03		Adjuvant **Number of participants:** LD IIV4-AS: 104 LD IIV3-AS: 104 **Inclusion criteria**: healthy adults	**Follow-up**: 21 days **Seroconversion** (IIV4 vs IIV3) A/H1N1 57.7 (47.6, 67.3) vs 54.8 (44.7, 64.6) A/H3N2 66.3 (56.4, 75.3) vs 64.4 (54.4, 73.6) B/Vic 65.4 (55.4, 74.4) vs 56.7 (46.7, 66.4) B/Yam 78.8 (69.7, 86.2) vs 26.9 (18.7, 36.5)* **Seroprotection** (≥1:40) A/H1N1 88.5 (80.7, 93.9) vs 93.3 (86.6, 97.3) A/H3N2 98.1 (93.2, 99.8) vs 100 (96.5, 100) B/Vic 97.1 (91.8, 99.4) vs 96.2 (90.4, 98.9) B/Yam 95.2 (89.1, 98.4) vs 75.0 (65.6, 83.0)* **Seroconversion Factor** A/H1N1 6.8 (5.0, 9.2) vs 6.9 (5.0, 9.4) A/H3N2 7.4 (5.8, 9.4) vs 6.4 (5.0–8.3) B/Vic 8.0 (6.1, 10.5) vs 8.1 (5.9, 11.0) B/Yam 8.1 (6.6, 10.0) vs 2.5 (2.1, 3.0)*	

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
	Manufacturer(s): GlaxoSmithKline **Details:** excluding B/Yam			**Non-inferiority** Details not reported	
Pépin S, Donazzolo Y, Jambrecina, et al. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine in adults. *Vaccine* 2013, *31(47):* 5572-5578. Eudra Clinical Trials (2011-001976-21)	**Name:** Fluzone Quadrivalent **Manufacturer(s):** Sanofi Pasteur **Dose:** 0.5mL , IM **Details:** inactive , 15µg per strain A/H1N1/ California/07/2009 A/H3N2/ Victoria/210/2009 B/Vic/ Brisbane/60/2008 B/Yam/Florida/4/2006 **Season:** 2011-2012 **Other vaccines:** IIV3 **Name:** Vaxigrip (2010-2011) **Manufacturer(s):** Sanofi Pasteur **Details:** A strains as above less B/Yam Investigational IIV3 **Manufacturer(s):** Sanofi Pasteur **Details:** A strains as above less B/Vic	RCT, phase III, double-blind, multi-centre	**Age:** 18-60 and >60 **Sex**: 45% male **Country**: France & Germany **Number of participants:** **IIV4:** 1112 18-60: 556 >60: 556 **IIV3** Vaxigrip (B/Vic) 18-60: 113 >60: 113 Investigational (B/Yam) 18-60: 110 >60: 113 **Inclusion criteria:** Excluded pregnant women and people who were immune suppressed	**Follow-up:** 21 days **Seroconversion** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) 18-60 years A/H1N1 72.2 (68.3, 75.9) vs 71.7 (62.4, 79.8) vs 69.1 (59.6, 77.6) A/H3N2 74.5 (70.6, 78.0) vs 77.0 (68.1, 84.4) vs 77.3 (68.3, 84.7) B/Vic 69.2 (65.2, 73.1) vs 61.1 (51.4, 70.1) vs 42.7 (33.3, 52.5) B/Yam 73.2 (70.1, 77.5) vs 46.0 (36.6, 55.6) vs 56.8 (47.0, 66.1) >60 years A/H1N1 59.2 (55.0, 63.3) vs 54.9 (45.2, 64.2) vs 68.5(59.0, 77.0) A/H3N2 56.6 (52.4, 60.8) vs 62.8 (53.2, 71.7) vs 61.6 (51.9, 70.6) B/Vic 46.1 (41.9, 50.4) vs 42.5 (33.2, 52.1) vs 25.9 (18.1, 35.0)* B/Yam 61.2 (57.0, 65.3) vs 23.9 (16.4, 32.8)* vs 56.8 (47.0, 66.1) **Seroprotection** (≥1:40) 18-60 years A/H1N1 96.4 (94.5, 97.8) vs 96.5 (91.2, 99.0) vs 94.5 (88.5, 98.0) A/H3N2 97.1 (95.4, 98.3) vs 97.3 (92.4, 99.4) vs 96.4 (91.0, 99.0) B/Vic 99.5 (98.4, 99.9) vs 99.1 (95.2, 100) vs 94.5 (88.5, 98.0) B/Yam 99.6 (98.7, 100) vs 97.3 (92.4, 99.4) vs 99.1 (95.0, 100) >60 years A/H1N1 90.1 (87.3, 92.4) vs 89.4 (82.2, 94.4) vs 91.0 (84.1, 95.6) A/H3N2 93.7 (91.3, 95.6) vs 95.6 (90.0, 98.5) vs 93.8 (87.5, 97.5)	**Rank**: **I** **Quality**: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
				B/Vic 97.5 (95.8, 98.6) vs 96.5 (91.2, 99.0) vs 92.0 (85.3, 96.3) B/Yam 99.8 (99.0, 100) vs 91.2 (84.3, 95.7)* vs 100 (96.8, 100) **GMFR** 18-60 years A/H1N1 14.3 (12.3, 16.6) vs 14.7 (10.5, 20.5) vs 18.1 (12.9, 25.5) A/H3N2 14.6 (12.7, 16.9) vs 19.4 (13.9, 27.2) vs 15.7 (11.5, 21.3) B/Vic 12.2 (10.6, 14.1) vs 12.1 (8.3, 17.6) vs 3.6 (2.9, 4.6)* B/Yam 13.2 (11.5, 15.1) vs 3.9 (3.1, 5.0)* vs 13.1 (9.8, 17.6) >60 years A/H1N1 7.7 (6.8, 8.7) vs 6.8 (5.1, 9.1) vs 7.8 (6.0, 10.2) A/H3N2 6.8 (6.0, 7.7) vs 9.0 (6.6, 12.3) vs 8.4 (6.1, 11.5) B/Vic 4.8 (4.3, 5.4) vs 5.0 (3.6, 6.7) vs 2.2 (1.8, 2.7)* B/Yam 7.2 (6.4, 8.1) vs 2.2 (1.8, 2.6)* vs 6.9(5.1, 9.4) **Non-inferiority, GMTR** (IIV3 ÷ IIV4) all ages combined A/H1N1 1.07 (0.92, 1.25) A/H3N2 0.90 (0.77, 1.04) B/Vic 0.92 (0.78, 1.09) B/Yam 1.06 (0.90, 1.25)	
GSK. A phase IIIA study of immunogenicity and safety of GSK Biologicals' quadrivalent split virion influenza vaccine FLU-Q-QIV in adults aged 18 years and older. *ClinicalTrials.gov* (NCT01440387) Last updated: 2013-Sept-05	**Name:** Flulaval Quadrivalent (GSK2282512A) **Manufacturer(s):** GSK **Dose:** 0.5mL , IM **Details:** 15µg/strain A/H1N1/California/07/2009 A/H3N2/Victoria/210/2009 B/Vic/Brisbane/60/2008 B/Yam/Florida/4/2006 **Season:** 2011-12 **Other vaccines:** NA (open-label)	Phase III, open label efficacy trial	**Age:** 18-60 years Mean(SD) 40.9 (13.3) **Sex :** 39% male **Country:** Canada **Number of participants:** 56 **Inclusion criteria**: Stable health 18-60 years **Age:** >60 years Mean(SD) 68.6	**Follow-up:** 21 days **Seroconversion** 18-60 years A/H1N1 50 (37, 63) A/H3N2 48 (35, 61) B/Vic 34 (22, 47) B/Yam 36 (24, 49)>60 years A/H1N1 62 (49, 74) A/H3N2 59 (46, 71) B/Vic 61 (47, 73) B/Yam 62 (49, 74) **Seroprotection** (≥1:40) 18-60 years A/H1N1 98 (91, 99) A/H3N2 96 (89, 99) B/Vic 100 --	**Rank:** II-1 **Quality:** Fair (open-label

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
			(4.7) **Sex :** 46% male **Country:** Canada **Number of participants:** 56 **Inclusion criteria**: Stable health 61 years & older	B/Yam 100 -- >60 years A/H1N1 93 (84, 98) A/H3N2 95 (86, 99) B/Vic 98 (84, 98) B/Yam 100 -- **GMFR** 18-60 years A/H1N1 4.8 (3.3, 7.0) A/H3N2 4.8 (3.5, 6.6) B/Vic 3.4 (2.5, 4.6) B/Yam 3.1 (2.4, 4.0) >60 years A/H1N1 8.9 (5.8, 13.7) A/H3N2 6.9 (4.7, 10.1) B/Vic 6.2 (4.3, 8.8) B/Yam 6.2 (4.6, 8.4)	
Greenberg PD, Robertson AC, Noss JM, et al. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults. *Vaccine*, 2013; 31:770-776. (NCT00988143)	**Name:** Quadrivalent Influenza Vaccine (QIV) **Manufacturer:** Sanofi Pasteur **Dose:** 0.5 mL, IM **Details:** inactive split-virion, 15 µg A/H1N1/ Brisbane/59/2007 A/H3N2/ Uruguay/716 /2007 B/Vic/ Brisbane/60/2008 B/Yam/ Florida/04/2006 **Season:** 2009-2010 **Other vaccine:** IIV3 for 2008-09 or 2009-10 **Details:** B/Vic OR B/Yam, not both	RCT, phase II, open-label, multicentre	**Age:** 18-89 years; mean(SD) 55.5 (17.7) **Sex(male):** 33 **Country:** USA **Number of participants:** **IIV4:** 189 18-60: 94 61+: 96 **IIV3s:** B/Vic: 187 18-60: 93 61+: 94 B/Yam: 188 18-60: 94 61+: 94 **Inclusion criteria**: healthy adults	**Follow-up:** 21-28 days, active **Seroconversion** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) 18-60 years old A/H1N1 60 vs 69 vs 63 A/H3N2 67 vs 79 vs 74 B/Vic 89 vs 71 vs 29* B/Yam 60 vs 40 vs 55 61 years & older A/H1N1 58 vs 42 vs 41 A/H3N2 58 vs 61 vs 53 B/Vic 47 vs 41 vs 11* B/Yam 56 vs 17* vs 33 **Seroprotection** (≥1:40) 18-60 years old A/H1N1 97 vs 96 vs 99 A/H3N2 96 vs 97 vs 95 B/Vic 89 vs 96 vs 65* B/Yam 60 vs 40* vs 55 61 years & older A/H1N1 89 vs 84 vs 85 A/H3N2 94 vs 96 vs 94 B/Vic 81 vs 84 vs 60* B/Yam 90 vs 71* vs 88 **GMFR**	**Rank: I** **Quality:** Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
