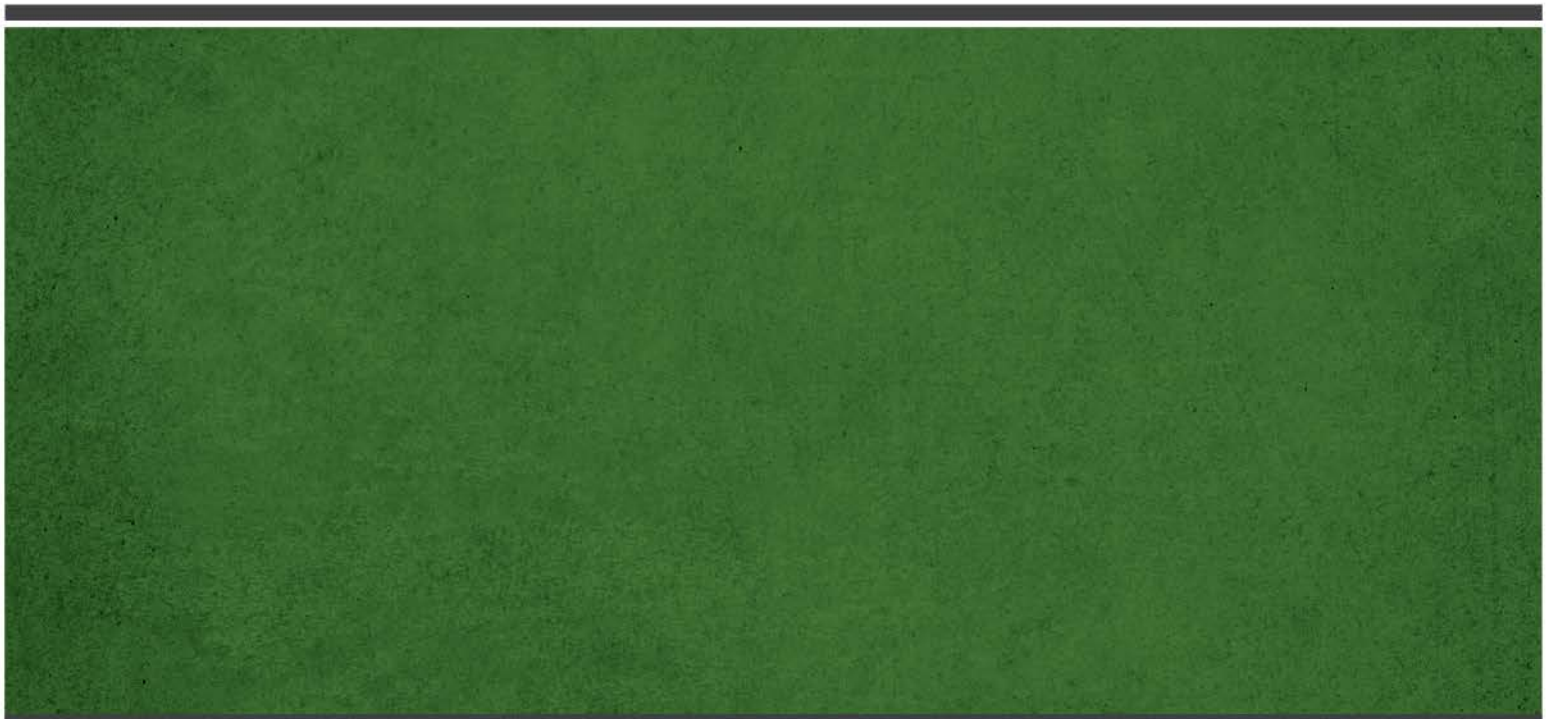
ADDENDUM – Influvac® Use in Children

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

Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2017–2018



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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. PHAC 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 PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

This addendum to the Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2017–2018 has been issued to address updated recommendations regarding the use of the Influvac® trivalent inactivated influenza vaccine in children 3–17 years of age.

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I. NACI RECOMMENDATION

Use of Influvac® Trivalent Inactivated Influenza Vaccine in Children

The recent authorization by Health Canada, extending the indication for the use of Influvac® (BGP Pharma ULC) to include children 3–17 years of age, provided the impetus for NACI to review the recommendation on the use of the vaccine. After careful review of available evidence, NACI has revised its recommendation on the use of Influvac®, a trivalent inactivated influenza vaccine (TIV):

NACI recommends that Influvac® should be considered among the TIVs offered to children 3–17 years of age when a quadrivalent influenza vaccine is not available (Strong NACI Recommendation).

NACI concludes that there is fair evidence of vaccine effectiveness, immunogenicity and safety to recommend the use of Influvac® for children 3–17 years of age (Grade B Evidence). There is insufficient evidence, in quantity and quality, to recommend the use of Influvac® for children younger than three years of age (Grade I Evidence). The recommendation on the use of Influvac® in children is a change from previous NACI statements, as Influvac® was not previously recommended by NACI for use in persons younger than 18 years of age.

Notwithstanding this new recommendation on the use of Influvac® (a TIV), NACI continues to recommend that a quadrivalent formulation of influenza vaccine be used for children younger than 18 years of age. If a quadrivalent vaccine is not available, a TIV should be used (see Choice of Vaccine Product for Children below for more details).

An updated summary of the characteristics of influenza vaccines available in Canada for the 2017–2018 influenza season can be found in Appendix A. For complete prescribing information, readers should consult the product leaflets or information contained within the authorized product monographs available through Health Canada's Drug Product Database.

Please refer to Appendix B for an explanation of NACI methodology for the grading of evidence.

Choice of Vaccine Product for Children

The current recommendations on the choice of influenza vaccine currently available for use in Canada are summarized below by pediatric age group. Additional details regarding the NACI recommendations on choice of vaccine product for children 6–23 months of age and 2–17 years of age can be found in the NACI Advisory Committee Statement: Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2017–2018.

Children 6–23 Months of Age
There are three types of vaccines authorized for use in this age group: quadrivalent inactivated influenza vaccine (QIV), TIV, and adjuvanted TIV.

NACI recommends that, given the burden of influenza B disease, QIV should be used. If QIV is not available, either unadjuvanted or adjuvanted TIV should be used.

Children 2–17 Years of Age
In children without contraindications to the influenza vaccine, any of the following vaccines can be used: quadrivalent live attenuated influenza vaccine (LAIV), QIV, or TIV. The current evidence does not support a recommendation for the preferential use of LAIV in children 2–17 years of age.

Given the burden of influenza B disease in children and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI continues to recommend that a quadrivalent formulation of influenza vaccine be used in children 2–17 years of age. If a quadrivalent vaccine is not available, TIV should be used.

II. BACKGROUND

Influvac® Trivalent Inactivated Influenza Vaccine

Influvac® is a surface antigen, subunit TIV that contains 15 µg of haemagglutinin (HA) per strain, administered as a 0.5 mL dose using a pre-filled syringe. First marketed in 1982[1], Influvac® is currently authorized for use in 85 countries[2]. The thimerosal-free formulation of Influvac® was introduced for the 2004–2005 influenza season in the Northern Hemisphere and for the 2005 influenza season in the Southern Hemisphere.

Influvac® has been approved for use in Canada since 2005 for persons 18 years of age and older. In May 2017, Health Canada authorized an indication extension for Influvac® to include children 3–17 years of age, based on a review of published literature submitted by the manufacturer[3]. Although Influvac® is indicated for persons six months and older in other jurisdictions, such as Australia[4] and the European Union[5], the indication for the use of Influvac® in children less than three years of age was not sought by the manufacturer for Canada, citing that the safety and efficacy of the vaccine have not been established for this younger age group[3]. Rationale supporting the regulatory decisions to authorize Influvac® for use in children less than three years of age in other jurisdictions is unavailable. Full details of the composition of Influvac® can be found in its product monograph[3].

To inform NACI's recommendation on the use of Influvac® in persons less than 18 years of age, a systematic literature review of the current evidence on the efficacy and effectiveness, immunogenicity, and safety for the pediatric use of Influvac® was conducted.

III. LITERATURE REVIEW METHODS

Search Strategy
A search strategy was developed with Federal Science Librarians (Health Library) using parameters developed by the NACI Influenza Working Group. EMBASE (1974 to 21 June 2017), Global Health (1973 to 21 June 2017), International Pharmaceutical Abstracts (1970 to 29 June 2017), MEDLINE (1947 to 21 June 2017), ProQuest Public Health Database (1963 to 29 June 2017), and Scopus (1960 to 29 June 2017) electronic databases were searched from inception using the following keyword search string structure and, when applicable, controlled vocabulary: (Influvac [OR synonyms]) AND (children [OR synonyms]). These keywords were used to search the titles and abstracts of articles, as well as the full-text when available in the

database, to increase the sensitivity (i.e., comprehensiveness) of the search. The searches were restricted to articles published in English and French. The full electronic search strategies are presented in Appendix C.

Identification of Eligible Studies

Studies retrieved from the database searches were loaded into RefWorks (ProQuest LLC, Ann Arbor, MI) with duplicate records removed. First, title and abstract information returned by the database searches were screened for potential eligibility. Second, the full-texts of studies deemed potentially eligible, or for which insufficient information was available to determine eligibility (e.g., no abstract), after title and abstract screening, were retrieved for further assessment. Both steps were performed independently by two reviewers.

Studies were included for review if they met the following criteria:

1. Study population is within the age range of interest (less than 18 years of age); or contains less than 10% of the study population outside the age range of interest; or a separate analysis was conducted for the age range of interest; and
2. Study investigated and reported Influvac® vaccine efficacy or effectiveness, immunogenicity (seroprotection, seroconversion, or serological assessments of haemagglutination inhibition [HI] assay antibody titres), or safety (local and systemic reactogenicity or adverse events following immunization [AEFI]).

Studies were excluded if they met one or more of the following criteria:

1. Non-human study;
2. Non-English and non-French language publication;
3. Secondary research (e.g., literature review, systematic review, meta-analysis); or
4. Editorial, opinion or news report.

The reference lists of included studies were independently handsearched by two reviewers to identify additional relevant publications. The reference lists of relevant secondary research articles retrieved from the database searches and of the most recent version of the product monograph for Influvac®[3] were also handsearched.

Data Extraction

Two reviewers independently extracted data from the studies included for review and any disagreements or discrepancies were resolved by discussion and consensus. A data abstraction template was used to capture information on a study's design, population, intervention, and outcome(s) of interest.

Several included publications have data sets that overlap either partially or completely. To avoid the extraction of repetitive, duplicate, or redundant data, these publications were condensed and described under a single primary reference in the evidence tables. The publication chosen for the primary reference in these cases was defined as the publication containing the analysis that is most relevant to the objectives of the present systematic review. Unique studies were considered primary references.

Qualitative Synthesis

Information extracted from the included studies was synthesized narratively and the overall patterns in the data were described for the outcomes of interest.

Methodological Quality Assessment
The methodological quality of studies was independently assessed by two reviewers, based on study methodology. The design-specific parameters outlined by Harris et al. (2001)[6] were used for rating the internal validity of individual studies (Appendix D). Included studies with study designs that are not covered by Harris et al. criteria (e.g., pre-post, non-randomized controlled or surveillance studies) could not be rated using the criteria, but were still appraised for critical methodological limitations.

IV. EVIDENCE SUMMARY

The study identification and selection process and study details are summarized in section IV.1. Evidence relating to efficacy and effectiveness is summarized in section IV.2. Studies of immunogenicity are presented in section IV.3. Vaccine safety findings are summarized in section IV.4.

IV.1 Study Inclusion and Characteristics

The process for study identification, screening and inclusion is summarized visually in Appendix E. Database searches and subsequent hand searches yielded a total of 199 unique records for title and abstract screening. Full-text screening of 92 records identified a total of 20 studies that were eligible for qualitative synthesis[7-26]. Of the 20 published studies included for review, three were identified by handsearching the reference lists of relevant review articles retrieved through the database searches[8, 12, 24]. Three included studies were funded[20] or conducted[16, 25] by the manufacturer. All included studies were available as English language publications. Unpublished pharmacovigilance data for Influvac® were also provided by the manufacturer to the NACI Influenza Working Group[2]. Therefore, a total of 21 studies were included in the synthesis.

Extracted study data are presented in the evidence table in Appendix F for efficacy and effectiveness, Appendix G for immunogenicity and Appendix H for safety findings (confidential unpublished safety data provided by the manufacturer[2] are not summarized in the evidence table). Of the 21 included studies, three pairs of related studies were identified[10, 12, 13, 18, 19, 22]. One study from each of the three pairs of related studies was further identified as a primary reference for the present review[10, 12, 18]. Extracted data for these three primary references were supplemented with non-duplicative findings from their respective related studies as indicated in Appendices F through H.

After consolidation of studies with overlapping data sets, a total of 18 primary references were included in the present review, including 10 clinical trials[9-12, 16-18, 23, 25, 26], seven vaccine safety surveillance studies (Level III Evidence)[7, 8, 14, 15, 20, 21, 24], and one unpublished vaccine safety study by the manufacturer (Level III Evidence)[2]. Of the 10 clinical trials, two were double-blind randomized controlled trials (RCTs) (Level I Evidence)[12, 18], one was an endpoint-blind RCT (Level I Evidence)[25], two were non-randomized controlled trials (Level II-1 Evidence)[23, 26], and five were pre-post studies (Level III Evidence)[9-11, 16, 17].

Quality assessment was performed for the 17 published primary references included for review. Of these, three studies with study designs evaluable by Harris et al. received “fair” ratings[12, 18, 25]. For all other study designs that were not evaluable with the Harris et al. criteria, no critical flaws were noted besides the intrinsic limitations of those designs. However, of note, one pre-

post immunogenicity study did not assess HI titres after the second vaccine dose in vaccine-naïve children[17].

A few studies included in the present review were not among those submitted by the manufacturer to Health Canada for the purpose of obtaining licensure for the pediatric use of Influvac®[7, 15, 19, 21]. Conversely, several studies submitted by the manufacturer for the pediatric indication extension were excluded from the present review due to:

- Publication in a language other than English or French[27-29];
- Interim analysis being superseded by a later publication included for review[30];
- A lack of specific reporting on Influvac®[31];
- Reporting only secondary research[32];
- Reporting outcomes in aggregate (i.e., no separate reporting by vaccine brand)[33]; and
- Inclusion of a substantial proportion of subjects outside the age range of interest[34].

IV.2 Efficacy and Effectiveness

Two studies assessed the effectiveness of Influvac® in children[18, 26].