			18-89 year old adults, continued	18-60 years old A/H1N1 5.2(4.0, 6.8) vs 7.6(5.6, 10.2) vs 7.3(5.4, 10) A/H3N2 7.3(5.5, 9.8) vs 14(10, 19.6) vs 14.3(9.8, 20.8) B/Vic 5.2(4.1, 6.6) vs 6.8(5.3, 8.8) vs 2.2(1.8, 2.6)* B/Yam 6.0(4.7, 7.8) vs 3.2(2.6, 4.0)* vs 5.5(4.1, 7.3) 61 years & older A/H1N1 5.0(4.0, 6.3) vs 2.9(2.3, 3.5) vs 3.2(2.6, 4.1) A/H3N2 5.7(4.3, 7.5) vs 5.2(4.0, 6.8) vs 6.0(4.3, 8.4) B/Vic 3.4(2.8, 4.2) vs 2.8(2.3, 3.4) vs 1.6(1.4, 1.8)* B/Yam 4.1(3.3, 5.1) vs 1.8(1.5, 2.1)* vs 2.6(2.2, 3.2) **Non-inferiority, GMTR** (IIV3 ÷ IIV4) all ages combined A/H1N1 0.89 (0.70, 1.12) A/H3N2 1.15 (0.93, 1.42) B/Vic 1.06 (0.87, 1.31) B/Yam 0.90 (0.70, 1.14)	
Kieninger D, et al. Immunogenicity, reactogenicity and safety of an inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine: a phase III, randomized trial in adults aged ≥18 years. *BMC Infect Dis*, 2013, 13:343. (NCT01204671)	**Name:** FLU Q-QIV **Manufacturer(s):** GlaxoSmithKline **Dose:** 0.5mL (15ug/antigen) **Admin:** IM **Details:** inactive split-virion A/H1N1/ California/7/2009 A/H3N2/ Victoria/210/2009 B/Vic/ Brisbane/60/2008 B/Yam/Florida/4/2006 **Season:** 2010-2011 **Other vaccine:** IIV3 **Name:** Fluarix for 2008-09 **Manufacturer(s):** GlaxoSmithKline **Details:** B/Vic or B/Yam, not both	RCT, phase III, partially-blinded, multicentre	**Age:** 18-92 **Median:** 64 years **Sex:** 43.4% male **Country:** Germany, Spain, Korea, Taiwan, & USA **Number of participants** **IIV4:** 2971 **IIV3:** B/Vic/ 991 B/Yam/ 594 **Inclusion criteria**: healthy adults	**Follow-up:** 21 days **Seroconversion (**IIV4 vs IIV3-B/Vic vs B/Yam) A/H1N1 77.5 vs 77.2 vs 80.2 A/H3N2 71.5 vs 65.8 vs 70.0 B/Vic 58.1 vs 55.4 vs 45.6 (NS) B/Yam 67.1 vs 45.6* vs 59.1 **Seroprotection** (≥1:40) A/H1N1 91.3 vs 91.8 vs 92.7 A/H3N2 96.8 vs 95.9 vs 96.8 B/Vic 98.8 vs 98.5 vs 96.1 B/Yam 99.1 vs 97.9 vs 99.6 **GMFR** A/H1N1 13.7 vs 13.9 vs 14.9 A/H3N2 9.3 vs 7.8 vs 9.5 B/Vic 5.5 vs 5.4 vs 3.6* B/Yam 5.9 vs 3.8* vs 5.8 **GMTR Non-inferiority** (IIV3 ÷ IIV4; upper CI <1.5) A/H1N1 1.07 (0.96, 1.18) A/H3N2 0.98 (0.90, 1.07) B/Vic 0.98 (0.90, 1.07) B/Yam 0.97 (0.89, 1.07) **Seroconverson Non-inferiority** (IIV3 - IIV4; upper CI <10%) A/H1N1 1.1% (-2.0, 4.1) A/H3N2 -3.7% (-7.1, -0.3) B/Vic -2.7% (-7.3, 1.8)	**Rank: I** **Quality:** Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
				B/Yam -2.7% (-7.5, 2.0)	
GSK. Immunogenicity, reactogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine FLU Q-QIV (GSK2282512A) when administered intramuscularly to adults 18 years of age and older. *ClinicalTrials.gov* (NCT01196975) Last updated: 2012- Nov- 21	**Name:** FLU Q-QIV (GSK2282512A) **Manufacturer(s):** GlaxoSmithKline **Dose:** 1 dose **Admin:** IM **Details:** inactive split-virion; 15µg A/H1N1/ California/7/2009 A/H3N2/ Victoria/210/2009 B/Vic/ Brisbane/60/2008 B/Yam/ Florida/4/2006 **Season:** 2010-2011 **Other vaccine:** IIV3 **Name:** FluLaval **Manufacturer(s):** GlaxoSmithKline **Details:** B/Vic OR B/Yam	RCT, phase III, double-blind, multicentre	**Age:** 18+ Mean(SD) 50.1(19.3) **Sex:** 38.7% male **Country:** USA, Canada & Mexico **Number of participants:** **IIV4:** 1246 18-60 years: 775 >60 years: 466 **IIV3:** B/Vic 18-60: 127 >60: 77 B/Yam 18-60: 135 >60: 76 **Inclusion criteria**: healthy adults	**Follow-up:** 21 days **Seroconversion** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) 18-60 years A/H1N1 79.5 vs 75.6 vs 71.8% A/H3N2 70.2 vs 77.9 vs 77.0 B/Vic 67.4 vs 60.3 vs 37.8 B/Yam 64.5 vs 41.7 vs 65.2 >60 years A/H1N1 66.1 vs 51.9 vs 54.7 A/H3N2 60.3 vs 64.9 vs 59.2 B/Vic 35.0 vs 29.9 vs 14.7 B/Yam 38.6 vs 19.5 vs 25.0 **Seroprotection** 18-60 years A/H1N1 98.1 vs 98.4 vs 94.1 A/H3N2 93.1 vs 96.1 vs 96.3 B/Vic 97.4 vs 95.3 vs 79.2 B/Yam 99.9 vs 98.4 vs 99.2 >60 years A/H1N1 86.5 vs 83.1 vs 72.4 A/H3N2 86.7 vs 85.7 vs 82.9 B/Vic 94.6 vs 93.5 vs 78.9 B/Yam 99.8 vs 97.4 vs 96.0 **GMFR** 18-60 years A/H1N1 15.8 (14.1, 17.7) vs 12.0 (9.2, 15.6) vs 11.0 (8.6, 14.1) A/H3N2 9.1 (8.3, 10.1) vs 12.2 (9.3, 15.8) vs 12.0 (9.2, 15.6) B/Vic 9.5 (8.5, 10.5) vs 6.8 (5.3, 8.7) vs 3.4 (2.8, 4.1) B/Yam 7.0 (6.3, 7.7) vs 3.2 (2.6, 3.8) vs 6.3 (5.0, 8.0) >60 years A/H1N1 7.7 (6.8, 8.7) vs 6.0 (4.3, 8.5) vs 6.2 (4.3, 9.0) A/H3N2 6.0 (5.4, 6.8) vs 8.5 (6.1, 11.8) vs 6.2 (4.5, 8.6) B/Vic 3.3 (2.9, 3.6) vs 2.4 (1.9, 3.0) vs 1.8 (1.4, 2.3) B/Yam 3.2 (3.0, 3.6) vs 1.9 (1.5, 2.3) vs 2.3 (1.8, 2.8) **Non-inferiority** Details not reported (data on ClinicalTrials.gov)	**Rank: I** **Quality:** Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
Sanofi Pasteur. Safety and immunogenicity trial among adults administered quadrivalent influenza vaccine. *ClinicalTrials.gov* (NCT01218646) Last updated: 2013-Sept-13 Also: Presentation to NACI by A. Chit, 2013-Feb-18	**Name:** Fluzone Quadrivalent IIV4 **Manufacturer(s):** Sanofi Pasteur **Dose:** 0.5mL , IM **Details:** 15µg/strain A/H1N1/California/07/2009 A/H3N2/Perth/16/2008 B/Vic/Brisbane/60/2008 B/Yam/Florida/4/2006 **Season:** 2010-2011 **Other vaccines:** IIV3 **Name:** Fluzone & investigational **Manufacturer(s):** Sanofi Pasteur **Details:** 1) FluZone for 2010-11 with A strains above & B/Vic only; 2) Investigational with A strains above & B/Yam only	RCT, phase III, double-blind, multi-centre	**Age:** 65+ years Mean(SE) 72.6 (5.6) **Sex :** 45% male **Country:** USA **Number of participants:** **IIV4:** 220 **IIV3:** 1) FluZone,B/Vic: 219 2) B/Yam: 225 **Exclusion criteria**: Uncontrolled chronic disease, current alcohol or drug abuse	**Follow-up:** 21 days **Seroconversion** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) A/H1N1 65.9 vs 66.7 vs 72.9 A/H3N2 69.1 vs 55.7 vs 62.9 B/Vic 28.6 vs 18.7 vs 8.6* B/Yam 33.2 vs 9.1* vs 31.2 **Seroprotection** (≥1:40) A/H1N1 91.4 vs 91.3 vs 91.8 A/H3N2 100 vs 95.4 vs 95.9 B/Vic 77.7 vs 71.7 vs 60.2 B/Yam 73.2 vs 46.1 vs 67.4 **GMFR** A/H1N1 10.6 vs 10.8 vs 12.8 A/H3N2 9.6 vs 6.0 vs 8.5 B/Vic 2.7 vs 2.0 vs 1.5 B/Yam 3.0 vs 1.5 vs 2.8 **GMT Non-inferiority** (Data: A. Chit) A/H1N1 0.85 (0.67, 1.09) A/H3N2 1.55 (1.25, 1.92) B/Vic 1.27 (1.05, 1.55) – not superior B/Yam 1.11 (0.90, 1.37) - superior **Seroconversion Non-inferiority** (Data: A Chit) A/H1N1 -3.9 (-11.5, 3.6) - inferior A/H3N2 9.8 (2.0, 17.2) – not inferior B/Vic 9.9 (2.0, 17.7) - superior B/Yam 2.0 (-6.7, 10.6) - superior	**Rank: I** **Quality:** Good