One study included for review assessed the effectiveness of Influvac® to prevent laboratory-confirmed influenza infection as a secondary outcome. Jansen et al. (2008) conducted a double-blind RCT comparing Influvac® plus heptavalent pneumococcal conjugate (PCV7) vaccination, Influvac® plus placebo vaccination, and control hepatitis B plus placebo vaccination in children aged 18–72 months with a previously reported physician-diagnosed respiratory tract infection (RTI) (n=579)[18]. The study found that the receipt of Influvac® plus PCV7 vaccine (relative risk [RR]: 0.48, 95% confidence interval [CI]: 0.25–0.93) and Influvac® plus placebo (RR: 0.49, 95% CI: 0.25–0.97) were both statistically significantly associated with a lower risk of laboratory-confirmed influenza infection compared to immunization with a non-influenza vaccine (i.e., hepatitis B vaccine). The Influvac® plus PCV7 vaccine group saw a statistically significant reduction in the incidence of febrile RTI by 24% (incidence rate ratio [IRR]: 0.76, 95% CI: 0.58–0.99) while a non-statistically different incidence rate was observed for the Influvac® plus placebo group (IRR: 0.87, 95% CI: 0.68–1.12) compared with the control group. Statistically significant reductions in the incidence of acute otitis media were observed for the Influvac® plus PCV7 (IRR: 0.43, 95% CI: 0.20–0.94) and Influvac® plus placebo (IRR: 0.29, 95% CI: 0.12–0.70) groups compared with the control group.

The community-based, pragmatic, non-randomized controlled trial by Ghendon et al. (2006) investigated the effectiveness of influenza vaccination to protect against influenza-like illness (ILI; sudden onset of fever >38°C and cough or sore throat) in healthy children aged 3–17 years in kindergartens (3–6 years of age) and schools (7–17 years of age) of four communities of Moscow, Russia[26]. Children in two communities received the Influvac® vaccine (coverage rate of 69.7% among 40,611 children) while children in two control communities were not routinely immunized (coverage rate of <1% among 60,946 children). Vaccine effectiveness against ILI was found to be 60.9% for children attending kindergartens, 68.8% for children attending schools, and 63.7% overall.

No efficacy studies for Influvac® were identified.

IV.3 Immunogenicity

The HI assay is a commonly used laboratory test to quantify the level of serum antibodies produced in response to vaccine antigens. The concentration of observed serum HI antibodies is calculated as the geometric mean titre (GMT), which is the mean of the logarithmic values of serum antibody titres. Serological assessments of immune response, such as seroprotection, seroconversion and geometric mean fold rise (GMFR; also referred to as mean fold increase) after vaccination, derived from HI titres are accepted standards for the evaluation and licensing of new influenza vaccines[35]. Seroprotection rate is the proportion of subjects achieving an HI titre of ≥1:40 post-vaccination. An HI titre of 1:40 has been suggested to correlate with an efficacy of 50–70% against clinical symptoms of influenza in healthy adults, but may vary depending on individual characteristics, population, age and vaccine type[36]. A similar correlate for protection between antibody titre and vaccine efficacy has not been determined for children. Seroconversion rate is the proportion of subjects achieving significant increase from pre- to post-vaccination HI titres (≤1:10 to ≥1:40 or at least four-fold rise in HI titres). GMFR is the ratio of the post- and pre-vaccination HI titres. Correlates of protection against influenza have not been well established for other serological assessments, such as microneutralization assay[37] or neuraminidase inhibition assay[38], and therefore findings for these assays were not included in the present literature review.

With regard to seasonal inactivated influenza vaccines, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has previously recommended specific protective thresholds for the three aforementioned serological assessments to be considered for each vaccine strain (e.g., H1N1, H3N2, B)[35]. Although CHMP has revised its guideline on influenza vaccines not to rely on serological assays with predefined protective thresholds to establish benefit[39], the previously used thresholds are presented to aid in interpretation of immunogenicity study findings, as follows for adult subjects 18–60 years of age:

- Seroprotection in over 70% of subjects
- Seroconversion in over 40% of subjects
- Mean fold increase of over 2.5

CHMP criteria were not established for children, but the adult criteria have been used by manufacturers to evaluate influenza vaccine immunogenicity in pediatric trials[40].

The United States (US) Department of Health and Human Services (HHS) published the following criteria for clinical data necessary to support the licensure of seasonal inactivated influenza vaccines for adults younger than 65 years of age and for the pediatric population (criteria for adults 65 years of age and older are not presented):

- Lower limit of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%
- Lower limit of the two-sided 95% CI for the percent of subjects achieving seroprotection should meet or exceed 70%[41].

For clinical trials comparing two influenza vaccines, the US HHS recommends the following criteria to assess the non-inferiority of a new vaccine compared to a licensed vaccine for all age groups: the upper limit of the two-sided 95% CI for the ratio of post-vaccination GMTs (established vaccine versus new vaccine) for all three vaccine strains should not exceed 1.5 and the upper limit of the two-sided 95% CI of the difference between seroconversion rates (established vaccine minus new vaccine) for all three vaccine strains should not exceed 10%[41].

Health Canada has not published similar criteria for the assessment of influenza vaccine immunogenicity.

Healthy Children
Two studies assessed the immunogenicity of Influvac® in healthy children[17, 25].

Zhu et al. (2008) conducted an endpoint-blind RCT in 300 healthy children 3–12 years of age, 300 healthy adults 18–59 years of age and 240 healthy elderly persons 60 years of age and older to assess the immunogenicity of Influvac® compared to another subunit TIV, Agrippal® (Seqirus; marketed in Canada as Agriflu®), in these age groups[25]. In per-protocol analysis, Influvac® achieved seroprotection rates of 95–99%, seroconversion rates of 87–92%, and mean fold increases of 17.4–23.3 in healthy children for the three vaccine virus strains. The lower limits of the 95% CI of the ratio of post-vaccination GMTs comparing Influvac® to Agrippal® for children aged 3–12 years (1.42–1.63), 3–5 years (0.94–1.29) and 6–12 years (1.44–1.70) were above the study-defined non-inferiority margin of 0.35, indicating that the immunogenicity of Influvac® was at least comparable to Agrippal® in these age groups.

El-Madhun et al. (1998) conducted a pre-post study examining the effect of previous exposure to the influenza virus (i.e., natural priming) on immune response following vaccination with Influvac®[17]. The study population consisted of a group of persons, including 18 children aged 2–3 years, who had not been previously vaccinated against influenza and were undergoing tonsillectomy. Study subjects did not have any serious health problems, with the exception of frequent tonsillar infections. Of the 18 children, based on the presence of pre-vaccination serum antibodies, 14 were determined to be primed by influenza A(H3N2), one was primed by influenza A(H1N1), and three were primed by influenza B. All children primed by an influenza virus strain achieved at least a four-fold increase from pre- to post-vaccination antibody titres for that strain 28–42 days after the first of two half doses of vaccine, whereas no substantial increase in HI titres was observed in children who were not primed by that strain. Serology was not assessed after the second dose of vaccine. A two-dose schedule is required to achieve protection in children less than nine years of age receiving seasonal influenza vaccine for the first time[42].

Children with Chronic Health Conditions
Six studies assessed the immunogenicity of Influvac® in children with specific chronic health conditions: acute lymphoblastic leukemia (ALL)[9, 10, 23], hemophilia[11], asthma[12], chronic lung disease, and congenital heart disease[16].

In a multi-arm pre-post study, Brydak et al. (1998) assessed the immunogenicity of Influvac® in children aged 7–16 years with ALL (n=45) compared by previous influenza vaccination status and with a control group of unvaccinated healthy children aged 8–15 years (n=23)[10]. A majority of the subjects with ALL completed chemotherapy treatment at least one month before immunization (n=43 of 45). Serological assessment was completed at three weeks and six months post-vaccination with Influvac®. Children aged 7–16 years with ALL who were previously vaccinated (n=25) achieved seroprotection rates of 52.0–92.0% (>60% for two of three vaccine strains) and 68.0–100.0%, seroconversion rates of 52.0–92.0% and 68.0–100.0%, and mean fold increases of 17.2–26.7 and 22.1–38.2 for the three strains assessed at three weeks and at six months post-vaccination respectively. Among children aged 7–11 years with ALL who were not previously immunized with influenza vaccine (n=20), Influvac® achieved similar seroprotection rates of 55.0–85.0% (>60% for two of three vaccine strains) and 90.0–100.0%, seroconversion rates of 55.0–80.0% and 90.0–100.0%, and mean fold increases of 15.7–22.6 and 30.3–39.3 for the three strains assessed at three weeks and at six months post-vaccination

respectively. Post-vaccination HI titres were statistically significantly higher for vaccinated children with ALL compared to unvaccinated healthy children. In a follow-up study, Brydak et al. (2000) did not find statistically significant differences in post-vaccination immune response in ALL subjects by time since completion of chemotherapy treatment[9].

In another multi-arm, pre-post study by Brydak et al. (1998), the immune response elicited by Influvac® was assessed in a group of hemophiliac patients aged 10–19 years who have been previously vaccinated against influenza (n=38) and compared to healthy controls who did not receive influenza vaccination during this study or previously (n=23)[11]. For the vaccinated group of hemophiliac patients, the mean fold increase was observed to range from 3.9–10.9 and 8.4–28.6 for all three vaccine strains assessed at three weeks and at six months post-vaccination respectively. Seroprotection rates were found to be 52.6–60.5% (>60% for one of three vaccine strains) and 76.3–97.4% for the three vaccine strains assessed at three weeks and at six months post-vaccination respectively. The seroconversion rate was found to be 39.5–42.1% and 71.1–86.8% for all three vaccine strains assessed at three weeks and at six months post-vaccination respectively. These observed measures of immune response appear to be higher for vaccinated hemophiliac patients than unvaccinated controls. Post-vaccination HI titres in vaccinated hemophiliac patients were statistically significantly higher than pre-vaccination titres and titres observed for unvaccinated controls. In stratified analysis by severity of hemophilia, children suffering from severe and mild hemophilia had similar GMTs and mean fold increases for influenza A and B strains at 6 months post-vaccination with Influvac®[22]. Seroprotection and seroconversion rates were similar for both severities of hemophiliacs for influenza A(H3N2) and B; however, patients with severe hemophilia had lower rates of seroprotection and seroconversion compared to patients with mild hemophilia for influenza A(H1N1) at 3 weeks and 6 months post-vaccination.

Shahgholi et al. (2010) conducted a non-randomized controlled trial assessing the immunogenicity of Influvac® in children aged 1–18 years with ALL in first remission and receiving maintenance therapy (n=32) compared to healthy sibling controls (n=30)[23]. Compared to pre-vaccination HI titres, ALL patients showed statistically significantly elevated protective responses for the three vaccine strains assessed at four weeks post-vaccination. Post-vaccination GMTs were not statistically significantly different between ALL patients and healthy controls for influenza A(H1N1) and B, but was statistically significantly lower in ALL patients for influenza A(H3N2) (p=0.041). Seroprotection rates were lower in vaccinated ALL patients (26.0–63.3%) than vaccinated healthy controls (73.0–88.0%), with a statistically significantly lower seroprotection rate for the H1N1 (p=0.04) and B (p=0.001) antigens. Seroconversion rates ranged from 40.6–59.4% for vaccinated ALL patients and from 53.3–83.3% for controls. Seroconversion rates were statistically significantly lower for the H1N1 and B antigens (p=0.04 and 0.038 respectively), but not for the H3N2 antigen.

Bueving et al. (2004) conducted a double-blind RCT in children 6–18 years of age with asthma to assess the immunogenicity of Influvac® (n=347) compared to placebo (n=349)[12]. Influvac® achieved statistically significantly higher seroprotection rates (85.6–98.5%) and seroconversion rates (26.5–59.9%) compared to placebo for the three vaccine strains at 14–21 days after vaccination.

In a single-arm pre-post study in 52 children aged 6 months to 4 years with chronic lung disease and/or congenital heart disease, Daubeney et al. (1997) found that Influvac® achieved seroprotection rates of 55–71% (>60% for two of three vaccine strains), seroconversion rates of 55–71% and mean fold increases of 5.8–10.8 for the three vaccine strains[16].

IV.4 Safety

Fourteen published studies were identified that assessed the safety of Influvac® in children[7-9, 12, 14-16, 18, 20, 21, 23-26]. The manufacturer also provided unpublished pharmacovigilance data for Influvac®[2].

All clinical trials included for review that assessed safety and tolerability found Influvac® to be safe and well tolerated in healthy children[19, 25, 26] and in children with specific chronic health conditions[10, 13, 16, 23]. A surveillance study recorded one child between 6 months and 4 years of age who had received Influvac® that experienced a severe adverse event (SAE); the precise age of the child and nature of the SAE are not reported, but it was reported that the child improved within days[21]. Several other studies noted that no SAEs following vaccination were observed for Influvac®[13, 16, 19, 25, 26]. Among the clinical trials included for review, reported local reactions include erythema[13, 16, 19, 23], interference with limb movement[19], stiff or painful arm[13], pain[13, 23], swelling[19, 23], and tenderness[19]. Reported systemic reactions include fever[16, 19, 23, 25], headache[19, 25], increased irritability[16], insomnia[16], malaise[19], and myalgia[13, 19]. Local and systemic reactions were noted to be mostly mild and transient, resolving within a few days[16, 19, 25].

Several observational studies were identified that examined AEFI in children and reported product-specific findings, including for Influvac®[7, 8, 14, 15, 20, 21, 24].

Between 1998 and 2007, four cases of AEFI related to Influvac® were reported to the Danish Medicines Agency for children 2–3 years of age, three of which were classified as serious; however, details of the AEFI were not reported. AEFI were not reported for the other pediatric age groups (less than 18 years of age)[7].

In Western Australia during the 2010 Southern Hemisphere influenza season, a split virion TIV (Fluvax® and Fluvax Junior®, CSL) was found to be associated with higher rates of febrile convulsions following vaccination in children less than 5 years of age compared to previous seasons[43]. As a comparator to Fluvax® and Fluvax Junior®, resulting safety surveillance investigations of febrile events following influenza vaccine administration found statistically significantly lower risk of febrile reactions in children 6 months to four and five years for Influvac® in Australia[8, 24] and New Zealand[20].

A web-based active AEFI surveillance system (Vaxtracker) for the state of New South Wales in Australia found that pediatric recipients (<10 years of age) of Influvac® reported lower frequencies of any AEFI (3.1%; n=32) compared to Fluarix® (11.6%; n=43), Vaxigrip® (21.7%; n=212) and all influenza vaccine brands (17.9%; n=290) for the 2012 and 2013 Southern Hemisphere influenza seasons[14].

The Australian national vaccine safety surveillance system (AusVaxSafety) reported AEFI, including fever, by influenza vaccine brand for the 2015 Southern Hemisphere season. Influvac®, however, was administered in insufficient numbers in children aged six months to four years (n=47) to allow for a reliable comparison of differences in reported fever rates with other vaccine brands[21].

An Australian state-based passive surveillance system identified one pediatric case of anaphylaxis following vaccination with Influvac® during the 2008 and 2009 Southern Hemisphere influenza seasons[15]. An anaphylaxis incidence rate for Influvac® was not available.

The manufacturer's enhanced passive surveillance system did not identify any unexpected reactogenicity in children and adults for Influvac® over the 2015–2016 Northern Hemisphere influenza season[2].

IV.5 Conclusion

The present literature review identified evidence on the effectiveness, immunogenicity and safety of the Influvac® TIV for pediatric use, but few studies were of stronger methodological rigor (i.e., Level I Evidence)[12, 18, 25]. No efficacy studies were identified. Despite the limited quantity and quality of the body of evidence, the overall direction of findings from the identified studies is consistent across the outcomes of interest. Influvac® was found to be effective, immunogenic and safe in healthy children and in children with specific chronic health conditions.

Only two studies were identified that examined the effectiveness of Influvac®. These studies did not compare Influvac® with other influenza vaccines. A double-blind RCT found Influvac® to be effective in reducing the risk of laboratory-confirmed influenza infection, incidence of febrile RTI, and acute otitis media among children aged 18–72 months with a previously reported physician-diagnosed RTI[18]. Among children 3–17 years of age, a community-based, pragmatic non-randomized controlled trial found Influvac® to be effective against ILI compared to no vaccination[26].

Several clinical trials were identified that found that Influvac® elicited a protective immune response in healthy children[17, 25] as well as in children with specific chronic health conditions[9-12, 16, 23]. A double-blind RCT found that Influvac® was no less immunogenic than another licensed subunit TIV (Agrippal®) in healthy children aged 3–12 years[25]. In children aged 6–18 years with asthma, recipients of Influvac® achieved statistically significantly higher serological responses compared to placebo in a double-blind RCT[12]. Results from a few trials with comparatively weaker study designs (i.e., pre-post study, non-randomized controlled trial), mostly in older children (e.g., six years of age and older), found that Influvac® is able to induce elevated serological immune responses in children with ALL[9, 10], hemophilia[11], and chronic lung disease or congenital heart disease[16]. A small pre-post study of children who had frequent tonsillar infections but were otherwise healthy and were not previously vaccinated for influenza found that Influvac® may elicit a stronger immune response in naturally primed children 2–3 years of age after the first of two half doses of vaccine compared to unprimed children[17]. However, it should be noted that a two-dose schedule is required to achieve protection in vaccine-naïve children less than nine years of age[42].

Clinical trials that reported on adverse events and vaccine safety surveillance studies found Influvac® to be safe and well tolerated in children[7, 8, 10, 13-16, 19-21, 23-26]. Among these vaccine safety studies, few SAEs were reported in children vaccinated with Influvac®[7, 21].

Evidence Gaps

There is a paucity of evidence for Influvac® use in children younger than three years of age, particularly in children aged 6–23 months. Evidence on the effectiveness and immunogenicity of Influvac® in children younger than three years of age is limited to a few clinical trials[16-18, 23], with only two pre-post immunogenicity studies having study subjects that are entirely or mostly within this age group[16, 17]. Only a few studies reporting on the safety of Influvac® included children younger than three years of age[2, 14, 16, 19, 23].

Evidence on how Influvac® compares with other TIVs in children is limited to a single clinical trial of immunogenicity and safety with another subunit TIV as comparator[25]. No information is available on how Influvac® compares with split virion TIV, adjuvanted TIV, or QIV.

V. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AEFI	Adverse events following immunization
ALL	Acute lymphoblastic leukemia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CTAB	Cetyltrimethyl-ammonium bromide
ED	Emergency department
GMFR	Geometric mean fold rise
GMT	Geometric mean titre
HA	Haemagglutinin
HBV	Hepatitis B vaccine
HHS	Department of Health and Human Services (US)
HI	Haemagglutination inhibition
ICD	International Classification of Diseases
ILI	Influenza-like illness
IM	Intramuscular
IRR	Incidence rate ratio
LAIV	Live attenuated influenza vaccine
NA	Not applicable
NACI	National Advisory Committee on Immunization
NR	Not reported
OR	Odds ratio
PCR	Polymerase chain reaction
PCV7	Heptavalent pneumococcal conjugate
PHAC	Public Health Agency of Canada
QIV	Quadrivalent inactivated influenza vaccine
RCT	Randomized controlled trial
RR	Relative risk
RTI	Respiratory tract infection
SAE	Severe adverse event
TIV	Trivalent inactivated influenza vaccine
US	United States

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Appendix A: Characteristics of Influenza Vaccines Available for Use in Canada, 2017–2018*

Manufacturer and Product name	**BGP Pharma ULC (Mylan) Influvac®**	**GSK Fluviral®**	**Seqirus Agriflu®**	**Seqirus Fluad Pediatric® and Fluad®**	**Sanofi Pasteur Vaxigrip®**	**Sanofi Pasteur Fluzone®**	**Sanofi Pasteur Fluzone® High-Dose**	**AstraZeneca FluMist® Quadrivalent**	**GSK Flulaval® Tetra**	**Sanofi Pasteur Fluzone® Quadrivalent**
Vaccine preparations	TIV	TIV	TIV	TIV	TIV	TIV	TIV	LAIV	QIV	QIV
Vaccine type	Inactivated, surface antigen subunit	Inactivated, split virus	Inactivated, subunit	Inactivated, subunit	Inactivated, split virus	Inactivated, split virus	Inactivated, split virus	Live attenuated	Inactivated, split virus	Inactivated, split virus
Route of administration	IM**	IM	IM	IM	IM	IM	IM	Intranasal spray	IM	IM
Authorized ages for use	≥3 years***	≥6 months	≥6 months	Pediatric: 6–23 months Adult: ≥65 years	≥6 months	≥6 months	≥65 years	2–59 years	≥6 months	≥6 months
Antigen content (each of strains)	15 µg HA per 0.5 mL dose	15 µg HA per 0.5 mL dose	15 µg HA per 0.5 mL dose	Pediatric: 7 µg HA per 0.25 mL dose Adult: 15 µg HA per 0.5 mL dose	15 µg HA per 0.5 mL dose	15 µg HA per 0.5 mL dose	60 µg HA per 0.5 mL dose	$10^{6.5-7.5}$ fluorescent focus units of live attenuated reassortants per 0.2 mL dose given as 0.1 mL in each nostril	15 µg HA per 0.5 mL dose	15 µg HA per 0.5 mL dose
Adjuvant	No	No	No	MF59 (oil-in-water emulsion)	No	No	No	No	No	No
Formats available	Single dose pre-filled syringes with Luer tip	5 mL multi-dose vial	5 mL multi-dose vial Single dose pre-filled syringes without a needle	Single dose pre-filled syringes without a needle	5 mL multi-dose vial Single dose ampoule Single-dose pre-filled syringes with or without a needle	5 mL multi-dose vial Single dose ampoule Single dose pre-filled syringes without a needle	Single dose pre-filled syringes	Prefilled single use glass sprayer	5 mL multi-dose vial	5 mL multi-dose vial Single dose vials Single dose pre-filled syringes without attached needle

Manufacturer and Product name	**BGP Pharma ULC (Mylan) Influvac®**	**GSK Fluviral®**	**Seqirus Agriflu®**	**Seqirus Fluad Pediatric®** and **Fluad®**	**Sanofi Pasteur Vaxigrip®**	**Sanofi Pasteur Fluzone®**	**Sanofi Pasteur Fluzone® High-Dose**	**AstraZeneca FluMist® Quadrivalent**	**GSK Flulaval® Tetra**	**Sanofi Pasteur Fluzone® Quadrivalent**
Post puncture shelf life for multi-dose vials	NA	28 days	28 days	NA	7 days	28 days	NA	NA	28 days	Up to expiry date indicated on vial label
Thimerosal	No	Yes	Yes (multi-dose vials only)	No	Yes (multi-dose vials only)	Yes (multi-dose vials only)	No	No	Yes	Yes (multi-dose vials only)
Antibiotics (traces)	Gentamicin	None	Kanamycin Neomycin	Kanamycin Neomycin	Neomycin	None	None	Gentamicin	None	None
Other clinically relevant non-medicinal ingredients*	Egg protein, Chicken protein, Formalde-hyde, CTAB, Polysorbate 80	Egg protein, α-tocopheryl hydrogen succinate, Polysorbate 80, Formalde-hyde, Ethanol, Sodium deoxy-cholate, Sucrose	Egg protein, Formalde-hyde, Polysorbate 80, CTAB	Egg protein, Formalde-hyde, Polysorbate 80, CTAB	Egg protein, Formalde-hyde, Triton X-100	Egg protein, Formalde-hyde, Triton X-100, Gelatin, Sucrose	Formalde-hyde, Egg protein, Triton X-100	Egg protein, Gelatin hydrosylate, Sucrose, Arginine, Monosodium glutamate	Egg protein, α-tocopheryl hydrogen succinate, Polysorbate 80, Formalde-hyde, Ethanol, Sodium deoxy-cholate, Sucrose	Egg protein, Formaldehyde, Triton X-100, Sucrose

Abbreviations: CTAB, cetyltrimethyl-ammonium bromide; HA, haemagglutinin; IM, intramuscular; LAIV, live attenuated influenza vaccine; NA, not applicable; QIV, quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine.

* Full details of the composition of each vaccine authorized for use in Canada and a brief description of its manufacturing process can be found in the product monograph.
** Refer to product monograph for alternate route(s) of administration
*** Change in authorized age indication for the 2017–2018 influenza season

Appendix B: NACI Recommendations: Strength of Recommendation and Grade of Evidence

STRENGTH OF NACI RECOMMENDATION	GRADE OF EVIDENCE
Based on factors not isolated to strength of evidence (e.g. public health need)	***Based on assessment of the body of evidence***
Strong "*should/should not be* offered" ➢ Known/Anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not") ➢ Implication: A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present	A - *good evidence* to recommend
	B - *fair evidence* to recommend
	C - *conflicting evidence*, however other factors may influence decision-making
	D - *fair evidence* to recommend against
	E - *good evidence* to recommend against
	I - *insufficient evidence* (in quality or quantity), however other factors may influence decision-making
Discretionary "*may be* considered" ➢ Known/Anticipated advantages closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists ➢ Implication: A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.	A - *good evidence* to recommend
	B - *fair evidence* to recommend
	C - *conflicting evidence*, however other factors may influence decision-making
	D - *fair evidence* to recommend against
	E - *good evidence* to recommend against
	I - *insufficient evidence* (in quality or quantity), however other factors may influence decision-making

Appendix C: Search Strategy and Results

Set #	Searches	Results
EMBASE (1974 to 20 June 2017), Global Health (1973 to 20 June 2017) and MEDLINE (1947 to 20 June 2017)		
1	influenza vaccine/ or influenza vaccination/	55633
2	exp influenza/pc or exp Influenza virus/pc	36160
3	(exp influenza/ or exp Influenza virus/) and (vaccine/ or virus vaccine/ or inactivated virus vaccine/ or vaccination/)	37518
4	((flu or influenza* or H?N? or (trivalent or inactiv* subunit*)) and (vaccin* or immuni?ation*)).tw,kw.	104418
5	or/1-4 [Flu Vaccine]	128519
6	(abbott or solvay or BGP Pharma or Mylan).mf,ad,tn,ti,ab.	51292
7	5 and 6 [Flu Vaccine by Abbott or Solvay]	389
8	influvac*.af.	349
9	7 or 8 [Influvac or suspected Influvac]	576
10	limit 9 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in Global Health,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	112
11	juvenile/ or exp child/ or exp adolescent/	5959007
12	(baby or babies or infan* or child* or youth* or juvenile* or adolescen* or p?ediatric*).tw,kw.	4505804
13	9 and (11 or 12)	120
14	10 or 13 [Influvac + Children]	162
15	limit 14 to (english or french)	137
16	(baby or babies or infan* or child* or youth* or juvenile* or adolescen* or p?ediatric*).mp.	7812184
17	11 or 16	8047584
18	9 and (11 or 16)	128
19	10 or 18	170
20	limit 19 to (english or french) [Expanding Pediatric Limit]	144
21	20 use oemezd	92
22	Influenza Vaccines/	44253
23	Influenza, Human/pc [Prevention & Control]	18537
24	(Influenza, Human/ or exp influenzavirus a/ or exp influenzavirus b/) and exp vaccines/	23917
25	((flu or influenza* or H?N? or (trivalent or inactiv* subunit*)) and (vaccin* or immuni?ation*)).tw,kf.	103905
26	or/22-25 [Flu Vaccine]	120373
27	(abbott or solvay or BGP Pharma or Mylan).af.	90837
28	26 and 27 [Flu Vaccine by Abbott or Solvay or BGP Pharma]	497
29	influvac*.af.	349
30	28 or 29 [Influvac or suspected Influvac]	683
31	limit 30 to "all child (0 to 18 years)" [Limit not valid in Embase,Global Health; records were retained]	615
32	exp Pediatrics/ or exp Infant/ or exp Child/ or Adolescent/	6510773
33	(baby or babies or infan* or child* or youth* or juvenile* or adolescen* or p?ediatric*).tw,kw.	4505804
34	30 and (32 or 33)	144
35	31 or 34 [Influvac + Children]	618
36	(baby or babies or infan* or child* or youth* or juvenile* or adolescen* or	7812184

Set #	Searches	Results
	p?ediatric*).mp.	
37	30 and (32 or 36)	151
38	31 or 37	618
39	limit 38 to (english or french)	560
40	39 use ppezv	17
41	exp influenza viruses/ or influenzavirus a/ or influenzavirus b/	103893
42	exp vaccination/ or exp vaccines/ or exp immunization/	780965
43	((flu or influenza* or H?N? or (trivalent or inactiv* subunit*)) and (vaccin* or immuni?ation*)).mp.	134380
44	(41 and 42) or 43	134619
45	(abbott or solvay or BGP Pharma or Mylan).af.	90837
46	44 and 45	576
47	influvac*.af.	349
48	46 or 47	757
49	exp children/ or exp adolescents/ or exp infants/ or exp paediatrics/	6030218
50	(baby or babies or infan* or child* or youth* or juvenile* or adolescen* or p?ediatric*).mp.	7812184
51	48 and (49 or 50)	166
52	limit 51 to (english or french)	148
53	52 use cagf	13
54	21 or 40 or 53	122
55	remove duplicates from 54	106
International Pharmaceutical Abstracts (1970 to 29 June 2017)		
1	("influenza vaccines" or (influenza and vaccines)).sh,hw.	1695
2	((flu or influenza* or H?N? or (trivalent or inactiv* subunit*)) and (vaccin* or immuni?ation*)).mp.	2482
3	1 or 2	2482
4	(abbott or solvay or BGP Pharma or Mylan).mp.	241
5	3 and 4	1
6	Influvac*.mp.	14
7	5 or 6	15
8	(baby or babies or infan* or child* or youth* or juvenile* or adolescen* or p?ediatric*).mp.	35612
9	7 and 8	0
1	("influenza vaccines" or (influenza and vaccines)).sh,hw.	1695
2	((flu or influenza* or H?N? or (trivalent or inactiv* subunit*)) and (vaccin* or immuni?ation*)).mp.	2482
3	1 or 2	2482
4	(abbott or solvay or BGP Pharma or Mylan).mp.	241
5	3 and 4	1
ProQuest Public Health Database (1963 to 29 June 2017)		
-	(((((ti,ab,ft(flu OR influenza* OR H?N? OR (trivalent OR inactiv* subunit*)) AND (vaccin* OR immuni?ation*)) OR mesh.Exact("Influenza Vaccines")) OR ((mesh.Exact("Influenza, Human" OR "influenzas a" OR "influenzas b") OR SU.EXACT("Influenza")) AND (SU.EXACT("Immunization") OR SU.EXACT("Vaccines") OR mesh.Exact("vaccines")))) AND ti,ab,ft((abbott OR solvay OR "BGP Pharma" OR Mylan) NEAR/5 vaccin*)) OR ti,ab,ft(influvac*)) AND (SU.EXACT("Children & youth") OR SU.EXACT("Newborn babies") OR SU.EXACT("Babies") OR SU.EXACT("Teenagers") OR mesh.Exact("Pediatrics" OR	43