Schneider, Sprenger, Hoepelman, et al. Antibody response to tetravalent influenza subunit vaccine in patients infected with human immunodeficiency virus type 1. *Int J Antimicrob Agents* 1996; 6:195-200.	**Name:** Tetravalent Influenza Vaccine **Manufacturer(s):** Solvay-Duphar **Dose:** 0.5 mL **Admin:** IM. **Details:** 15 µg A/H1N1/Singapore/ 6/86 A/H3N2/ Beijing/353/ 89 B/Yam/Panama/45/90 B/Vic/Beijing/I/87 **Season:** 1991-1992 **Placebo/other vaccine:** NA	Non-randomized clinical trial	**Age – mean (range):** HIV: 39 (24-64) Control: 35(24-42) **Sex(% male):** HIV: 94.4 Control: 73.7 **Country:** Netherlands **Setting:** clinic **Number:** HIV positive: 54 Healthy Control**:** 19	**Follow-up:** 15-37 days **HI titres:** Median (mean)-pre and post immunization Healthy adults A/H1N1 5 – 9 (11 – 42) A/H3N2 5 – 24 (11 – 93) B/Vic 12 – 51 (52 – 213) B/Yam 5 – 12 (9 – 58) HIV-positive A/H1N1 5 – 192 (12 – 398) A/H3N2 5 – 106 (7 – 181) B/Vic 68 – 626 (62 – 1583) B/Yam 8 – 96 (24 – 634)	**Rank:** II-1 **Quality:** Fair

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
Inactivated – Children					
Langley J, Martinez CA, Chatterjee A, et al. Immunogenicity and safety of an inactivated quadrivalent influenza vaccine candidate: a phase III randomized controlled trial in children. *J Infect Dis* 2013; 208:544-553. (NCT01198756) Langley, continued	**Name:** Quadrivalent Influenza Vaccine (IIV4) **Manufacturer(s):** GlaxoSmithKline **Dose:** 0.5 mL **Admin:** IM **Details:** inactive split-virion, 15 µg A/H1N1/ Brisbane/59/2007 A/H3N2/ Uruguay/716 /2007 B/Vic/ Brisbane/ 60/2008 B/Yam/ Florida/04/2006 **Season:** 2009-2010 **Comparator vaccine:** Trivalent Influenza Vaccine **Manufacturer(s):** GlaxoSmithKline **Details:** same as above, with either B/Vic or B/Yam	RCT, phase III, double-blind, multi-centre	**Age:** 3-17 years Mean (SD): 8.9 (4.2) **Sex:** 51.5% male **Country:** Canada, United States, Mexico, Spain, and Taiwan **Number of participants** **IIV4:** 932; **IIV3:** B/Vic/ 929 B/Yam/ 932 **Inclusion criteria**: stable health, 3-17 years	**Follow-up:** 28 days (after final) **Seroconversion** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) A/H1N1 84.4 (81.8, 86.7) vs 86.8 (84.3, 89.0) vs 85.5 (83.0, 87.8) A/H3N2 70.1 (66.9, 73.1) vs 67.8 (64.6, 70.9) vs 69.6 (66.5, 72.7) B/Vic 74.5 (71.5, 77.4) vs 71.5 (68.4, 74.5) vs 29.9 (26.9, 33.1)* B/Yam 75.2 (72.2, 78.1) vs 41.3 (38.0, 44.6)* vs 73.4 (70.4, 76.3) **Seroprotection** (≥1 40) A/H1N1 96.8 (95.4, 97.9) vs 97.4 (96.1, 98.3) vs 96.6 (95.2, 97.7) A/H3N2 92.9 (91.0, 94.5) vs 92.8 (90.8, 94.4) vs 93.3 (91.4, 94.8) B/Vic 95.4 (93.8, 96.7) vs 96.3 (94.9, 97.5) vs 73.3 (70.3, 76.2)* B/Yam 99.0 (98.1, 99.5) vs 92.4 (90.5, 94.1)* vs 99.4 (98.7, 99.8) **GMFR** A/H1N1 12.3 (11.3, 13.4) vs 13.3 (12.3, 14.4) vs 14.4 (13.3, 15.7) A/H3N2 7.9 (7.3, 8.6) vs 7.4 (6.8, 8.0) vs 7.8 (7.2, 8.5) B/Vic 10.1 (9.2, 11.1) vs 9.5 (8.6, 10.5) vs 2.6 (2.5, 2.8)* B/Yam 8.9 (8.1, 9.7) vs 3.4 (3.1, 3.6)* vs 8.8 (8.1, 9.6) **GMTR Non-inferiority** (IIV3 ÷ IIV4) A/H1N1 1.15 (1.06, 1.25) A/H3N2 0.99 (0.92, 1.07) B/Vic 0.96 (0.87, 1.07) B/Yam 1.08 (0.99, 1.16) **Seroconverson Non-inferiority** (IIV3 - IIV4) A/H1N1 1.8% (-1.0, 4.8) A/H3N2 -1.4% (-5.0, 2.4) B/Vic -3.0% (-7.2 , 1.1) B/Yam -1.8% (-5.9 , 2.3)	**Rank I** **Quality: Good**
		Subset: open-label (IIV4 only)	**Age:** 6-35 months Mean (SD): 21 (8.7) **Sex:** 52.5% male	**<u>Open-label (IIV4 ONLY)</u>** **Seroconversion** A/H1N1 84.9 (80.0, 89.1)	

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
			Number of participants: **IIV4:** 301 **Inclusion criteria:** Stable health 6-35 months	A/H3N2 73.0 (67.1, 78.3) B/Vic 84.6 (79.6, 88.7) B/Yam 93.8 (90.2, 96.4) **Seroprotection** ≥1:40) A/H1N1 89.6 (85.2, 93.0) A/H3N2 74.5 (68.8, 79.7) B/Vic 88.0 (83.4, 91.7) B/Yam 96.5 (93.5, 98.4) **GMFR** A/H1N1 12.0 (10.5, 13.6) A/H3N2 10.9 (9.6, 12.4) B/Vic 14.6 (12.8, 16.6) B/Yam 24.9 (22.0, 28.3)	
Domachowske BJ, Pankov-Culot H, Bautista M, et al. A randomized trial of candidate inactivated quadrivalent influenza vaccine versus trivalent influenza vaccines in children aged 3–17 years. *J Infect Dis* 2013; 207:1878-1887. (NCT01196988)	**Name:** Quadrivalent Influenza Vaccine (IIV4) **Manufacturer(s):** GlaxoSmithKline **Dose:** 0.5 mL (primed: 1 dose; unprimed: 2 doses given 28 days apart) **Admin:** IM **Details**: inactive split-virion, 15 µg A/H1N1/California/7/2009 A/H3N2/ Victoria/210/2009) B/Vic/ Brisbane/60/2008 B/Yam/ Brisbane/3/2007 **Season:** 2010-2011 **Comparator vaccine:** Trivalent Influenza Vaccine **Name:** Fluarix **Manufacturer(s):** GlaxoSmithKline **Details:** same as above, with inclusion of <u>either</u> B/Vic or B/Yam	RCT, phase III, double-blind, multicenter	**Age:** 3-17 years, mean: 7.8 years; **Sex (% male):** 51.8; **Country:** Czech Republic, France, Germany, Philippines, and USA **Number of participants** **IIV4:** 915; **IIV3:** 1823 B/Vic/ 912 B/Yam/ 911 **Inclusion criteria**: healthy children 3-17 years	**Follow-up:** 28 days after final **Seroconversion** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) A/H1N1 91.4 (89.2, 93.3) vs 89.9 (87.6, 91.8) vs 91.6 (89.5, 93.5) A/H3N2 72.3 (69.0, 75.4) vs 70.7 (67.4, 73.8) vs 71.9 (68.6, 75.0) B/Vic 70.0 (66.7, 73.2) vs 68.5 (65.2, 71.6) vs 29.6 (26.5, 32.9)* B/Yam 72.5 (69.3, 75.6) vs 37.0 (33.7, 40.5)* vs 70.8 (67.5, 73.9) **Seroprotection** (≥1 40) A/H1N1 96.6 (95.1, 97.7) vs 96.9 (95.5, 98.0) vs 97.1 (95.7, 98.2) A/H3N2 98.0 (96.7, 98.8) vs 97.8 (96.5, 98.7) vs 96.5 (95.0, 97.7) B/Vic 97.3 (96.0, 98.3) vs 96.6 (95.1, 97.7) vs 79.8 (76.8, 82.5)* B/Yam 99.2 (98.4, 99.7) vs 94.4 (92.6, 95.9)* vs 99.6 (98.9, 99.9) **GMFR** A/H1N1 18.0 (16.6, 19.5) vs 17.4 (16.0, 18.8) vs 19.2 (17.7, 20.9) A/H3N2 7.9 (7.3, 8.6) vs 7.2 (6.7, 7.8) vs 7.5 (6.9, 8.1) B/Vic 7.9 (7.3, 8.6) vs 7.9 (7.2, 8.6) vs 2.7(2.5, 2.9)* B/Yam 7.4 (6.8, 8.0) vs 2.9 (2.7, 3.1*) vs 7.6(7.0, 8.3) **GMTR Non-inferiority** (upper CI for GMTR)	**Rank: I** **Quality:** Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