Set #	Searches	Results
	"Infant" OR "Child" OR "Adolescent") OR ti,ab(baby OR babies OR infan* OR child* OR youth* OR juvenile* OR adolescen* OR p?ediatric*)) AND stype.exact("Scholarly Journals") AND la.exact("English" OR "French")	
Scopus (1960 to 29 June 2017)		
-	((TITLE-ABS-KEY(((flu OR influenza* OR h?n? OR (trivalent OR inactiv* AND subunit*)) AND (vaccin* OR immunisation* OR immunization*))) AND TITLE-ABS-KEY((abbott OR solvay OR "bgp pharma" OR mylan) W/3 vaccin*)) OR ALL(influvac*)) AND TITLE-ABS-KEY(baby OR babies OR infan* OR child* OR youth* OR juvenile* OR adolescen* OR pediatric* OR paediatric*) AND LANGUAGE(English OR French)	117

Appendix D: Level of Evidence Based on Research Design and Quality (Internal Validity) Rating of Evidence

Table D1: Ranking Individual Studies: Levels of Evidence Based on Research Design

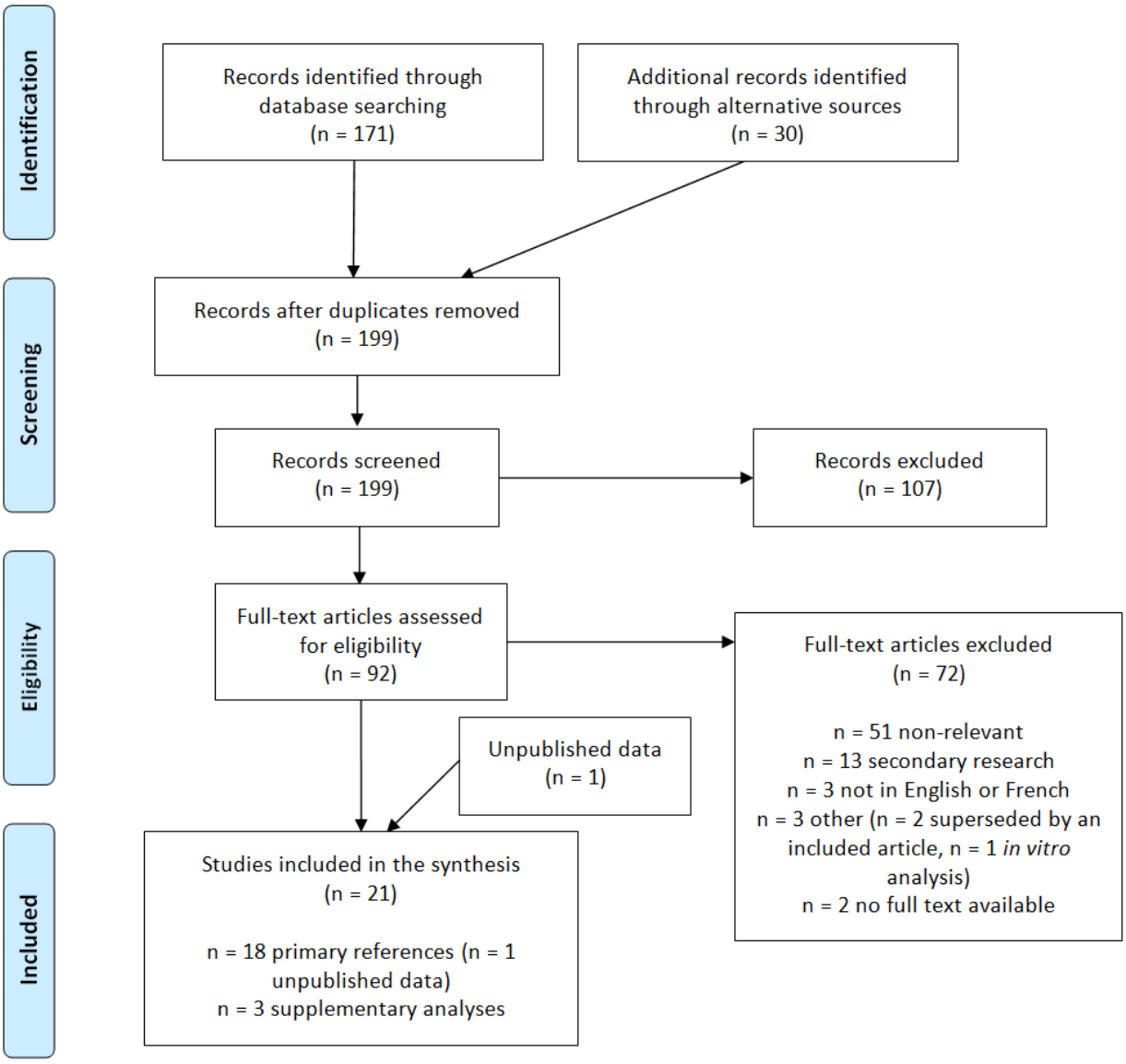
Level	Description
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table D2: Ranking Individual Studies: Quality (Internal Validity) Rating of Evidence

Quality Rating	Description
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.

* General design-specific criteria are outlined in Harris et al. (2001)[6].

Appendix E: Flow Diagram of the Study Selection Process for Literature Evidence on the Efficacy and Effectiveness, Immunogenicity and Safety of the Influvac® Trivalent Inactivated Influenza Vaccine in Children



Appendix F: Summary of Literature Evidence Related to the Efficacy and Effectiveness of Influvac® Trivalent Inactivated Influenza Vaccine in Children

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr>
<td>Ghendon et al. (2006)[26]</td>
<td>Design
Non-randomized controlled trial

Influenza season
2001–2002

Location
Russia

Follow-up
Morbidity: 4 months post-vaccination (December 2001–March 2002)

Adverse events: 3–5 days post-vaccination</td>
<td>Influenza vaccine
Influvac® TIV

Dose and administration
1 dose (15 µg per strain)

Strains
2001–2002 formulation:
A/New Caledonia/20/99 (H1N1)
A/Moscow/10/99 (H3N2)
B/Sichuan/379/99</td>
<td>Population definition
Healthy children without contraindications

Study groups
Intervention: Mass immunization campaign (coverage rate 69.7%)

Control: No immunization campaign (coverage rate <1.0%)

Sample size
Intervention: n=40,611
Control: n=60,946

Age
3–17 years

Sex
NR</td>
<td>Incidence rate of ILI defined as sudden onset of fever >38°C and cough or sore throat

<table>
<tr><th rowspan="2">Age group (years)</th><th colspan="2">Morbidity (%)</th></tr>
<tr><th>Intervention</th><th>Control</th></tr>
<tr><td>3–6</td><td>14.8</td><td>37.9</td></tr>
<tr><td>7–17</td><td>6.4</td><td>20.5</td></tr>
<tr><td>Total</td><td>7.7</td><td>23.6</td></tr>
</table>

Vaccine effectiveness
Definition: Difference in attack rate of ILI between non-immunized and immunized children divided by attack rate of ILI in non-immunized children only

<table>
<tr><th>Age group (years)</th><th>Vaccine effectiveness* (%)</th><th>p-value</th></tr>
<tr><td>3–6</td><td>60.9</td><td><0.001</td></tr>
<tr><td>7–17</td><td>68.8</td><td><0.001</td></tr>
<tr><td>Total</td><td>63.7</td><td><0.001</td></tr>
</table>
* Comparing vaccinated with unvaccinated persons</td>
<td>Level II-1</td>
<td>NA</td>
</tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr>
<td>Jansen et al. (2008a)[18]

Supplemented with additional details from Jansen et al. (2008b)[19] on AEFI.</td>
<td>Design
Double-blind RCT (placebo-controlled)

Influenza seasons
2003–2004
2004–2005
2005–2006

Location
The Netherlands

Follow-up
2003–2004 and 2004–2005 seasons: 18 months post-vaccination

2005–2006 season: 6 months post-vaccination

Adverse events: 7 days post-vaccination</td>
<td>Influenza vaccine
Influvac® TIV

Dose and administration
2 doses, 4–8 weeks apart

2003–2004 and 2004–2005 cohorts received an additional vaccination in the following year

Strains
2003–2004 formulation:
A/New Caledonia/20/99 (H1N1)
A/Moscow/10/99 (H3N2)
B/Hong Kong/330/01

2004–2005 formulation:
A/New Caledonia/20/99 (H1N1)
A/Fuijan/411/2002 (H3N2)
B/Shanghai/361/2002

2005–2006 formulation:
A/New Caledonia/20/99 (H1N1)
A/California/7/2004 (H3N2)
B/Shanghai/361/2002</td>
<td>Population definition
Unvaccinated children aged 18–72 months with previously diagnosed RTI

Study groups
TIV plus PCV7

TIV plus placebo

HBV plus placebo (control)

Sample size
TIV plus PCV7: n=197
TIV plus placebo: n=187
HBV plus placebo (control): n=195

Age (mean)
TIV plus PCV7: 3.0 years
TIV plus placebo: 3.1 years
HBV plus placebo (control): 3.1 years

Sex
TIV plus PCV7: 41.4% female
TIV plus placebo: 44.4% female
HBV plus placebo: 49.7% female

The study groups were similar with regard to age, sex and medical history.</td>
<td>Primary outcome
• Febrile RTI defined as having fever ≥38.0°C for at least two consecutive days accompanied by at least two signs of RTI (general weakness/malaise, rhinitis, sore throat, ear-ache, coughing, wheezing/shortness of breath, shivering/muscle aches) with a moderate or severe severity score.

<table>
<tr><th>Group</th><th>Incidence rate (per 1000 days) (95% CI)</th><th>Incidence rate ratio (95% CI)</th></tr>
<tr><td>TIV plus PCV7</td><td>5.2 (4.2–6.5)</td><td>0.76 (0.58–0.99)</td></tr>
<tr><td>TIV plus placebo</td><td>6.0 (5.0–7.2)</td><td>0.87 (0.68–1.12)</td></tr>
<tr><td>HBV plus placebo (control)</td><td>6.9 (5.9–8.2)</td><td>-</td></tr>
</table>
Secondary outcomes
• Laboratory-confirmed influenza defined by the presence of influenza A or B as determined by real-time PCR of a nasopharyngeal swab. A swab was only taken if a child's parent reported febrile RTI.

Of the children who received Influvac® plus PCV7, 4% had confirmed influenza, while 9% of children in the control group (HBV plus placebo) had laboratory-confirmed influenza. The relative risk for patients who received Influvac® plus PCV7 compared to those who received HBV plus placebo was 0.48 (95% CI: 0.25–0.93).

Of the children who received Influvac® plus placebo, 5% had confirmed influenza, while 9% of children in the control group (HBV plus placebo) had laboratory-confirmed influenza. The relative risk for patients who received Influvac® compared to those who received HBV plus placebo was 0.49 (95% CI: 0.25–0.97).

Findings by influenza virus type were not reported.</td>
<td>Level I</td>
<td>Fair

14–20% loss to follow up.</td>
</tr>
</table>

<table>
<tr><th colspan="4">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td></td><td>

Primary care visit defined as a visit to a general practitioner’s office.

<table>
<tr><th>Group</th><th>Incidence rate (per 1000 days) (95% CI)</th><th>Incidence rate ratio (95% CI)</th></tr>
<tr><td>TIV plus PCV7</td><td>2.2
(1.6–3.0)</td><td>0.75
(0.50–1.12)</td></tr>
<tr><td>TIV plus placebo</td><td>2.0
(1.4–2.7)</td><td>0.67
(0.45–1.02)</td></tr>
<tr><td>HBV plus placebo (control)</td><td>2.9
(2.3–3.7)</td><td>-</td></tr>
</table>

Antibiotic prescription defined as the prescription of an antibiotic resulting from febrile RTI episode

<table>
<tr><th>Group</th><th>Incidence rate (per 1000 days) (95% CI)</th><th>Incidence rate ratio (95% CI)</th></tr>
<tr><td>TIV plus PCV7</td><td>1.0
(0.6–1.6)</td><td>0.73
(0.40–1.32)</td></tr>
<tr><td>TIV plus placebo</td><td>1.2
(0.8–1.9)</td><td>0.89
(0.50–1.61)</td></tr>
<tr><td>HBV plus placebo (control)</td><td>1.4
(0.9–2.1)</td><td>-</td></tr>
</table>

Acute otitis media defined as a physician-diagnosed episode of acute otitis media

<table>
<tr><th>Group</th><th>Incidence rate (per 1000 days) (95% CI)</th><th>Incidence rate ratio (95% CI)</th></tr>
<tr><td>TIV plus PCV7</td><td>0.5
(0.3–1.0)</td><td>0.43
(0.20–0.94)</td></tr>
<tr><td>TIV plus placebo</td><td>0.4
(0.2–0.8)</td><td>0.29
(0.12–0.70)</td></tr>
<tr><td>HBV plus placebo (control)</td><td>1.2
(0.8–1.9)</td><td>-</td></tr>
</table>
Notes
Effects of influenza vaccination outside of the influenza seasons are not presented.
</td><td></td><td></td></tr>
</table>

Abbreviations: Refer to section V. List of Abbreviations.

Appendix G: Summary of Literature Evidence Related to the Immunogenicity of Influvac® Trivalent Inactivated Influenza Vaccine in Children

<table>
<tr><th colspan="4">STUDY DETAILS</th><th colspan="3">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr>
<td>Brydak et al. (2000)[9]</td>
<td>Design
Pre-post study

Location
Poland

Follow-up
3 weeks and 6 weeks post-vaccination</td>
<td>Influenza vaccine
Influvac® TIV

Dose and administration
1 dose (15 µg per strain)

Strains
1996–1997 formulation:
A/Singapore/6/86 (H1N1)
A/Wuhan/359/95 (H3N2)
B/Beijing/184/93</td>
<td>Population definition
Children with ALL (groups A and B)

Study groups
A: Chemotherapy completed before 1991

B: Chemotherapy completed after 1991

Unvaccinated controls (healthy children)

Sample size
Group A: n=10
Group B: n=12
Controls: n=22

Age
6–13 years

Sex
NR</td>
<td>3 week post-vaccination:

GMT
<table>
<tr><th>Strain</th><th>Group A</th><th>Group B</th><th>Controls</th></tr>
<tr><td>H1N1</td><td>37.3</td><td>33.6</td><td>3.1–3.3</td></tr>
<tr><td>H3N2</td><td>52.8</td><td>40.0</td><td>1.3–1.8</td></tr>
<tr><td>B</td><td>80.0</td><td>75.5</td><td>1.2–2.7</td></tr>
</table>
GMFR
<table>
<tr><th>Strain</th><th>Group A</th><th>Group B</th><th>Controls</th></tr>
<tr><td>H1N1</td><td>18.7</td><td>18.7</td><td>2.4–2.8</td></tr>
<tr><td>H3N2</td><td>11.5</td><td>25.0</td><td><1.0</td></tr>
<tr><td>B</td><td>20.5</td><td>37.8</td><td><1.0–2.0</td></tr>
</table>
Seroprotection rate
<table>
<tr><th>Strain</th><th>Group A (%)</th><th>Group B (%)</th><th>Controls (%)</th></tr>
<tr><td>H1N1</td><td>60.0</td><td>41.7</td><td>0.0–8.3</td></tr>
<tr><td>H3N2</td><td>80.0</td><td>50.0</td><td>0.0</td></tr>
<tr><td>B</td><td>100.0</td><td>83.3</td><td>0.0</td></tr>
</table>
Seroconversion rate
<table>
<tr><th>Strain</th><th>Group A (%)</th><th>Group B (%)</th><th>Controls (%)</th></tr>
<tr><td>H1N1</td><td>60.0</td><td>41.7</td><td>0.0–10.0</td></tr>
<tr><td>H3N2</td><td>80.0</td><td>50.0</td><td>0.0</td></tr>
<tr><td>B</td><td>100.0</td><td>83.3</td><td>0.0–8.3</td></tr>
</table>
6 month post-vaccination:

GMT
<table>
<tr><th>Strain</th><th>Group A</th><th>Group B</th><th>Controls</th></tr>
<tr><td>H1N1</td><td>65.0</td><td>26.2</td><td>3.7–4.8</td></tr>
<tr><td>H3N2</td><td>91.9</td><td>100.8</td><td>7.1–7.9</td></tr>
<tr><td>B</td><td>113.1</td><td>134.5</td><td>33.6–34.8</td></tr>
</table>
GMFR
<table>
<tr><th>Strain</th><th>Group A</th><th>Group B</th><th>Controls</th></tr>
<tr><td>H1N1</td><td>32.5</td><td>14.6</td><td>3.1–3.7</td></tr>
<tr><td>H3N2</td><td>20.0</td><td>63.0</td><td>2.3–2.6</td></tr>
<tr><td>B</td><td>29.0</td><td>67.3</td><td>17.7–26.7</td></tr>
</table>
</td>
<td>Level III</td>
<td>NA</td>
</tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Seroprotection rate
<table>
<tr><th>Strain</th><th>Group A (%)</th><th>Group B (%)</th><th>Controls (%)</th></tr>
<tr><td>H1N1</td><td>90.0</td><td>41.7</td><td>8.3–10.0</td></tr>
<tr><td>H3N2</td><td>100.0</td><td>100.0</td><td>8.3–10.0</td></tr>
<tr><td>B</td><td>100.0</td><td>83.3</td><td>50.0</td></tr>
</table>
Seroconversion rate
<table>
<tr><th>Strain</th><th>Group A (%)</th><th>Group B (%)</th><th>Controls (%)</th></tr>
<tr><td>H1N1</td><td>90.0</td><td>41.7</td><td>8.3–10.0</td></tr>
<tr><td>H3N2</td><td>100.0</td><td>100.0</td><td>0.0–10.0</td></tr>
<tr><td>B</td><td>100.0</td><td>83.3</td><td>16.7–50.0</td></tr>
</table>
Notes

Subjects were vaccinated with FluShield® (Wyeth) in the 1993–1994 influenza season and with Influvac® in the 1996–1997 influenza season. Data for the 1996–1997 influenza season is presented.
Results are also available for subjects vaccinated for the first time in the 1996–1997 influenza season, but are not presented.
Though not stated explicitly in the article, the study subjects likely overlap with Brydak et al. (1998a)[10].
</td><td></td><td></td></tr>
<tr><td>Brydak et al. (1998a)[10]</td><td>Design
Pre-post study

Location
Poland

Follow-up
3 weeks and 6 weeks post-vaccination</td><td>Influenza vaccine
Influvac® TIV

Dose and administration
1 dose (15 µg per strain)

Strains
1996–1997 formulation:
A/Singapore/6/86 (H1N1)
A/Wuhan/359/95 (H3N2)
B/Beijing/184/93</td><td>Population definition
Children with ALL (groups A and B)

Study groups
A: Vaccinated in the 1993–1994 influenza season

B: Unvaccinated prior to the 1996–1997 influenza season

Unvaccinated controls (healthy children)

Sample size
Group A: n=25
Group B: n=20
Controls: n=23</td><td>3 week post-vaccination:

GMT
<table>
<tr><th>Strain</th><th>Group A</th><th>Group B</th><th>Controls</th></tr>
<tr><td>H1N1</td><td>35.8</td><td>42.9</td><td>3.0</td></tr>
<tr><td>H3N2</td><td>44.7</td><td>62.8</td><td>1.8</td></tr>
<tr><td>B</td><td>80.0</td><td>77.3</td><td>2.8</td></tr>
</table>
GMFR
<table>
<tr><th>Strain</th><th>Group A</th><th>Group B</th><th>Controls</th></tr>
<tr><td>H1N1</td><td>18.8</td><td>22.6</td><td>2.1</td></tr>
<tr><td>H3N2</td><td>17.2</td><td>15.7</td><td>NA</td></tr>
<tr><td>B</td><td>26.7</td><td>15.8</td><td>1.5</td></tr>
</table>
Seroprotection rate
<table>
<tr><th>Strain</th><th>Group A (%)</th><th>Group B (%)</th><th>Controls (%)</th></tr>
<tr><td>H1N1</td><td>52.0</td><td>55.0</td><td>4.3</td></tr>
<tr><td>H3N2</td><td>64.0</td><td>85.0</td><td>0.0</td></tr>
<tr><td>B</td><td>92.0</td><td>75.0</td><td>0.0</td></tr>
</table></td><td>Level III</td><td>NA</td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td>Age
Group A: 7–16 years
Group B: 7–11 years
Controls: 8–15 years

Sex
NR</td><td>Seroconversion rate
<table>
<tr><th>Strain</th><th>Group A (%)</th><th>Group B (%)</th><th>Controls (%)</th></tr>
<tr><td>H1N1</td><td>52.0</td><td>55.0</td><td>4.3</td></tr>
<tr><td>H3N2</td><td>60.0</td><td>80.0</td><td>0.0</td></tr>
<tr><td>B</td><td>92.0</td><td>70.0</td><td>0.0</td></tr>
</table>
6 month post-vaccination:

GMT
<table>
<tr><th>Strain</th><th>Group A</th><th>Group B</th><th>Controls</th></tr>
<tr><td>H1N1</td><td>41.9</td><td>74.6</td><td>4.5</td></tr>
<tr><td>H3N2</td><td>91.9</td><td>121.3</td><td>6.7</td></tr>
<tr><td>B</td><td>114.7</td><td>149.3</td><td>23.0</td></tr>
</table>
GMFR
<table>
<tr><th>Strain</th><th>Group A</th><th>Group B</th><th>Controls</th></tr>
<tr><td>H1N1</td><td>22.1</td><td>39.3</td><td>3.2</td></tr>
<tr><td>H3N2</td><td>35.3</td><td>30.3</td><td>2.3</td></tr>
<tr><td>B</td><td>38.2</td><td>30.5</td><td>12.1</td></tr>
</table>
Seroprotection rate
<table>
<tr><th>Strain</th><th>Group A (%)</th><th>Group B (%)</th><th>Controls (%)</th></tr>
<tr><td>H1N1</td><td>68.0</td><td>90.0</td><td>8.7</td></tr>
<tr><td>H3N2</td><td>100.0</td><td>100.0</td><td>4.3</td></tr>
<tr><td>B</td><td>92.0</td><td>100.0</td><td>30.4</td></tr>
</table>
Seroconversion rate
<table>
<tr><th>Strain</th><th>Group A (%)</th><th>Group B (%)</th><th>Controls (%)</th></tr>
<tr><td>H1N1</td><td>68.0</td><td>90.0</td><td>8.7</td></tr>
<tr><td>H3N2</td><td>100.0</td><td>100.0</td><td>4.3</td></tr>
<tr><td>B</td><td>92.0</td><td>95.0</td><td>30.4</td></tr>
</table>
Notes
• Though not stated explicitly in the article, the study subjects likely overlap with Brydak et al. (2000)[9].
• The controls included in this study are the same subjects as the controls in Brydak et al. (1998b)[11].</td><td></td><td></td></tr>
<tr><td>Brydak et al. (1998b)[11]

Supplemented with additional details from Rokicka-Milewska et</td><td>Design
Pre-post study

Location
Poland

Follow-up
3 weeks and 6</td><td>Influenza vaccine
Influvac® TIV

Dose and administration
1 dose (15 µg per strain)</td><td>Population definition
Children with hemophilia who have previously been vaccinated for influenza in the 1993–1994</td><td>3 week post-vaccination:

GMT
<table>
<tr><th>Strain</th><th>Hemophiliac patients</th><th>Controls</th></tr>
<tr><td>H1N1</td><td>28.3</td><td>3.0</td></tr>
<tr><td>H3N2</td><td>29.3</td><td>1.8</td></tr>
<tr><td>B</td><td>35.2</td><td>2.8</td></tr>
</table></td><td>Level III</td><td>NA</td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td>al. (1999)[22] on the stratified analysis by severity of hemophilia (mild vs. severe).</td><td>weeks post-vaccination</td><td>Strains
1996–1997 formulation:
A/Singapore/6/86 (H1N1)
A/Wuhan/359/95 (H3N2)
B/Beijing/184/93</td><td>season

Study groups
Hemophiliac patients

Unvaccinated controls (healthy children)

Sample size
Hemophiliac patients: n=38 (n=26 severe and 12 mild)
Controls: n=23

Age
Hemophiliac patients: 10–19 years
Controls: 8–15 years

Sex
NR</td><td>GMFR
<table><tr><th>Strain</th><th>Hemophiliac patients</th><th>Controls</th></tr><tr><td>H1N1</td><td>6.7</td><td>2.1</td></tr><tr><td>H3N2</td><td>10.9</td><td><1.0</td></tr><tr><td>B</td><td>3.9</td><td>1.5</td></tr></table>Seroprotection rate<table><tr><th>Strain</th><th>Hemophiliac patients (%)</th><th>Controls (%)</th></tr><tr><td>H1N1</td><td>57.9</td><td>4.3</td></tr><tr><td>H3N2</td><td>52.6</td><td>0.0</td></tr><tr><td>B</td><td>60.5</td><td>0.0</td></tr></table>Seroconversion rate<table><tr><th>Strain</th><th>Hemophiliac patients (%)</th><th>Controls (%)</th></tr><tr><td>H1N1</td><td>42.1</td><td>4.3</td></tr><tr><td>H3N2</td><td>42.1</td><td>0.0</td></tr><tr><td>B</td><td>39.5</td><td>0.0</td></tr></table>6 month post-vaccination:

GMT<table><tr><th>Strain</th><th>Hemophiliac patients</th><th>Controls</th></tr><tr><td>H1N1</td><td>45.7</td><td>4.5</td></tr><tr><td>H3N2</td><td>77.1</td><td>6.7</td></tr><tr><td>B</td><td>75.3</td><td>23.0</td></tr></table>GMFR<table><tr><th>Strain</th><th>Hemophiliac patients</th><th>Controls</th></tr><tr><td>H1N1</td><td>10.9</td><td>3.2</td></tr><tr><td>H3N2</td><td>28.6</td><td>2.3</td></tr><tr><td>B</td><td>8.4</td><td>12.1</td></tr></table>Seroprotection rate<table><tr><th>Strain</th><th>Hemophiliac patients (%)</th><th>Controls (%)</th></tr><tr><td>H1N1</td><td>76.3</td><td>8.7</td></tr><tr><td>H3N2</td><td>92.1</td><td>4.3</td></tr><tr><td>B</td><td>97.4</td><td>30.4</td></tr></table></td><td></td><td></td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Seroconversion rate
<table>
<tr><th>Strain</th><th>Hemophiliac patients (%)</th><th>Controls (%)</th></tr>
<tr><td>H1N1</td><td>71.1</td><td>8.7</td></tr>
<tr><td>H3N2</td><td>84.2</td><td>4.3</td></tr>
<tr><td>B</td><td>86.8</td><td>30.4</td></tr>
</table>
Stratified analysis by severity of hemophilia
Patients with mild and severe hemophilia had similar GMTs and GMFRs for influenza A and B strains at 6 months post-vaccination. Seroprotection and seroconversion rates were similar for both groups for influenza A(H3N2) and B; however, patients with severe hemophilia had a lower rate of seroprotection compared to patients with mild hemophilia for influenza A(H1N1) at 3 weeks and 6 months post-vaccination (61.5–65.4% vs. 83.3%). Patients with severe hemophilia also had lower rates of seroconversion for influenza A(H1N1) compared to patients with mild hemophilia at 3 weeks and 6 months post-vaccination (46.2–53.8% vs. 66.7%).