				A/H1N1 1.15 A/H3N2 1.05 B/Vic 1.09 B/Yam 1.18 IIV4 vs IIV3 of alternate B lineage (lower CI) B/Vic 2.36 B/Yam 2.63 **Seroconversion Non-inferiority** (upper CI for seroconversion) A/H1N1 1.86 A/H3N2 2.86 B/Vic 2.98 B/Yam 2.65 IIV4 vs IIV3 of alternate B lineage (lower CI limit) B/Vic 30.87 B/Yam 35.78	
Domanchowske, continued		Subset: open-label (IIV4)	**Age:** 6-35 months, mean: 1.4 years **Sex (% male):** 57.4 **Number of participants**: 3027 **IIV4:** 277 **Inclusion criteria**: healthy children 6-35 months	**Seroconversion** (4-fold rise) **Open-label (IIV4 ONLY)** A/H1N1 78.0 (72.1, 83.2) A/H3N2 68.5 (62.1, 74.5) B/Vic 68.1 (61.7, 74.1) B/Yam 82.3 (76.8, 87.0) **Seroprotection** (≥1 40) A/H1N1 79.9 (74.2, 84.9) A/H3N2 72.2 (66.0, 77.9) B/Vic 71.4 (65.1, 77.1) B/Yam 90.6 (86.1, 94.0) **GMFR** A/H1N1 11.7 (10.2, 13.4) A/H3N2 10.4 (9.0, 11.9) B/Vic 9.7 (8.5, 11.2) B/Yam 12.9 (11.0, 15.3)	**Rank:** **II-1** **Quality:** Good
Greenberg DP, Robertson A, Landolfi VA, et al. Safety and immunogenicity of an inactivated quadrivalent	**Name:** Quadrivalent influenza vaccine **Manufacturer:** Sanofi Pasteur **Dose:** 30µg HA/strain/mL (6-35 mon: 0.25mL; 36 mon-8 yrs: 0.5mL; primed 1 dose, unprimed 2 doses)	RCT, phase III, observer blinded, multicentre	**Age:** 6 mon-8 yrs Mean(SE) 4.1 (2) **Sex :** 50.6% male **Country:** USA **Number of participants:**	**Follow-up:** 28 days after final **Seroconversion** Not reported **Seroprotection** (≥1 40) A/H1N1 98.6 (98.1, 99.1) vs 98.6 (97.3, 99.4) vs 98.0 (96.5, 99.0) A/H3N2 99.7 (99.3, 99.9) vs 99.1 (98.0, 99.7) vs 99.5 (98.5, 99.9)	**Rank**: **I** **Quality**: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
influenza vaccine in children 6 months to 8 years of age. *Ped Infect Dis J.* 2014; Jan 19: ahead of print *ClinicalTrials.gov*. (NCT01240746)	**Admin:** IM **Details:** inactive split-virion; A/H1N1/ California/7/09 A/H3N2/ Victoria/210/09 B/Vic/ Brisbane/60/08 B/Yam/ Florida/04/06 **Season:** Nov 2010- June 2012 **Other vaccine:** same as above, with inclusion of either B/Vic (licensed 2010-11 IIV3) or B/Yam (investigational IIV3)		**IIV4:** 2902 **IIV3:** B/Vic: 736 (Bris) B/Yam: 725 (Fl) **Inclusion criteria**: Generally healthy	B/Vic 78.6 (76.9, 80.3) vs 71.9 (68.1, 75.6) vs 33.7 (29.9, 37.7)* B/Yam 71.6 (69.7, 73.4) vs 29.1 (25.4, 33.0)* vs 69.6 (65.7, 73.2) **GMFR** Not reported **GMTR Non-inferiority** A/H1N1 1. 03 (0.93, 1.14) A/H3N2 0.99 (0.91, 1.08) B/Vic 1.34 (1.20, 1.50) B/Yam 1.06 (0.94, 1.18) IIV4 vs IIV3 of alternate B lineage (superior if LCI >1.50) B/Vic 4.42 (3.94, 4.97) B/Yam 3.79 (3.39, 4.23) **Seroconversion Non-inferiority** A/H1N1 0.9% (-0.9, 3.0) A/H3N2 3.8 (1.4, 6.3) B/Vic 10.7 (6.4, 15.1) B/Yam 2.0 (-2.2, 6.4) **IIV4 vs IIV3 of alternate B lineage** (superior if LCI >10%) B/Vic 51.8% (47.9, 55.3) B/Yam 48.2 (44.3, 51.6)	
Jain VK, Rivera L, Zaman K, et al. Vaccine for prevention of mild and moderate-to-severe influenza in children. *NEJM* 2013*; 369(26)*:2481-2491. *ClinicalTrials.gov*. (NCT01218308)	**Name:** Quadrivalent influenza vaccine GSK2282512A **Manufacturer:** GlaxoSmithKline **Dose:** 15 µg, 0.5 mL (primed: 1 dose; unprimed: 2 doses) **Admin:** IM **Details:** inactive split-virion ; A/H1N1/ California/7/09 A/H3N2/ Victoria/210/09 B/Vic/ Brisbane/60/08 B/Yam/ Florida/4/06 **Season:** Dec 2010-Oct 2011 **Other vaccine:** Havrix (Hepatitis A vaccine), 0.5 mL/dose	RCT, phase III, double-blind, multicentre	**Age:** 3-8 years; mean(SD): 5.4 (1.65) **Sex:** 51.7% male **Country:** Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Phillipines, Turkey, and Thailand **Setting:** multicentre **Number of participants** **Vaccine:** 544 **Hepatitis A:** 163	**Follow-up**: 28 days **Seroconversion** (IIV4 vs Havrix) A/H1N1 95.8 vs 0.9% A/H3N2 84.2 vs 1.7 B/Vic 93.0 vs 2.6 B/Yam 95.2 vs 0.9 **Seroprotection** (≥1:40) A/H1N1 98.7 vs 32.2% A/H3N2 97.4 vs 51.6 B/Vic 96.9 vs 31.7 B/Yam 98.9 vs 38.5 **GMFR** A/H1N1 20.8 (19.0, 22.8) vs 1.0 (0.9, 1.2)* A/H3N2 10.9 (9.8, 12.1) vs 1.0 (0.9, 1.2)* B/Vic 17.5 (16.0, 19.1) vs 1.1 (1.0, 1.3)* B/Yam 22.3 (20.1, 24.8) vs 1.0 (1.0, 1.1)*	**Rank**: **I** **Quality**: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
			Inclusion criteria: healthy children		
Live Attenuated Influenza Vaccine (LAIV) – Adults					
MedImmune. A randomized, partially blind active controlled study to evaluate the immunogenicity of MEDI8662 in adults 18-49 years of age. *ClinicalTrails.gov* (NCT00952705) Last updated: 2011-Dec-09	**Name:** Q/LAIV-BFS (MEDI8662) **Manufacturer(s):** MedImmune **Dose:** 0.2 mL (single dose, 1 nostril) **Admin:** nasal spray **Details:** cold-adapted, attenuated A/H1N1/ South Dakota/6/2007 A/H3N2/ Uruguay/716/2007 B/Vic/ Malaysia/2506/2004 B/Yam/ Florida/4/2006 **Season:** 2010-2011 **Other vaccine:** FluMist **Details:** LAIV3, 0.2 mL; two formulations – one with B/Vic and one with B/Yam	RCT, phase III, double-blind, multicentre	**Age:** 18-49 years; mean(SD): 33.9 (9.3) **Sex (% male):** 42.4 **Country:** USA **Number of participants:** **LAIV4:** 1169 **LAIV3:** B/Vic: 288 B/Yam: 290 **Inclusion criteria**: healthy adults	**Follow-up:**: 21-28 days **Seroconversion** (LAIV4 vs LAIV3 – comparisons to both LAIV3 vaccines for A strains, but only to matched B lineage) A/H1N1 5.4 vs 6.5% A/H3N2 4.7 vs 4.8 B/Vic 7.5 vs 10.3 B/Yam 8.2 vs 9.5 **Seroprotection** (≥1:32) A/H1N1 25.3 vs 22.5% A/H3N2 25.8 vs 23.4 B/Vic 55.5 vs 52.7 B/Yam 78.7 vs 75.2 **Non-inferiority, GMTR** (IIV3 ÷ IIV4) A/H1N1 0.95 (0.87, 1.03) A/H3N2 0.93 (0.85, 1.00) B/Vic 0.97 (0.87, 1.10) B/Yam 0.90 (0.79, 1.02)	**Rank**: **I** **Quality**: Good
Block LS, Yi T, Sheldon E, et al. A randomized, double-blind noninferiority study of quadrivalent live attenuated influenza vaccine in adults. *Vaccine* 2011; 29:9391-9397. (NCT00860067)	**Name:** Quadrivalent Live Attenuated Influenza Vaccine **Manufacturer(s):** MedImmune **Dose:** 0.2 mL (single dose) **Admin:** nasal spray **Details:** cold-adapted, attenuated A/H1N1/ South Dakota/6/2007 A/H3N2/ Uruguay/716/2007 B/Vic/ Malaysia/2506/2004 B/Yam/ Florida/4/2006 **Season:** 2009-2010 **Other vaccine:** LAIV3	RCT, phase III, double-blind, multicentre	**Age:** 18-49 years; median: 32.0 **Sex (% male):** 44.8 **Country:** USA **Setting:** 18 clinical sites **Number of participants:** **LAIV4:** 1180 **LAIV3:** B/Yam: 292	**Follow-up:** 1 month **Seroconversion** ((LAIV4 vs LAIV3 – comparisons to both LAIV3 vaccines for A strains, but only to matched B lineage) A/H1N1 5.2 vs 5.3% A/H3N2 5.0 vs 4.2 B/Vic 12.3 vs 11.8 B/Yam 10.0 vs 10.3 **Seroprotection** (≥1:32) A/H1N1 16.0 vs 16.9% A/H3N2 21.1 vs 22.6 B/Vic 74.6 vs 77.4 B/Yam 65.3 vs 64.3 **GMTR**	**Rank: I** **Quality:** Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95 CI) *Significant difference	Quality of Evidence