Notes
The controls included in this study are the same subjects as the controls in Brydak et al. (1998a)[10].</td><td></td><td></td></tr>
<tr><td>Bueving (2004a)[12]

Supplemented with additional details from Bueving et al. (2004b)[13] on AEFI and asthma exacerbation following vaccination.</td><td>Design
Double-blind RCT (placebo-controlled)

Location
The Netherlands

Follow-up
14–21 days and 4–5 months post-vaccination

Adverse events: 7 days post-vaccination (findings presented in Appendix H)</td><td>Influenza vaccine
Influvac® TIV (reported as a Solvay TIV)

Dose and administration
1 dose (15 µg per strain)

Strains
1999–2000 formulation:
A/Beijing/262/95-like (H1N1)
A/Sydney/5/97-like (H3N2)
B/Beijing/184/93-like

2000–2001 formulation:
A/New Caledonia/20/99 (H1N1)
A/Moscow/10/99-like</td><td>Population definition
Children 6–18 years of age with asthma, without other chronic diseases

Sample size
Vaccine: n=347
Placebo: n=349

Age (mean)
Vaccine: 10.5 years
Placebo: 10.6 years

Sex
Vaccine: 48.1% female
Placebo: 43.6% female</td><td>14–21 days post-vaccination:

GMT
<table>
<tr><th>Strain</th><th>Vaccine</th><th>Placebo</th><th>p-value</th></tr>
<tr><td>H1N1</td><td>200.7</td><td>23.0</td><td><0.001</td></tr>
<tr><td>H3N2</td><td>227.1</td><td>79.4</td><td><0.001</td></tr>
<tr><td>B</td><td>358.4</td><td>157.6</td><td><0.001</td></tr>
</table>
Seroprotection rate
<table>
<tr><th>Strain</th><th>Vaccine (%)</th><th>Placebo (%)</th><th>p-value</th></tr>
<tr><td>H1N1</td><td>85.6</td><td>38.9</td><td><0.001</td></tr>
<tr><td>H3N2</td><td>98.5</td><td>79.2</td><td><0.001</td></tr>
<tr><td>B</td><td>95.3</td><td>87.7</td><td><0.001</td></tr>
</table>
Seroconversion rate
<table>
<tr><th>Strain</th><th>Vaccine (%)</th><th>Placebo (%)</th><th>p-value</th></tr>
<tr><td>H1N1</td><td>59.9</td><td>0.9</td><td><0.001</td></tr>
<tr><td>H3N2</td><td>27.1</td><td>1.2</td><td><0.001</td></tr>
<tr><td>B</td><td>26.5</td><td>0.0</td><td><0.001</td></tr>
</table></td><td>Level I</td><td>Fair

Conducted per-protocol analyses.</td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td>(H3N2)
B/Beijing/184/93-like

Children could only participate in one of the two seasons</td><td></td><td>4–5 months post-vaccination:

GMT<table><tr><th>Strain</th><th>Vaccine</th><th>Placebo</th><th>p-value</th></tr><tr><td>H1N1</td><td>188.0</td><td>38.0</td><td><0.001</td></tr><tr><td>H3N2</td><td>186.3</td><td>88.3</td><td><0.001</td></tr><tr><td>B</td><td>1.8</td><td>0.9</td><td><0.001</td></tr></table>Seroconversion rate*<table><tr><th>Strain</th><th>Vaccine (%)</th><th>Placebo (%)</th><th>p-value</th></tr><tr><td>H1N1</td><td>7.0</td><td>17.5</td><td><0.001</td></tr><tr><td>H3N2</td><td>1.2</td><td>4.0</td><td>0.03</td></tr><tr><td>B</td><td>1.8</td><td>0.9</td><td>0.26</td></tr></table>* Seroconversion at 4–5 months post-vaccination was calculated by comparing the sample taken at 4–5 months post-vaccination to the sample taken at 14–21 days post-vaccination.</td><td></td><td></td></tr>
<tr><td>Daubeney et al. (1997)[16]</td><td>Design
Pre-post study

Location
United Kingdom

Follow-up
Up to 72 hours post-vaccination</td><td>Influenza vaccine
Influvac® TIV

Dose and administration
2 doses (7.5 µg per strain), 4 weeks apart

Strains
A/Singapore/6/86 (H1N1)
A/Shangdong/9/93 (H3N2)
B/Panama/45/90</td><td>Population definition
Children with chronic respiratory disease, congenital heart disease, or both.

Sample size
n=52

Age
Mean (range): 19.5 months (6 months–4 years)

Sex
NR</td><td>GMT<table><tr><th>Strain</th><th>GMT pre-vaccination (95% CI)</th><th>GMT post-vaccination (95% CI)</th></tr><tr><td>H1N1</td><td>5.2 (4.8–5.6)</td><td>56.0 (38.1–82.3)</td></tr><tr><td>H3N2</td><td>13.1 (8.7–19.6)</td><td>76.2 (40.9–142.2)</td></tr><tr><td>B</td><td>6.2 (5.1–7.6)</td><td>65.3 (44.3–96.4)</td></tr></table>GMFR<table><tr><th>Strain</th><th>GMFR (95% CI)</th></tr><tr><td>H1N1</td><td>10.8 (7.5–15.4)</td></tr><tr><td>H3N2</td><td>5.8 (4.3–7.9)</td></tr><tr><td>B</td><td>10.5 (7.4–14.8)</td></tr></table>Seroprotection rate<table><tr><th>Strain</th><th>Seroprotection rate (95% CI) (%)</th></tr><tr><td>H1N1</td><td>71 (56–83)</td></tr><tr><td>H3N2</td><td>55 (40–69)</td></tr><tr><td>B</td><td>71 (56–83)</td></tr></table>Seroconversion rate<table><tr><th>Strain</th><th>Seroconversion rate (95% CI) (%)</th></tr><tr><td>H1N1</td><td>71 (56–81)</td></tr><tr><td>H3N2</td><td>55 (40–69)</td></tr><tr><td>B</td><td>69 (54–81)</td></tr></table></td><td>Level III</td><td>NA</td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr>
<td>El-Madhun et al. (1998)[17]</td>
<td>Design
Pre-post study

Location
Norway

Follow-up
6–8, 12–20 and 28–42 days post-vaccination after the first dose of the vaccine</td>
<td>Influenza vaccine
Influvac® TIV (reported as a Solvay subunit TIV)

Dose and administration
2 doses (7.5 µg per strain), 28–42 days apart

Strains
A/Texas/36/91 (H1N1)
A/Johannesburg/33/94 (H3N2)
B/Harbin/7/94</td>
<td>Population definition
Children with a history of frequent tonsillar infections scheduled for tonsillectomy, without any other serious health problem and without previous vaccination against influenza.

Study groups
Primed and unprimed, based on presence of pre-vaccination antibodies to each vaccine strain

Sample size
n=18, with n=14 primed by influenza A(H3N2), 1 by influenza A(H1N1) and 3 by influenza B

Age
2–3 years

Sex
27.8% female</td>
<td>6–8 days post-vaccination (after first dose):

GMT
<table>
<tr><th>Strain</th><th>Primed</th><th>Unprimed</th></tr>
<tr><td>H1N1</td><td>Not available</td><td>10</td></tr>
<tr><td>H3N2</td><td>640</td><td>10</td></tr>
<tr><td>B</td><td>101</td><td>10</td></tr>
</table>
Seroprotection rate
<table>
<tr><th>Strain</th><th>Primed (%)</th><th>Unprimed (%)</th></tr>
<tr><td>H1N1</td><td>Not available</td><td>0</td></tr>
<tr><td>H3N2</td><td>100</td><td>0</td></tr>
<tr><td>B</td><td>100</td><td>0</td></tr>
</table>
12–20 days post-vaccination (after first dose):

GMT
<table>
<tr><th>Strain</th><th>Primed</th><th>Unprimed</th></tr>
<tr><td>H1N1</td><td>Not available</td><td>18</td></tr>
<tr><td>H3N2</td><td>1581</td><td>14</td></tr>
<tr><td>B</td><td>160</td><td>10</td></tr>
</table>
Seroprotection rate
<table>
<tr><th>Strain</th><th>Primed (%)</th><th>Unprimed (%)</th></tr>
<tr><td>H1N1</td><td>Not available</td><td>16.7</td></tr>
<tr><td>H3N2</td><td>100</td><td>0</td></tr>
<tr><td>B</td><td>100</td><td>0</td></tr>
</table>
28–42 days post-vaccination (after first dose):

GMT
<table>
<tr><th>Strain</th><th>Primed</th><th>Unprimed</th></tr>
<tr><td>H1N1</td><td>Not available</td><td>15</td></tr>
<tr><td>H3N2</td><td>1634</td><td>12</td></tr>
<tr><td>B</td><td>640</td><td>14</td></tr>
</table>
Seroprotection rate
<table>
<tr><th>Strain</th><th>Primed (%)</th><th>Unprimed (%)</th></tr>
<tr><td>H1N1</td><td>Not available</td><td>15.4</td></tr>
<tr><td>H3N2</td><td>100</td><td>0</td></tr>
<tr><td>B</td><td>100</td><td>27.3</td></tr>
</table>
</td>
<td>Level III</td>
<td>NA</td>
</tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Seroconversion rate
Significant increase in antibody (four-fold or higher) occurred at 6–8 or 12–20 days post-vaccination after the first dose in the primed group. No significant increase was observed after the first dose for the unprimed children.

Notes
• The study also included eight adults. However, analysis was done separately for children and adults. Only the findings in children are presented.
• Serology was not assessed after the second dose in vaccine-naïve children.</td><td></td><td></td></tr>
<tr><td>Shahgholi et al. (2010)[23]</td><td>Design
Non-randomized controlled trial

Location
Iran

Follow-up
4 weeks post-vaccination

Adverse events: 5 days post-vaccination (findings presented in Appendix H)</td><td>Influenza vaccine
Influvac® TIV

Dose and administration
<36 months of age: 2 doses (0.25mL), 3–4 weeks apart

36 months–13 years of age: 2 doses (0.5mL), 3–4 weeks apart

>13 years of age: 1 dose (0.5mL)

Strains
2007–2008 formulation:
A/Solomon Islands/3/2006 (H1N1)
A/Wisconsin/67/2005 (H3N2)
B/Malaysia/2506/2004-like</td><td>Population definition
Children 1–18 years of age diagnosed with ALL in first remission and receiving maintenance therapy and healthy children (siblings) as controls.

Sample size
ALL: n=32
Controls: n=30

Age (mean)
ALL: 10.65 years
Controls: 10.8 years

Sex
ALL: 34.4% female
Controls: 46.7% female</td><td>4 weeks post-vaccination:

GMT
<table>
<tr><th rowspan="2">Strain</th><th colspan="3">Pre-vaccine GMT (95% CI)</th><th colspan="3">Post-vaccine GMT (95% CI)</th></tr>
<tr><th>ALL</th><th>Controls</th><th>p-value</th><th>ALL</th><th>Controls</th><th>p-value</th></tr>
<tr><td>H1N1</td><td>32.5 (24.8–42.6)</td><td>31.5 (23.0–44.0)</td><td>0.873</td><td>52.9 (37.7–73.8)</td><td>76.4 (55.0–106.4)</td><td>0.130</td></tr>
<tr><td>H3N2</td><td>54.0 (40.0–77.0)</td><td>54.0 (35.2–83.0)</td><td>0.946</td><td>81.9 (55.8–120.0)</td><td>145.4 (100.0–212.5)</td><td>0.041</td></tr>
<tr><td>B</td><td>12.8 (10.6–15.2)</td><td>17.0 (12.3–23.4)</td><td>0.136</td><td>25.5 (18.5–35.0)</td><td>38.1 (26.6–54.3)</td><td>0.106</td></tr>
</table>
Seroprotection rate
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Seroprotection rate (%)</th></tr>
<tr><th>ALL</th><th>Controls</th></tr>
<tr><td>H1N1</td><td>43.4</td><td>88.0</td></tr>
<tr><td>H3N2</td><td>63.3</td><td>80.0</td></tr>
<tr><td>B</td><td>26.0</td><td>73.0</td></tr>
</table>
The protective response between the ALL and control groups for influenza A(H3N2) antigen did not differ significantly. However, the response rate for influenza A(H1N1) and B antigens in ALL patients was significantly lower than healthy controls (p=0.04 and 0.001, respectively).</td><td>Level II-1</td><td>NA

Siblings were used as controls, but similarities in important confounders were not assessed.</td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td>No significant differences were found for the gender and age distributions of the two groups.</td><td>Seroconversion rate
<table>
<tr><th>Strain</th><th>Group</th><th>Post-vaccination (95% CI) (%)</th><th>Odds ratio (95% CI)</th></tr>
<tr><td rowspan="2">H1N1</td><td>ALL</td><td>56.2 (26.9–73.1)</td><td rowspan="2">3.1 (1.1–9.7)</td></tr>
<tr><td>Controls</td><td>80 (81.9–105.6)</td></tr>
<tr><td rowspan="2">H3N2</td><td>ALL</td><td>40.6 (11.6–55.1)</td><td rowspan="2">NR</td></tr>
<tr><td>Controls</td><td>53.3 (53.8–96.2)</td></tr>
<tr><td rowspan="2">B</td><td>ALL</td><td>59.4 (38.6–83.6)</td><td rowspan="2">3.4 (1.1–11.3)</td></tr>
<tr><td>Controls</td><td>83.3 (81.9–105.6)</td></tr>
</table>
The seroconversion rates for influenza A(H1N1) and B were significantly lower in ALL patients than healthy controls (p=0.04 and 0.038, respectively), not for influenza A(H3N2).</td><td></td><td></td></tr>
<tr><td>Zhu et al. (2008)[25]</td><td>Design
Endpoint-blind RCT

Location
China

Follow-up
4 weeks post-vaccination

Adverse events: 29 days post-vaccination (findings presented in Appendix H)</td><td>Influenza vaccine
Influvac® TIV
Agrippal® TIV

Dose and administration
1 dose (15 µg per strain)

Strains
2005–2006 formulation:
A/New Caledonia/20/99 (H1N1)
A/New York/55/2004 (H3N2)
B/Jiangsu/10/2003</td><td>Population definition
Healthy children 3–12 years of age

Study groups
Vaccination with Influvac®

Vaccination with Agrippal®

Sample size
n=300 randomized 2:1 to receive either Influvac® or Agrippal®.