	Name: FluMist **Details:** LAIV3 - one with B/Vic and one with B/Yam		B/Vic: 297 **Inclusion criteria**: healthy adults	A/H1N1 1.16 vs 1.14 A/H3N2 1.13 vs 1.12 B/Vic 1.37 vs 1.27 B/Yam 1.40 vs 1.35 **Non-inferiority, GMTR** (IIV3 ÷ IIV4) A/H1N1 1.09 (1.01, 1.18) A/H3N2 1.05 (0.96, 1.14) B/Vic 0.92 (0.82, 1.03) B/Yam 1.10 (0.97, 1.25)	
LAIV – Children					
Block LS, Falloon J, Hirschfield AJ, et al. Immunogenicity and safety of a quadrivalent live attenuated influenza vaccine in children. *Pediatr Infect Dis J* 2012; 31:745-751. (NCT01091246)	**Name:** Quadrivalent LAIV **Manufacturer(s):** MedImmune **Dose:** 0.2 mL 2–8 years: 2 doses 9–17 years: 1 dose **Admin:** nasal spray **Details:** cold-adapted, attenuated A/H1N1/ South Dakota/6/2007 A/H3N2/ Uruguay/716/2007 B/Vic/ Malaysia/2506/2004 B/Yam/ Florida/4/2006 **Season:** 2010-2011 **Other vaccine:** LAIV3 **Name:** FluMist **Details:** B/Yam OR B/Vic	RCT, phase III, double blind, multi-centre	**Age:** 2-17 years mean(SD): 6.74 (3.8) **Sex (% male):** 49.2 **Country:** USA **Number of participants:** **LAIV4:** 1350 **LAIV3:** B/Yam: 448 B/Vic: 450 **Inclusion criteria**: healthy children	**Follow-up:** 28 days after last dose **Seroconversion** (LAIV4 vs LAIV3 - combined except for unmatched) A/H1N1 6.3 vs 8.2 A/H3N2 3.9 vs 3.6 B/Vic 39.1 vs 38.4 vs 17.2 B/Yam 43.4 vs 44.9 vs 14.2 **Seroprotection** (≥1:32) A/H1N1 43.1 vs 43.8 A/H3N2 55.7 vs 55.4 B/Vic 65.5 vs 66.6 B/Yam 76.5 vs 81.6 **Non-inferiority, GMTR** (IIV3 ÷ IIV4) A/H1N1 1.07 (0.98, 1.16) A/H3N2 1.04 (0.94, 1.14) B/Vic 1.05 (0.93, 1.18) B/Yam 1.21 (1.07, 1.37)	**Rank: I** **Quality: Good**

APPENDIX G: SUMMARY OF EVIDENCE RELATED TO SAFETY OF QUADRIVALENT INFLUENZA VACCINES

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95 CI) * Significant difference	Quality of Evidence
Inactivated Influenza Vaccines – Adults					
Beran J, Peeters M, Dewe W, et al. Immunogenicity and safety of quadrivalent versus trivalent inactivated influenza vaccine: a randomized, controlled trial in adults. *BMC Infect Dis 2013*; 13:224-234. (NCT00714285)	**Name:** Quadrivalent Influenza Vaccine (IIV4) **Manufacturer(s):** GlaxoSmithKline **Dose:** 0.5 mL **Admin:** IM **Details:** inactive split-virion 15µg: A/H1N1/Solomon Islands/03/2006 A/H3N2/ Wisconsin/67/2005 B/Vic/ Malaysia/2506/2004 B/Yam/ Jiangsu/10/2003 **Season:** 2007-2008 **Other vaccine:** Trivalent Influenza Vaccine (IIV3) **Manufacturer(s):** GlaxoSmithKline **Details:** excluding B/Yam	RCT, phase I/II, single-centre, single-blind	**Age:** 18-59 years mean(SD): 37.6 (12.3) **Sex (% male):** 40 **Country:** Czech Republic **Number of participants in no adjuvant vaccines:** IIV4: 104 IIV3: 105	**Follow-up**: 7 days: solicited AEs-active 21 days: unsolicited AEs and SAEs-passive 6 months: potential immune-mediated diseases - passive **Reactogenicity** IIV4 vs IIV3 Pain 72.4 (62.8, 80.7) vs 49.5 (39.6, 59.5)* Redness 2.9 (0.6, 8.1) vs 1.0 (0 , 5.2) Swelling 2.9 (0.6, 8.1) vs 1.9 (0.2, 6.7) Fever (>37^{0}C) 1.0 (0, 5.2) vs 1.0 (0, 5.2) Fatigue 30.5 (21.9, 40.2) vs 31.4 (22.7, 41.2) Nausea 7.6 (3.3, 14.5) vs 7.6 (3.3, 14.5) Chills 3.8 (1.0, 9.5) vs 3.8 (1.0, 9.5) Myalgia 16.2 (9.7, 24.7) vs 3.8 (1.0, 9.5)* Headache 22.9 (15.2, 32.1) vs 21.9 (14.4, 31.0) Arthralgia 5.7 (2.1, 12.0) vs 10.5 (5.3, 18.0) Any 79.0(70.0, 86.4) vs 67.6(57.8, 76.4)* **Serious adverse events** No vaccine-related SAE	**Rank**: I **Quality: Good**
	Name: Low Dose Quadrivalent Influenza Vaccine (LD IIV4-AS) **Manufacturer(s):** GlaxoSmithKline **Dose:** 0.5 mL **Admin:** IM, **Details:** inactive split-virion, 5µg HA/strain with 62.5 µL of AS03 A/H1N1/Solomon Islands/03/2006 A/H3N2/ Wisconsin/67/2005 B/Vic/ Malaysia/2506/2004 B/Yam/ Jiangsu/10/2003 **Season:** 2007-2008		**Number of participants in adjuvanted groups:** LD IIV4-AS: 104 LD IIV3-AS: 104 **Inclusion criteria**: healthy adults	**Reactogenicity - IIV4-AS vs IIV3-AS** Pain 76.0 (66.6, 83.8) vs 70.5 (60.8, 79.0) Redness 5.8 (2.1, 12.1) vs 4.8 (1.6, 10.8) Swelling 3.8 (1.1, 9.6) vs 6.7 (2.7, 13.3) Fever (>37^{0}C) 2.9 (0.6, 8.2) vs 1.9 (0.2, 6.7) Fatigue 45.2 (35.4, 55.3) vs 34.3 (25.3, 44.2) Nausea 9.6 (4.7, 17.0) vs 7.6 (3.3, 14.5) Shivers/chills 9.6 (4.7, 17.0) vs 8.6 (4.0, 15.6) Myalgia 38.5 (29.1, 48.5) vs31.4 (22.7, 41.2) Headache 31.7 (22.9, 41.6) vs 24.8 (16.9, 34.1) Arthralgia 24.0 (16.2, 33.4) vs 12.4 (6.8, 20.2)* Any 86.5 (78.4, 92.4) vs 77.1 (67.9, 84.8)*	

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95 CI) * Significant difference	Quality of Evidence
	Comparator vaccine: LD IIV3-AS03 **Manufacturer(s):** GlaxoSmithKline **Details:** excluding B/Yam			**Serious adverse events** IIV3 - 1 event (haemorrhage after tonsillectomy) – unrelated	
GSK. Immunogenicity, reactogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine FLU Q-QIV (GSK2282512A) when administered intramuscularly to adults 18 years of age and older. *ClinicalTrials.gov* (NCT01196975) Last updated: 2012- Nov- 21	**Name:** GSK2282512A **Manufacturer(s):** GlaxoSmithKline **Dose:** 1 dose, 0.5mL **Admin:** IM **Details:** inactive split-virion; 15mcg A/H1N1/ California/7/2009 A/H3N2/ Victoria/210/2009 B/Vic/ Brisbane/60/2008 B/Yam/ Florida/4/2006 **Season:** 2010-2011 **Other vaccine:** IIV3 **Name:** FluLaval **Manufacturer(s):** GlaxoSmithKline **Details:** IIV3-B/Vic -OR- IIV3-B/Yam	RCT, phase III, double-blind, multicentre	**Age:** 18+ Mean(SD) 50.1(19.3) **Sex:** 38.7% male **Country:** USA, Canada & Mexico **Number of participants:** **IIV4:** 1246 849 18-64 years 397 65+ years **IIV3:** B/Vic/ 204 (136+68) B/Yam/ 211 (144+68) **Inclusion criteria**: healthy adults	**Follow-up:** 3 days (solicited symptoms); 28 days (unsolicited AEs and SAEs) **Reactogenicity** (IIV4 vs IIV3-combined) Pain 59.5 vs 42.9* Redness 1.7 vs 0 Swelling 0 vs 0 Fever (>37^{0}C) 1.5 vs 0 Malaise 21.5 vs 19.3 Shivers/chills 8.8 vs 6.8 Myalgia 0.8 vs 0.9 Headache 21.5 vs 21.2 Arthralgia 7.0 vs 7.5 **Serious adverse events** Not reported	**Rank: I** **Quality: Good**