Age (mean)
Influvac®: 8.2 years
Agrippal®: 8.1 years

Sex
Influvac®: 50.0% female
Agrippal®: 50.0% female</td><td>29 days post-vaccination:

GMT
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Pre-vaccine GMT (95% CI)</th><th colspan="2">Post-vaccine GMT (95% CI)</th></tr>
<tr><th>Influvac®</th><th>Agrippal®</th><th>Influvac®</th><th>Agrippal®</th></tr>
<tr><td>H1N1</td><td>69.5 (60.3–80.1)</td><td>63.3 (51.6–77.7)</td><td>1212.1 (982–1495)</td><td>814.2 (616–1076)</td></tr>
<tr><td>H3N2</td><td>34.1 (28.2–41.2)</td><td>40.3 (31.2–52.1)</td><td>670.6 (558–806)</td><td>471.1 (364–609)</td></tr>
<tr><td>B</td><td>34.5 (28.8–41.3)</td><td>31.7 (24.8–40.4)</td><td>802.2 (647–994)</td><td>492.2 (369–657)</td></tr>
</table>
GMFR
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">GMFR (95% CI)</th></tr>
<tr><th>Influvac®</th><th>Agrippal®</th></tr>
<tr><td>H1N1</td><td>17.4 (14.3–21.2)</td><td>12.9 (9.9–16.7)</td></tr>
<tr><td>H3N2</td><td>19.7 (15.7–24.7)</td><td>11.7 (8.7–15.7)</td></tr>
<tr><td>B</td><td>23.3 (18.7–28.9)</td><td>15.5 (12.1–19.9)</td></tr>
</table>
GMFR for Influvac® by age subgroup
<table>
<tr><th>Strain</th><th>Children aged 3–5 years (95% CI)</th><th>Children aged 6–12 years (95% CI)</th></tr>
<tr><td>H1N1</td><td>9.1 (6.2–13.5)</td><td>20.1 (16.2–24.9)</td></tr>
<tr><td>H3N2</td><td>19.4 (11.1–34.1)</td><td>19.7 (15.4–25.2)</td></tr>
<tr><td>B</td><td>18.6 (10.5–33.1)</td><td>24.4 (19.4–30.8)</td></tr>
</table></td><td>Level I</td><td>Fair

Conducted per-protocol analyses. Study was endpoint-blind (not double-blind).</td></tr>
</table>

<table>
<tr><th colspan="4">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
Seroprotection rate
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Seroprotection rate (95% CI) (%)</th></tr>
<tr><th>Influvac®</th><th>Agrippal®</th></tr>
<tr><td>H1N1</td><td>99 (97–100)</td><td>99 (94–100)</td></tr>
<tr><td>H3N2</td><td>98 (95–100)</td><td>99 (94–100)</td></tr>
<tr><td>B</td><td>95 (91–98)</td><td>93 (85–97)</td></tr>
</table>
Seroprotection rate for Influvac® by age subgroup
<table>
<tr><th>Strain</th><th>Children aged 3–5 years (95% CI) (%)</th><th>Children aged 6–12 years (95% CI) (%)</th></tr>
<tr><td>H1N1</td><td>97 (84–100)</td><td>96 (79–100)</td></tr>
<tr><td>H3N2</td><td>91 (75–98)</td><td>96 (79–100)</td></tr>
<tr><td>B</td><td>72 (53–86)</td><td>71 (49–87)</td></tr>
</table>
Seroconversion rate
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Seroconversion rate (95% CI) (%)</th></tr>
<tr><th>Influvac®</th><th>Agrippal®</th></tr>
<tr><td>H1N1</td><td>87 (81–91)</td><td>82 (73–89)</td></tr>
<tr><td>H3N2</td><td>87 (81–92)</td><td>80 (71–88)</td></tr>
<tr><td>B</td><td>92 (87–96)</td><td>86 (78–93)</td></tr>
</table>
Seroconversion rate for Influvac® by age subgroup
<table>
<tr><th>Strain</th><th>Children aged 3–5 (95% CI) (%)</th><th>Children aged 6–12 (95% CI) (%)</th></tr>
<tr><td>H1N1</td><td>81 (64–93)</td><td>88 (81–93)</td></tr>
<tr><td>H3N2</td><td>81 (64–93)</td><td>88 (82–93)</td></tr>
<tr><td>B</td><td>66 (47–81)</td><td>98 (94–98)</td></tr>
</table>
GMT ratios for Influvac®:Agrippal®
The lower limits of the 95% CI of the ratio of post-vaccination GMTs for children aged 3–12 years (1.42–1.63), 3–5 years (0.94–1.29) and 6–12 years (1.44–1.70) were above the study-defined non-inferiority margin of 0.35.
</td><td></td><td></td></tr>
</table>

Abbreviations: Refer to section V. List of Abbreviations.

Appendix H: Summary of Literature Evidence Related to the Safety of Influvac® Trivalent Inactivated Influenza Vaccine in Children

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td>Aagaard et al. (2011)[7]</td><td>Design
Passive surveillance

Influenza seasons
1998–2007

Location
Denmark</td><td>Influenza vaccine
Influvac® TIV

Other non-influenza vaccines</td><td>Population definition
Children <18 years of age

Age
NR

Sex
NR</td><td>AEFI defined as any noxious and unintended response to a drug that occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease.

4 AEFI were reported for children in the 2–3 year old age group, 3 of which were serious AEFI. Details about the AEFI were not provided.

No AEFI were reported in any other age groups.</td><td>Level III</td><td>NA</td></tr>
<tr><td>Armstrong et al. (2011)[8]</td><td>Design
Passive surveillance

Retrospective cohort study

Influenza season
2010

Location
Australia</td><td>Influenza vaccine
Influvac® TIV
Fluvax® TIV
Fluvax Junior® TIV

Dose and administration
6–36 months: 2 doses (7.5 µg per strain)

4 years of age: 2 doses (15 µg per strain)

Strains
2010 formulation:
A/California/7/2009-like (H1N1)
A/Perth/16/2009-like (H3N2)
B/Brisbane/60/2008-like</td><td>Surveillance:

Population definition
Children 6 months–4 years of age

Case definition: Child assigned ICD-10 code R56.0 (febrile convulsion) at ED within 72 hours of receipt of TIV or TIV-associated febrile convulsion cases that were reported by ED clinicians, primary care givers or vaccine providers.

Sample size
Cases: n=63

Age (mean)
1.85 years

Sex
39.7% female</td><td>Surveillance:

Febrile convulsions
<table>
<tr><th rowspan="2">Age group (years)</th><th colspan="4">Rate/1000 TIV doses (95% CI)</th></tr>
<tr><th>Influvac®</th><th>Fluvax®</th><th>Fluvax Junior®</th><th>Fluvax® and Fluvax Junior®</th></tr>
<tr><td>≤2</td><td>0.0 (0.0–1.8)</td><td>4.9 (3.4–7.1)</td><td>7.9 (5.3–11.8)</td><td>5.9 (4.5–7.7)</td></tr>
<tr><td>3–4</td><td>0.0 (0.0–1.5)</td><td>1.4 (0.7–2.9)</td><td>9.7 (3.8–24.7)</td><td>2.0 (1.1–3.6)</td></tr>
</table>
Febrile reactions (non-convulsive)*
<table>
<tr><th rowspan="2">Age group (years)</th><th colspan="4">Rate/1000 TIV doses (95% CI)</th></tr>
<tr><th>Influvac®</th><th>Fluvax®</th><th>Fluvax Junior®</th><th>Fluvax® and Fluvax Junior®</th></tr>
<tr><td>≤2</td><td>4.2 (2.2–8.0)</td><td>49.0 (43.7–54.9)</td><td>47.3 (40.2–55.6)</td><td>48.4 (44.1–53.1)</td></tr>
<tr><td>3–4</td><td>0.8 (0.2–2.9)</td><td>25.3 (21.3–30.0)</td><td>26.6 (14.9–47.0)</td><td>25.4 (21.5–29.9)</td></tr>
</table>
* Consists of passive reports made to the AEFI reporting system as opposed to active</td><td>Level III</td><td>NA</td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td>Cohort:

Population definition
Children less than five years of age who were vaccinated with TIV in 2010.

Sample size
n=360

Age
NR

Sex
NR</td><td>The RR of febrile reactions for combined Fluvax® & Fluvax Junior® compared to Influvac® was 11.4 (95% CI: 5.9–22.1) for children ≤2 years of age and 33.0 (95% CI: 8.2–133.2) in children 3–4 years of age.

Cohort:

<table><tr><th>Symptom</th><th colspan="4">Percentage of children with symptom (%)</th></tr><tr><th></th><th>Influvac®</th><th>Fluvax®</th><th>Fluvax Junior®</th><th>Fluvax® and Fluvax Junior®</th></tr><tr><td>Fever</td><td>17.3</td><td>52.3</td><td>61.0</td><td>56.5</td></tr><tr><td>Fatigue</td><td>10.9</td><td>29.4</td><td>37.0</td><td>33.0</td></tr><tr><td>Vomiting</td><td>2.7</td><td>14.7</td><td>20.0</td><td>17.2</td></tr><tr><td>Rigors</td><td>0.9</td><td>11.9</td><td>19.0</td><td>15.3</td></tr><tr><td>Swelling</td><td>10.9</td><td>12.8</td><td>13.0</td><td>12.9</td></tr><tr><td>Diarrhoea</td><td>0.9</td><td>6.4</td><td>4.0</td><td>5.3</td></tr><tr><td>Rash</td><td>0.9</td><td>5.5</td><td>2.0</td><td>3.8</td></tr><tr><td>Headache</td><td>0.9</td><td>3.7</td><td>3.0</td><td>3.4</td></tr><tr><td>Convulsions</td><td>0.0</td><td>2.8</td><td>0.0</td><td>1.4</td></tr><tr><td>Significant febrile adverse event</td><td>4.5</td><td>22.9</td><td>36.0</td><td>29.2</td></tr></table>
Fever (OR=5.1), fatigue (OR=3.5), vomiting (OR=6.0), and significant febrile adverse events (OR=7.0) were significantly more common in children who received one of the two Fluvax® vaccines than children who received the Influvac® vaccine.</td><td></td><td></td></tr>
<tr><td>Brydak et al. (2000)[9]</td><td>Design
Pre-post study

Location
Poland

Follow-up
3 weeks and 6 weeks post-vaccination</td><td>Influenza vaccine
Influvac® TIV

Dose and administration
1 dose (15 µg per strain)

Strains
1996–1997 formulation:
A/Singapore/6/86 (H1N1)
A/Wuhan/359/95</td><td>Population definition
Children with ALL (groups A and B)

Study groups
A: Chemotherapy completed before 1991

B: Chemotherapy completed after 1991</td><td>None of the vaccinated children showed symptoms of influenza virus inflections.

Vaccines were well tolerated and did not cause any severe adverse reactions.

Notes
• Subjects were vaccinated with FluShield® (Wyeth) in the 1993–1994 influenza season and with Influvac® in the 1996–1997 influenza season. Data for the 1996–1997 influenza season is presented.
• Results are also available for subjects vaccinated for the first time in the 1996–1997 influenza season, but are not presented.</td><td>Level III</td><td>NA</td></tr>
</table>

STUDY DETAILS					SUMMARY	
Study	**Study design**	**Influenza vaccine**	**Participants**	**Summary of key findings**	**Level of evidence**	**Quality**
		(H3N2) B/Beijing/184/93	Unvaccinated controls (healthy children) **Sample size** Group A: n=10 Group B: n=12 Controls: n=22 **Age** 6–13 years **Sex** NR	• Though not stated explicitly in the article, the study subjects likely overlap with Brydak et al. (1998a)[10].		
Bueving (2004a)[12] Supplemented with additional details from Bueving et al. (2004b)[13] on AEFI and asthma exacerbation following vaccination.	**Design** Double-blind RCT (placebo-controlled) **Location** The Netherlands **Follow-up** 14–21 days and 4–5 months post-vaccination Adverse events: 7 days post-vaccination	**Influenza vaccine** Influvac® TIV (reported as a Solvay TIV) **Administration** 1 dose (15 µg per strain) **Strains** 1999–2000 formulation: A/Beijing/262/95-like (H1N1) A/Sydney/5/97-like (H3N2) B/Beijing/184/93-like 2000–2001 formulation: A/New Caledonia/20/99 (H1N1) A/Moscow/10/99-like (H3N2) B/Beijing/184/93-like Children could only participate in one of the two seasons	**Population definition** Children 6–18 years of age with asthma, without other chronic diseases **Sample size** Vaccine: n=347 Placebo: n=349 **Age (mean)** Vaccine: 10.5 years Placebo: 10.6 years **Sex** Vaccine: 48.1% female Placebo: 43.6% female	**Adverse events** There was a significant difference in the proportion of local adverse events experienced in the vaccinated group compared to the placebo group. Local adverse events included erythema at the vaccination site and a stiff or painful arm. There was a 23% absolute difference between the two groups for erythema at the vaccination site and a 48% absolute difference for stiff or painful arm. In the 1999–2000 season, there was a significant difference in fever/shivers (8%), headaches (10%), and myalgia (18%) after injection between the vaccine group and the placebo group. In 2000–2001, only episodes of hoarseness (5%) were significantly different between the two groups. There were no other significant differences in systemic reactions between the two groups in either season (sickness, vomiting, diarrhoea, tiredness, sweating, sneezing, runny or stuffed-up nose, burning or watery eyes, sore throat). Of recorded asthma symptoms, the only significant difference occurred in the 1999–2000 season for episodes of cough (8%). There were no SAEs reported in either group. **Asthma exacerbation** The number of asthma exacerbations was not significantly different between asthmatic patients who were vaccinated with Influvac® and those who received the placebo.	Level I	Fair Conducted per-protocol analyses.

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr>
<td>Cashman et al. (2014)[14]</td>
<td>Design
Active surveillance

Influenza seasons
2012
2013

Location
Australia

Follow-up
3 days and 42 days post-vaccination</td>
<td>Influenza vaccine
Influvac® TIV

Other TIVs</td>
<td>Population definition
Children aged less than 10 years receiving influenza vaccine

Sample size
Total: n=290
Total vaccinated with Influvac®: n=32

Survey response rate: 61% (n=290 of 477)

Age
NR

Sex
47% female</td>
<td>Adverse events following the first dose

<table>
<tr><th rowspan="2">Symptom</th><th colspan="2">Number of participants</th></tr>
<tr><th>Influvac®</th><th>Total</th></tr>
<tr><td>Any adverse event following the first dose</td><td>1</td><td>52</td></tr>
<tr><td>SAE</td><td>0</td><td>0</td></tr>
<tr><td>Sought medical attention</td><td>0</td><td>4</td></tr>
<tr><td>Reaction at injection site</td><td>1</td><td>23</td></tr>
<tr><td>Fever</td><td>1</td><td>8</td></tr>
<tr><td>Headaches</td><td>0</td><td>9</td></tr>
<tr><td>Fatigue</td><td>0</td><td>15</td></tr>
<tr><td>Joint pain</td><td>0</td><td>6</td></tr>
<tr><td>ILI</td><td>1</td><td>12</td></tr>
<tr><td>Lymph node swelling</td><td>0</td><td>3</td></tr>
<tr><td>Seizures</td><td>0</td><td>0</td></tr>
<tr><td>Muscle aches</td><td>0</td><td>14</td></tr>
<tr><td>Weakness</td><td>0</td><td>2</td></tr>
<tr><td>Other symptoms</td><td>0</td><td>9</td></tr>
</table>

Recipients of Influvac® reported lower frequencies of any AEFI (3.1%; n=32) compared to Fluarix® (11.6%; n=43), Vaxigrip® (21.7%; n=212) and all influenza vaccine brands (17.9%; n=290) for the 2012 and 2013 Southern Hemisphere influenza seasons.</td>
<td>Level III</td>
<td>NA</td>
</tr>
<tr>
<td>Cheng et al. (2015)[15]</td>
<td>Design
Passive surveillance

Influenza seasons
2007–2013 (Influvac® in schedule for 2008–2009 only)

Location
Australia

Follow-up
Within 24 hours of initial report</td>
<td>Influenza vaccine
Influvac® TIV

Other non-influenza vaccines

Dose and administration
1 dose</td>
<td>Population definition
Children less than 18 years of age with suspected anaphylaxis following immunization.