Kieninger D, Sheldon E, Lin WY, et al. Immunogenicity, reactogenicity and safety of an inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine: a phase III, randomized trial in adults aged ≥18 years. *BMC Infect Dis*, 13:343. (NCT01204671)	**Name:** FLU Q-QIV **Manufacturer(s):** GlaxoSmithKline **Dose:** 0.5mL (15ug/antigen) **Admin:** IM **Details:** inactive, split-virion A/H1N1/ California/7/2009 A/H3N2/ Victoria/210/2009 B/Vic/ Brisbane/60/2008 B/Yam/Florida/4/2006 **Season:** 2010-2011 **Other vaccine:** IIV3 **Name:** Fluarix for 2008-09 **Manufacturer(s):** GlaxoSmithKline **Details:** B/Vic or B/Yam	RCT, phase III, partially-blinded, multicentre	**Age:** 18-92 years **Median:** 64 **Sex:** 43.4% male **Country:** Germany, Spain, Korea, Taiwan, USA **Number of participants** **IIV4:** 2971 **IIV3:** B/Vic/ 991 B/Yam/ 594 **Inclusion criteria**: healthy adults	**Follow-up:** 7 days (solicited events)-active 21 days (AE)-passive 180 days (SAE)-passive **Reactogenicity** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) 1+ event: 12.5 vs 13.7 vs 15.1 1+ grade 3 events: 1.3 vs 0.7 vs 0.3 **AEs:** to day 20: 6.4 vs 5.9 vs 7.7 to day 180: 13.5 vs 22.5 vs 23.4 **Serious adverse events:** 21 days: 0.5 vs 0.6 vs 0.2 180 days: 2.3 vs 2.6 vs 0.1 180 days: 9 vs 3 vs 0 fatal events - unrelated to vaccine	**Rank**: **I** **Quality**: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95 CI) * Significant difference	Quality of Evidence
Greenberg PD, Robertson AC, Noss JM, et al. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults. *Vaccine* 2013; 31:770-776. (NCT00988143)	**Name:** Quadrivalent Influenza Vaccine (QIV) **Dose:** 0.5 mL **Admin:** IM **Details:** inactive split-virion, 15 µg A/H1N1/ Brisbane/59/2007 A/H3N2/ Uruguay/716 /2007 B/Vic/ Brisbane/60/2008 B/Yam/ Florida/04/2006 **Season:** 2009-2010 **Other vaccine:** Trivalent inactivated; **Details:** B/Vic (2009-10 IIV3) or B/Yam (2008-09 IIV3)	RCT, phase II, open-label, multicentre	**Age:** 18-89 years; mean(SD) 55.5 (17.7) **Sex(male):** 33 **Country:** USA **Number of participants:** **IIV4:** 189 **IIV3:** B/Vic 187 B/Yam 188 **Inclusion criteria**: healthy adults	**Follow-up:** 28 days, active **Reactogenicity:** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) Pain 47.4 vs 52.1 vs 43.2 Redness 1.1 vs 1.6 vs 1.6 Swelling 0.5 vs 3.2 vs 1.1 Fever (>37^{0}C) 0 vs 0.5 vs 0.5 Fatigue 10.5 vs 14.7 vs 12.1 Shivers/chills 2.6 vs 5.3 vs 3.2 Myalgia 23.7 vs 25.3 vs 16.8 Headache 15.8 vs 18.4 vs 18.0 **Unsolicited AEs** Any 17.4 vs 23.7 vs 24.2 **Serious adverse events** Two events: 1 IIV4 – benign paroxysmal positional vertigo & unspecified chest pain 12 days post vaccination- unrelated 1 IIV3 – unspecified GI bleeding 26 days post vaccination - unrelated to study vaccine	**Rank**: I **Quality**: Good
GSK. A Phase IIIA Study of immunogenicity and safety of GSK Biologicals' quadrivalent split virion influenza vaccine FLU-Q-QIV in adults aged 18 years and older. *ClinicalTrials.gov* (NCT01440387) Last updated: 2013-Sept-05)	**Name:** Flulaval Quadrivalent **Manufacturer(s):** GSK **Dose:** 0.5mL, IM **Details:** 15µg/strain A/H1N1/California/07/2009 A/H3N2/Victoria/210/2009 B/Vic/Brisbane/60/2008 B/Yam/Florida/4/2006 **Season:** Not stated **Other vaccines:** NA	Phase IIIA, open label efficacy trial	**Age:** 18-60 years Mean(SD) 40.9 (13.3) **Sex :** 39% male **Country:** USA **Number of participants:** 56	**Follow-up:** 21 days (solicited events); then passive **Reactogenicity** Fever 0 Malaise 17.8 Myalgia 37.5 Arthralgia 12.5 Headache 19.6 Pain 73.2 Redness 1.8 Swelling 1.8 **Adverse events:** 6 (Upper respiratory tract infections) **Serious Adverse Events**: 0	**Rank: II** **Quality:** Good
			Age: >60 years Mean(SD) 68.6 (4.7) (5.6) **Sex :** 46% male **Country:** USA **Number of participants:** 56	**Reactogenicity** Fever 0 Malaise 8.9 Myalgia 10.7 Arthralgia 5.4 Headache 8.9 Pain 33.9 Redness 0	

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95 CI) * Significant difference	Quality of Evidence
				Swelling 3.6 **Adverse event** 3 (Upper respiratory tract infections) **Serious Adverse Events**: 0	
Sanofi Pasteur. Safety and immunogenicity trial among adults administered quadrivalent influenza vaccine. *ClinicalTrials.gov* (NCT01218646) Last updated: 2013-Sept-13	**Name:** Fluzone Quadrivalent IIV4 **Manufacturer(s):** Sanofi Pasteur **Dose:** 0.5mL , IM **Details:** 15µg/strain A/H1N1/California/07/2009 A/H3N2/Perth/16/2008 B/Vic/Brisbane/60/2008 B/Yam/Florida/4/2006 **Season:** 2010-2011 **Other vaccines:** IIV3 **Name:** Fluzone & investigational **Manufacturer(s):** Sanofi Pasteur **Details:** FluZone for 2010-11 (A strains above & B/Vic); Investigational with A strains above & B/Yam	RCT, phase III, double-blind, multi-centre	**Age:** 65+ years Mean(SD) 72.6 (5.6) **Sex :** 45% male **Country:** USA **Number of participants:** **IIV4:** 220 **IIV3:** Fluzone- B/Vic/ 219 B/Yam/ 225	**Follow-up:** 21 days (solicited events); then passive **Reactogenicity** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) Fever 1.3 vs 0 vs 0.8 Malaise 10.6 vs 6.2 vs 11.6 Myalgia 18.2 vs 18.2 vs 14.2 Pain 32.6 vs 28.6 vs 23.1 Erythema 2.7 vs 1.3 vs 1.3 Swelling 1.8 vs 1.3 vs 0 Headache 13.3 vs 11.6 vs 11.6 **Serious adverse events:** IIV3-B/Vic: 2 (retinal detachment 16 days post-vaccination & cellulitis secondary to cat bite 9 days post-vaccination) IIV3-B/Yam: 1 (malignant melanoma diagnosed 7 days post vaccination) IIV4 – none None were considered related to study vaccine (A. Chit) Relatedness not documented (clinicaltrials.gov database)	**Rank**: **I** **Quality**: Good
	Name: Fluzone 2010-11 (IIV3) **Manufacturer**: Sanofi Pasteur **Dose:** 0.5mL, IM **Details**: 15µg/strain A/H1N1/California/07/2009 A/H3N2/Perth/16/2008 B/Vic/Brisbane/60/2008 **Season**: 2010-11	Open label	**Age:** 18-64 years Mean (SD) 46 (11.6) **Sex**: 58% male **Country**: USA **Number of participants:** IIV3 – B/Vic/ 64	**Follow-up:** 21 days (solicited events); then passive **Reactogenicity** Pain 48.4 Erythema 4.7 Swelling 7.8 Fever 3.1 Headache 25.0 Malaise 25.0 Myalgia 34.4 **Serious adverse events:** IIV3-B/Vic/ 0	
Pépin S, Donazzolo Y, Jambrecina, et al. Safety and immunogenicity of a quadrivalent	**Name:** Fluzone Quadrivalent **Manufacturer(s):** Sanofi Pasteur **Dose:** 0.5mL , IM **Details:** inactive , 15µg per	RCT, phase III, double-blind, multi-	**Age:** 18-60 and 60+ years **Sex:** 45% male **Country:** France & Germany	**Follow-up:** 7 days (solicited)-active 21 days (unsolicited)-passive 180 days (SAEs) passive **Reactogenicity -** IIV4 vs pooled IIV3 Nasopharyngitis 1.1 vs 0.9	**Rank**: **I** **Quality**: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95 CI) * Significant difference	Quality of Evidence