Case definition: The Brighton Collaboration Case Definition was used to define the level of certainty for an anaphylaxis event.

Sample size
Cases: n=1</td>
<td>Anaphylaxis following immunization
One anaphylaxis AEFI was reported for Influvac®. The level of certainty of an anaphylaxis event was 2, which indicates that symptoms included ≥1 major cardiovascular/respiratory and ≥1 minor symptoms involving ≥1 different systems, or ≥1 major dermatological and ≥1 minor cardiovascular/respiratory.

Notes
Influvac® was only in schedule in Australia for 2008–2009. Therefore, report of anaphylaxis following immunization for Influvac® only reflects this period and not the full study period.</td>
<td>Level III</td>
<td>NA</td>
</tr>
</table>

STUDY DETAILS					SUMMARY	
Study	**Study design**	**Influenza vaccine**	**Participants**	**Summary of key findings**	**Level of evidence**	**Quality**
			Age (mean) 9.4 years **Sex** Female			
Daubeney et al. (1997)[16]	**Design** Pre-post study **Location** United Kingdom **Follow-up** Up to 72 hours post-vaccination	**Influenza vaccine** Influvac® TIV **Dose and administration** 2 doses (7.5 µg per strain), 4 weeks apart **Strains** A/Singapore/6/86 (H1N1) A/Shangdong/9/93 (H3N2) B/Panama/45/90	**Population definition** Children with chronic respiratory disease, congenital heart disease, or both. **Sample size** n=52 **Age** Mean (range): 19.5 months (6 months–4 years) **Sex** NR	**Adverse events** AEs were recorded 24, 48 and 72 hours post-vaccination: • n=15 AEs in total • n=2 of 15 AEs were related to vaccination (2 cases of febrile episodes associated with cough) • n=4 of 15 AEs were arranged hospital admissions for cardiac catheterisation or jejunal biopsy • All hospitalizations were associated with underlying cardiac or respiratory conditions • n=12 of 52 (23%) subjects had local reactions, with the most commonly reported reaction being redness at injection site (n=6) • n=25 of 52 (48%) subjects had systemic reactions, with the most commonly reported reaction being fever (n=14), insomnia (n=13) and increased irritability (n=13) • All systemic and local reactions were noted to be minor and resolved within a few days	Level III	NA
Ghendon et al. (2006)[26]	**Design** Non-randomized controlled trial **Influenza season** 2001–2002 **Location** Russia **Follow-up** Morbidity: 4 months post-vaccination (December 2001–March 2002) Adverse events: 3–5 days post-vaccination	**Influenza vaccine** Influvac® TIV **Dose and administration** 1 dose (15 µg per strain) **Strains** 2001–2002 formulation: A/New Caledonia/20/99 (H1N1) A/Moscow/10/99 (H3N2) B/Sichuan/379/99	**Population definition** Healthy children without contraindications **Study groups** Intervention: Mass immunization campaign (coverage rate 69.7%) Control: No immunization campaign (coverage rate <1.0%) **Sample size** Intervention: n=40,611 Control: n=60,946 **Age** 3–17 years	**Adverse events** No SAEs were observed immediately after vaccination or 3–5 days post-vaccination.	Level II-1	NA

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td>Sex
NR</td><td></td><td></td><td></td></tr>
<tr><td>Jansen et al. (2008a)[18]

Supplemented with additional details from Jansen et al. (2008b)[19] on AEFI.</td><td>Design
Double-blind RCT (placebo-controlled)

Influenza seasons
2003–2004
2004–2005
2005–2006

Location
The Netherlands

Follow-up
2003–2004 and 2004–2005 seasons: 18 months post-vaccination

2005–2006 season: 6 months post-vaccination

Adverse events: 7 days post-vaccination</td><td>Influenza vaccine
Influvac® TIV

Other non-influenza vaccines

Dose and administration
2 doses, 4–8 weeks apart

2003–2004 and 2004–2005 cohorts received an additional vaccination in the following year

Strains
2003–2004 formulation:
A/New Caledonia/20/99 (H1N1)
A/Moscow/10/99 (H3N2)
B/Hong Kong/330/01

2004–2005 formulation:
A/New Caledonia/20/99 (H1N1)
A/Fuijan/411/2002 (H3N2)
B/Shanghai/361/2002

2005–2006 formulation:
A/New Caledonia/20/99 (H1N1)
A/California/7/2004 (H3N2)
B/Shanghai/361/2002</td><td>Population definition
Unvaccinated children aged 18–72 months with previously diagnosed respiratory tract infection

Study groups
TIV plus PCV7

TIV plus placebo

HBV plus placebo (control)

Sample size
TIV plus PCV7: n=197
TIV plus placebo: n=187
HBV plus placebo (control): n=195

Age (mean)
TIV plus PCV7: 3.0 years
TIV plus placebo: 3.1 years
HBV plus placebo (control): 3.1 years

Sex
TIV plus PCV7: 41.4% female
TIV plus placebo: 44.4% female
HBV plus placebo: 49.7% female

The study groups were similar with regard to age, sex</td><td>Adverse events
<table><tr><th>Type of adverse reaction</th><th colspan="3">Proportion with adverse event</th></tr><tr><th></th><th>TIV plus PCV7</th><th>TIV plus placebo</th><th>HBV plus placebo (control)</th></tr><tr><td>Local</td><td>66.8% (127/190)</td><td>37.8% (68/180)</td><td>36.0% (67/186)</td></tr><tr><td>Systemic</td><td>63.9% (117/183)</td><td>52.3% (90/172)</td><td>50.9% (88/173)</td></tr></table>
No immediate adverse events were recorded following vaccination.

The local adverse reactions recorded for TIV plus placebo, in descending order of incidence, were tenderness, swelling, erythema, and interference with limb movement.

The systemic adverse reactions recorded for TIV plus placebo, in descending order of incidence, were malaise, fever, headaches, and myalgia.

No severe reactions were recorded for all groups.</td><td>Level I</td><td>Fair

14–20% loss to follow up.</td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td>and medical history.</td><td></td><td></td><td></td></tr>
<tr><td>Petousis-Harris et al. (2012)[20]</td><td>Design
Retrospective survey (multi-centre)

Influenza seasons
2010
2011

Location
New Zealand</td><td>Influenza vaccine
Influvac® TIV
Fluvax® TIV

Other TIVs and a monovalent H1N1 vaccine

Strains
2010 and 2011 formulations:
A/California/7/2009 (H1N1)
A/Perth/16/2009 (H3N2)
B/Brisbane/60/2008</td><td>Population definition
Child aged 6 months–5 years vaccinated for influenza

Sample size
Influvac®: n=204
Fluvax®: n=865

Age (mean)
Influvac®: 35 months
Fluvax®: 36 months

Sex
Influvac®: 46% female
Fluvax®: 47% female</td><td>Febrile adverse events
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Vaccine</th><th rowspan="2">Odds ratio (95% CI)</th></tr>
<tr><th>Influvac® (%)</th><th>Fluvax® (%)</th></tr>
<tr><td>Convulsive seizures level 1–3</td><td>0.0</td><td>0.3</td><td>NA</td></tr>
<tr><td>Febrile with rigor</td><td>0.0</td><td>1.0</td><td>NA</td></tr>
<tr><td>Febrile and floppy/delirium</td><td>0.0</td><td>0.5</td><td>NA</td></tr>
<tr><td>Febrile with vomiting</td><td>2.0</td><td>6.5</td><td>0.29 (0.10–0.81)</td></tr>
<tr><td>Febrile with malaise/lethargy/ irritability/ headache</td><td>9.0</td><td>12.0</td><td>0.70 (0.41–1.18)</td></tr>
<tr><td>Any fever recalled occurring post-vaccination</td><td>19.0</td><td>28.0</td><td>0.61 (0.42–0.89)</td></tr>
<tr><td>Any fever recalled occurring within 24 hours of vaccination</td><td>17.0</td><td>25.0</td><td>0.59 (0.40–0.88)</td></tr>
<tr><td>Sought medical advice for fever</td><td>5.0</td><td>8.0</td><td>1.07 (0.5–2.30)</td></tr>
<tr><td>Hospital/ emergency</td><td>0.0</td><td>3.0</td><td>NA</td></tr>
<tr><td>Fever ≥38°C</td><td>5.0</td><td>13.0</td><td>0.51 (0.24–1.07)</td></tr>
</table>
Notes
Influvac® was only assessed in the 2010 season. Data for other vaccine brands not presented.</td><td>Level III</td><td>NA</td></tr>
<tr><td>Pillsbury et al. (2015)[21]</td><td>Design
Active surveillance

Influenza season
2015</td><td>Influenza vaccine
Influvac® TIV

Other TIVs</td><td>Population definition
Children aged 6 months–4 years receiving influenza vaccine</td><td>Five of 47 participants who received Influvac® had a fever and 2 of the 47 participants sought medical advice/attendance.

One of the participants vaccinated with Influvac® experienced a SAE, defined as any untoward medical event that resulted in death, was life-threatening or required hospitalization, and</td><td>Level III</td><td>NA</td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr><td></td><td>Location
Australia</td><td></td><td>Sample size
Total: n=3340
Vaccinated with Influvac®: n=47

Age (mean)
23.0 months

Sex
46.3% female</td><td>reported improvement within days (precise age of the child and nature of the SAE are not reported).

Influvac® was administered in insufficient numbers in children aged six months to four years (n=47) to allow for a reliable comparison of differences in reported fever rates with other vaccine brands.</td><td></td><td></td></tr>
<tr><td>Shahgholi et al. (2010)[23]</td><td>Design
Non-randomized controlled trial

Location
Iran

Follow-up
4 weeks post-vaccination

Adverse events: 5 days post-vaccination</td><td>Influenza vaccine
Influvac® TIV

Dose and administration
<36 months of age: 2 doses (0.25mL), 3–4 weeks apart

36 months–13 years of age: 2 doses (0.5mL), 3–4 weeks apart

>13 years of age: 1 dose (0.5mL)

Strains
2007–2008 formulation:
A/Solomon Islands/3/2006 (H1N1)
A/Wisconsin/67/2005 (H3N2)
B/Malaysia/2506/2004-like</td><td>Population definition
Children 1–18 years of age diagnosed with ALL in first remission and receiving maintenance therapy and healthy children (siblings) as controls.

Sample size
ALL: n=32
Controls: n=30

Age (mean)
ALL: 10.65 years
Controls: 10.8 years

Sex
ALL: 34.4% female
Controls: 46.7% female

No significant differences were found for the gender and age distributions of the two groups.</td><td>Adverse events<table><tr><th>Reaction</th><th colspan="2">Proportion of participants who experienced event (%)</th></tr><tr><th></th><th>ALL</th><th>Controls</th></tr><tr><td>Mild to moderate pain</td><td>0</td><td>0</td></tr><tr><td>Swelling</td><td>1</td><td>0</td></tr><tr><td>Redness at injection site</td><td>1</td><td>1</td></tr></table>Complete reactogenicity data was available for 56% of participants. No SAEs were reported.
Axillary temperature >37.8°C during 5 days after vaccination was reported in two ALL patients and one healthy control.
Rates of adverse reaction did not differ by dose or number of vaccine.
No relapse was observed during the study period and at least 3 months after completion of vaccination.</td><td>Level II-1</td><td>NA

Siblings were used as controls, but similarities in important confounders were not assessed.</td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level of evidence</th><th>Quality</th></tr>
<tr>
<td>Wood et al. (2012)[24]</td>
<td>Design
Active surveillance

Influenza seasons
2010
2011

Location
Australia</td>
<td>Influenza vaccine
Influvac® TIV (reported as a Solvay TIV)
Fluvax® TIV (reported as a CSL TIV)

Strains
2010 and 2011 formulations:
A/California/7/2009 (H1N1)
A/Perth/16/2009 (H3N2)
B/Brisbane/60/2008</td>
<td>Population definition
Children aged 6 months–5 years vaccinated for seasonal influenza in 2010 or 2011 at study site

Sample size
Influvac®: n=99
Fluvax®: n=73

Age (mean)
Influvac®: 2.7 years
Fluvax®: 3.3 years

Sex
NR</td>
<td>Febrile adverse events
<table>
<tr><th rowspan="2">Outcome</th><th colspan="3">Vaccine</th></tr>
<tr><th>Influvac® (%)</th><th>Fluvax® (%)</th><th>Relative risk (95% CI)</th></tr>
<tr><td>Parental reported fever</td><td>7.1</td><td>45.2</td><td>6.5 (3.1–13.9)</td></tr>
<tr><td>Parental reported fever (>38.5°C)</td><td>3.0</td><td>31.5</td><td>Not available</td></tr>
<tr><td>Parental report of medical attendance within 48hrs</td><td>2.0</td><td>16.4</td><td>8.2 (1.9–35.4)</td></tr>
</table>
There were no reports of febrile seizure for any of the vaccines. No participants vaccinated with Influvac® had a fever ≥40°C.</td>
<td>Level III</td>
<td>NA</td>
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<td>Zhu et al. (2008)[25]</td>
<td>Design
Endpoint-blind RCT
Location
China

Follow-up
4 weeks post-vaccination

Adverse events: 29 days post-vaccination</td>
<td>Influenza vaccine
Influvac® TIV
Agrippal® TIV

Dose and administration
1 dose (15 µg per strain)

Strains
2005–2006 formulation:
A/New Caledonia/20/99 (H1N1)
A/New York/55/2004 (H3N2)
B/Jiangsu/10/2003</td>
<td>Adverse events were recorded for both parts of the study, but a separate, open safety study was conducted prior to the RCT (see below for details on the open safety study and the entry in Appendix G for details on the RCT)

Population definition
Healthy children 3–12 years of age

Sample size
n=30

Age (mean)
7.6 years

Sex
50.0% female</td>
<td>Adverse events
Three children experienced local pain after vaccination with Influvac® during the safety trial, while nine children experienced mild pain or itching/pruritus during the RCT. No local reactions were reported in children vaccinated with Agrippal®.

In the RCT, one child had a headache and nine experienced fever after vaccination with Influvac®. There were reports of 2 children with headaches and 4 with fever after vaccination with Agrippal®. Two children who were vaccinated with Influvac® experienced mild inconvenience compared to one child vaccinated with Agrippal®. No systemic reactions were reported during the safety trial.

Episodes of acute tonsillitis (n=1), dizziness (n=1), and cough (n=1) were reported during the RCT in children vaccinated with Influvac®. No AEs were reported during the safety study or in children who were vaccinated with Agrippal®. No SAEs were reported during the safety trial or the RCT.</td>
<td>Level I</td>
<td>Fair

Conducted per-protocol analyses. Study was endpoint-blind (not double-blind).</td>
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Abbreviations: Refer to section V. List of Abbreviations.