inactivated influenza vaccine in adults. *Vaccine* 2013, *31(47):* 5572-5578. Eudra Clinical Trials (2011-001976-21)	strain A/H1N1/ California/07/2009 A/H3N2/ Victoria/210/2009 B/Vic/ Brisbane/60/2008 B/Yam/Florida/4/2006 **Season:** 2010-2011 **Other vaccines:** IIV3 **Name:** Vaxigrip (2010-2011) **Manufacturer(s):** Sanofi Pasteur **Details:** As above, less B/Yam Investigational IIV3, Sanofi-Pasteur, A strains as above and B/Yam/Florida/4/2006	centre	**Number of participants:** IIV4: 1112 18-60: 556 >60: 556 IIV3 Vaxigrip: 226 18-60: 113 >60: 113 Investigational:223 18-60: 110 >60: 113	Pruritius 1.3 vs 1.1 Systemic 38.1 (35.3, 41.0) vs 42.8 (38.1, 47.5) Unsolicited 21.2 (18.9, 23.8) vs 20.3 (16.6, 24.3) **Serious adverse events** SAE 2.3 (1.5, 3.4) vs 1.8 (0.8, 3.5) IIV4 – 2 deaths (cardiac arrest, breast cancer) – unrelated	
IIV: Children					
Langley J, Martinez CA, Chatterjee A, et al. Immunogenicity and Safety of an Inactivated Quadrivalent Influenza Vaccine Candidate: A Phase III Randomized Controlled Trial in Children. *J Infect Dis* 2013; 208:544-553. (NCT01198756)	**Name:** Quadrivalent Influenza Vaccine (IIV4) **Manufacturer(s):** GlaxoSmithKline **Dose:** 0.5 mL **Admin:** IM **Details:** inactive split-virion, 15 µg A/H1N1/ Brisbane/59/2007 A/H3N2/ Uruguay/716 /2007 B/Vic/ Brisbane/ 60/2008 B/Yam/ Florida/04/2006 **Season:** 2009-2010 **Comparator vaccine:** IIV3 **Manufacturer(s):** GlaxoSmithKline **Details:** B/Vic OR B/Yam	RCT, phase III, double-blind, multi-centre	**Age:** 3-17 years Mean (SD): 8.9 (4.2) **Sex:** 51.5% male **Country:** Canada, United States, Mexico, Spain, and Taiwan **Number of participants** **IIV4:** 932 **IIV3:** B/Vic/ 929 B/Yam/ 932 **Inclusion criteria**: stable health	**Follow-up:** 28 days -unsolicited AEs-passive 180 days - SAEs-MAEs and PIMDs-passive **AEs** **1+ events:** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) 30.4% vs 31.3% vs 29.5% **Serious adverse events** IIV4 - 3 (0.3%) children (4 events) – 2 events (generalized seizure & febrile seizure) - related IIV3-B/Vic - 6 (0.6%) children (12 events) - unrelated IIV3-B/Yam - 5 (0.5%) children (9 events) – unrelated	**Rank**: I **Quality**: Good
		Subset: open-label IIV4 only	**Age:** 6-35 months Mean (SD): 21 (8.7) **Sex:** 52.5% male **Number:** 301	**AEs** **At least one event:** 53.3% **Serious adverse events** 7 (2.3%) children from open label (10 events); 2 events considered related (angioedema & acute conjunctivitis)	
Domachowske BJ, Pankov-Culot H, Bautista M, et al. A randomized trial of candidate inactivated quadrivalent influenza vaccine	**Name:** Quadrivalent Influenza Vaccine (IIV4) **Manufacturer(s):** GlaxoSmithKline **Dose:** 0.5 mL **Admin:** IM **Details**: inactive split-virion , 15	RCT, phase III, double-blind, multicenter	**Age:** 3-17 years, mean: 7.8 years; **Sex (% male):** 51.8; **Country:** Czech Republic, France, Germany, Philippines, and USA	**Follow-up:** 28 days (unsolicited AEs) 6 mos. (SAE) **AEs:** (IIV4 vs IIV3-B/Vic vs IIV3-B/Yam) 31.0 vs 33.4 vs 33.8 Most common - nasopharyngitis 5.4 vs 6.6. vs 7.0	**Rank**: I **Quality**: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95 CI) * Significant difference	Quality of Evidence
versus trivalent influenza vaccines in children aged 3–17 years. *J Infect Dis* 2013; 207:1878-1887. (NCT01196988)	µg A/H1N1/California/7/2009 A/H3N2/ Victoria/210/2009 B/Vic/ Brisbane/60/2008 B/Yam/ Brisbane/3/2007 **Season:** 2010-2011 **Other vaccine:** IIV3 **Name:** Fluarix **Manufacturer(s):** GlaxoSmithKline **Details:** B/Vic or B/Yam		**Number: IIV4:** 915; **IIV3:** B/Vic/912; B/Yam/911 **Inclusion criteria**: healthy children 3-17 years old	**Serious adverse events** No vaccine-related SAE	
		Subset: open-label	**Age:** 6-35 months, means: 1.4 years **Sex (% male):** 57.4 **Number of participants** **Fluarix:** 277 **Inclusion criteria:** Health children 6-35 months old	**Reactogenicity ,** 7 day active follow-up **6-35 months** (Dose 1 vs Dose 2) Pain 33.9 vs 27 Redness 30.3 vs 27 Swelling 15.9 vs 15 Drowsiness 23.8 vs 18 Irritability 28.5 vs 30 Loss of appetite 20.2 vs 20 Fever 17.0 vs 20 **Serious adverse events** 9 (3.2%) children (18 events) - none vaccine-related	
Greenberg DP, Robertson A, Landolfi VA, et al. Safety and immunogenicity of an inactivated quadrivalent influenza vaccine in children 6 months to 8 years of age. *Ped Infect Dis J.* 2014; Jan 19: ahead of print *ClinicalTrials.gov*. (NCT01240746)	**Name:** Quadrivalent influenza vaccine **Manufacturer:** Sanofi Pasteur **Dose:** 30µg HA/strain/mL (6-35 mon: 0.25mL; 36+ mon: 0.5mL; primed: 1 dose; unprimed: 2 doses;) **Admin:** IM **Details:** inactive split-virion ; A/H1N1/ California/7/09 A/H3N2/ Victoria/210/09 B/Vic/ Brisbane/60/08 B/Yam/ Florida/04/06 **Season:** Nov 2010- June 2012 **Other vaccine:** same as above, with inclusion of either B/Vic (licensed 2010-11 IIV3) or B/Yam (investigational IIV3)	RCT, phase III, observer blinded, multicentre	**Age:** 6mon-8 yrs Mean(SE) 4.1 (2) **Sex :** 50.6% male **Country:** USA **Number of participants:** **IIV4:** 2902 **IIV3:** B/Vic: 736 (Bris) B/Yam: 725 (Fl) **Inclusion criteria**: Generally healthy	**Follow-up:** 7 days active follow-up 28 days unsolicted 6 months SAE **Reactogenicity** (IIV4 vs IIV3) Fever ≥38.0^{0}C: 5.1 vs 3.1% Fever ≥39.0^{0}C: 1.2 vs 0.3% **Adverse events**:: IIV4: 1 event: 1 (croup 3 days post vaccination)-related IIV3: 3 events: 2 (1 febrile seizure 8 hours after 2nd dose and 1 febrile seizure 1 day after first dose) - related and 1 (drowning) unrelated (details per A. Chit) Vaccine type unreported: 11 other febrile seizures reported but considered unrelated to vaccine	**Rank**: **I** **Quality**: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95 CI) * Significant difference	Quality of Evidence
Jain VK, Rivera L, Zaman K, et al. Vaccine for prevention of mild and moderate-to-severe influenza in children. *NEJM* 2013*; 369(26)*:2481-2491. *ClinicalTrials.gov*. (NCT01218308)	**Name:** Quadrivalent influenza vaccine GSK2282512A **Manufacturer:** GlaxoSmithKline **Dose:** 15 µg, 0.5 mL (primed: 1 dose; unprimed: 2 doses) **Admin:** IM **Details:** inactive split-virion ; A/H1N1/ California/7/09 A/H3N2/ Victoria/210/09 B/Vic/ Brisbane/60/08 B/Yam/ Florida/4/06 **Season:** Dec 2010-Oct 2011 **Other vaccine:** Havrix (Hepatitis A vaccine), 0.5 mL/dose	RCT, phase III, double-blind, multicentre	**Age:** 3-8 years; mean(SD): 5.4 (1.65) **Sex:** 51.7% male **Country:** Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Phillipines, Turkey, and Thailand **Setting:** multicentre **Number of participants** **Vaccine:** 2584 3-5 years: 917 5-8 years: 1667 **Hepatitis A:** 2584 3.5 years: 910 5-8 years: 1674 **Inclusion criteria**: healthy children	**Follow-up:** 7 days (solicited)-passive; 28 days, passive **Reactogenicity** (IIV4 vs Havrix) **3-8 years** Pain 47.7 vs 34.8* Redness 0.7 vs 0.2 Swelling 1.8 vs 0.4 **3-5 years** Fever 10.5 vs 9.9 Drowsiness 11.1 vs 10.4 Irritability 11.3 vs 10.2 Loss appetite 13.2 vs 13.4 **5-8 years** Fever (>38^{0}C) 5.6 vs 5.6 Fatigue 11.4 vs 8.8 Shivers/chills 3.8 vs 3.6 Myalgia 15.6 vs 11.7 Headache 14.7 vs 13.1 Arthralgia 8.7 vs 5.6 GI upset 8.1 vs 8.8 **Adverse events** IIV4 - 36 events (1.4%) – 1 (severe bronchitis) related Harvix – 24 events (0.9%) – 0 related	**Rank**: **I** **Quality**: Good
Live Attenuated Influenza Vaccine (LAIV)					
MedImmune. A randomized, partially blind active controlled study to evaluate the immunogenicity of MEDI8662 in adults 18-49 years of age. *ClinicalTrails.gov* (NCT00952705) Last updated: 2011-Dec-09	**Name:** Q/LAIV-BFS (MEDI8662) **Manufacturer(s):** MedImmune **Dose:** 0.2 mL (single dose) **Admin:** nasal spray **Details:** cold-adapted, attenuated A/H1N1/ South Dakota/6/2007 A/H3N2/ Uruguay/716/2007 B/Vic/ Malaysia/2506/2004 B/Yam/ Florida/4/2006 **Season:** 2010-2011 **Other vaccine:** LAIV3 **Name:** FluMist **Details:** B/Vic or B/Yam	RCT, phase III, double-blind, multicentre	**Age:** 18-49 years; mean(SD): 33.9(9.3) **Sex (% male):** 42.4 **Country:** USA **Setting:** multicenter **Number of participants** **LAIV4:** 1202 **LAIV3:** B/Vic/ 298 B/Yam/ 300 **Inclusion criteria**: healthy adults	**Follow-up:** 14 days (solicited)-active 28 days (unsolicited)-active 180 days (SAEs and new onset chronic diseases)-passive **Reactogenicity** (LAIV4 vs LAIV3) Sore throat: 17.3 vs 15.0 Fever (>37^{0}C) 1.6 vs 2.0 Fatigue 16.2 vs 17.5 Cough 9.6 vs 7.9 Runny nose 31.3 vs 37.6 Myalgia 8.4 vs 11.1 Headache 23.8 vs 24.4 Decreased appetite 5.3 vs 5.7 Any 50.6 vs 54.3 **Serious adverse events** 180 days: 1.3% vs 0.3% (relatedness to vaccine not	**Rank**: **I** **Quality:** Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95 CI) * Significant difference	Quality of Evidence
				reported in the clinicaltrials.gov database)	
Block LS, Yi T, Sheldon E, et al. A randomized, double-blind noninferiority study of quadrivalent live attenuated influenza vaccine in adults. *Vaccine* 2011; 29:9391-9397. (NCT00860067)	**Name:** LAIV4 **Manufacturer(s):** MedImmune **Dose:** 0.2 mL **Admin:** nasal spray **Details:** cold-adapted, attenuated A/H1N1/ South Dakota/6/2007, A/H3N2/ Uruguay/716/2007, B/Vic/ Malaysia/2506/2004) B/Yam/ Florida/4/2006 **Season:** 2009-2010 **Comparator vaccine:** LAIV3 **Name:** FluMist **Manufacturer(s):** MedImmune **Details:** B/Yam OR B/Vic	RCT, double-blind, active-controlled, multicentre	**Age:** 18-49 years; median: 32.0 **Sex (% male):** 44.8 **Country:** USA **Setting:** 18 clinical sites **Number of participants: 1800** **Vaccine:** 1200 **Placebo:** 927 (LAIV3-B/Yam/ 299; LAIV3-B/Vic/ 301) **Inclusion criteria**: healthy adults	**Follow-up:** 14 days (solicited symptoms)-active 28 days (unsolicited AEs)-passive 180 days (SAEs and new onset chronic diseases)-passive **Reactogenicity** (LAIV4 vs LAIV3) Sore throat 19.0 vs 19.8 Fever (>37^{0}C) 1.3 vs 1.5 Fatigue 17.6 vs 17.8 Cough 13.6 vs 12.6 Runny nose 43.6 vs 39.5 Myalgia 10.1 vs 9.9 Headache 28.2 vs 27.5 Decreased appetite 6.4 vs 5.4 Any 59.6 vs 60.0 **Serious adverse events** LAIV: 5 reported; 1 (bronchospasm) – related	**Rank**: **I** **Quality**: Good
LAIV – Children					
Block LS, Falloon J, Hirschfield AJ, et al. Immunogenicity and safety of a quadrivalent live attenuated influenza vaccine in children. *Pediatr Infect Dis J* 2012; 31:745-751. (NCT01091246) *Some data retrieved from clinicaltrials.gov	**Name:** LAIV4 **Manufacturer(s):** MedImmune **Dose:** 0.2 mL; 9–17 years: 1 dose; 2–8 years: 2 doses **Admin:** nasal spray **Details:** cold-adapted, temperature-sensitive, attenuated A/H1N1/ South Dakota/6/2007 A/H3N2/ Uruguay/716/2007 B/Vic/ Malaysia/2506/2004 B/Yam/ Florida/4/2006 **Season:** 2010-2011 **Comparator vaccine:** LAIV3 **Name:** FluMist **Manufacturer(s):** MedImmune **Details:** B/Yam OR B/Vic	RCT, phase III, double blind	**Age:** 2-17 years; mean(SD): 6.74(3.8) **Sex (% male):** 49.2 **Country:** USA **Setting:** multi-centre **Number of participants:** 2312 **Vaccine:** 1385 **LAIV3:** 927 LAIV3-B/Yam: 464 LAIV3-B/Vic: 463) **Inclusion criteria**: healthy children	**Follow-up:** 14 days (solicited symptoms)-active 28 days (unsolicited AE)-passive 180 days (SAE. new onset chronic diseases) passive **Reactogenicity** (LAIV4 vs LAIV3) **Restricted to 2-8 year olds, post dose 1 only** Sore throat 7.2 vs 6.5 Fever (>37.9^{0}C) 5.1 vs 3.1* Fatigue 8.5 vs 7.8 Cough 15.2 vs 15.5 Runny nose 31.6 vs 28.1 Myalgia 3.7 vs 3.9 Headache 8.4 vs 8.9 Decreased appetite 5.3 vs 5.9 Any 44.9 vs 43.3 **Reactogenicity** (LAIV4 vs LAIV3 & postdose1 vs postdose2) Fever (>37.9^{0}C) 5.7 vs 3.9 & 2.7 vs 4.2 Runny/stuffy nose 32.3 vs 32.0 & 20.9 vs 19.5 Sore throat 9.2 vs 10.3 & 4.1 vs 4.6 Cough 15.8 vs 16.8 & 12.7 vs 11.7 Headache 12.5 vs 12.2 & 5.4 vs 5.5 Myalgia 4.4 vs 4.6 & 1.2 vs 0.9	**Rank**: **I** **Quality: Good**

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95 CI) * Significant difference	Quality of Evidence
				Tiredness 9.8 vs 9.9 & 5.9 vs 5.3 Decreased appetite 5.5 vs 6.6 & 3.7 vs 3.3 **Serious adverse events** No vaccine-related SAE **New-onset chronic diseases** 1.4% vs 0.8%	

References:

(1) Center for Biologics Evaluation and Research. 2007. Guidance for industry: clinical data needed to support the licensure of seasonal inactivated influenza vaccines. 2013, from http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091990.pdf

(2) Committee for Proprietary Medicinal Products. 1997. *Note for guidance on harmonization of requirements for influenza vaccines*. (CPMP/BWP/214/96). London, UK: The European Agency for the Evaluation of Medicinal Products Retrieved from WWW.EUDRA.ORG/EMEA.HTML.

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