In 2010, increased febrile convulsions (FC) occurred after administration of inactivated trivalent influenza vaccine (TIV) in Australia. We systematically reviewed the rates of fever, FC and serious adverse events (SAEs) after TIV, focussing on published and unpublished clinical trial data from 2005 to 2012, and performed meta-analysis of fever rates. From 4,372 records in electronic databases, 18 randomised controlled trials (RCTs), 14 non-randomised clinical trials, six observational studies and 12 registered trials (five RCTs and seven non-randomised) were identified. In published RCTs, fever ≥ 38 °C rates after first dose of non-adjuvanted TIV were 6.7% and 6.9% for children aged 6–35 months and ≥ 3 years, respectively. Analysis of RCTs by vaccine manufacturer showed pooled fever estimates up to 5.1% with Sanofi or GlaxoSmithKline vaccines; bioCSL vaccines were used in two non-randomised clinical trials and seven non-randomised) were identified. In published RCTs, fever ≥ 38 °C rates after first dose of non-adjuvanted TIV were 6.7% and 6.9% for children aged 6–35 months and ≥ 3 years, respectively. Analysis of RCTs by vaccine manufacturer showed pooled fever estimates up to 5.1% with Sanofi or GlaxoSmithKline vaccines; bioCSL vaccines were used in two non-randomised clinical trials and one unpublished RCT and were associated with fever in 22.5–37.1% for children aged 6–35 months. In RCTs, FCs occurred at a rate of 1.1 per 1,000 vaccinated children. While most TIVs induced acceptably low fever rates, bioCSL influenza vaccines were associated with much higher rates of fever in young children. Future standardised study methodology and access to individual level data would be illuminating.

Introduction

In 2010, an unexpected and marked increase in fever and febrile convulsion (FC) rates in Australian children younger than five years was detected following receipt of the seasonal inactivated trivalent influenza vaccine (TIV). Despite its subsequent deregistration for children younger than five years, public concerns about vaccine safety have persisted, leading to markedly lower influenza vaccine uptake, especially in Western Australia [10]. Published data documenting the frequency and severity of fever after TIV in children are sparse. Furthermore, the age bands reported and fever cut-off values used vary widely, with limited application of standardised definitions such as those from the Brighton Collaboration [11]. We therefore systematically reviewed the evidence for influenza vaccine safety in children to examine the rates of fever, FCs and serious adverse events (SAEs as per standard definition [12]) associated with contemporary TIVs. We also aimed to assess the effect of age, vaccine type [5,6].
(adjuvanted or not) and vaccine manufacturer on the frequency of these adverse events.

**Methods**

An electronic literature search, without language restriction, was performed using Medline, Embase, Cochrane Library databases, LILACS, SCOPUS, and Web of Science for studies published between January 2005 and March or April 2012. Our focus was on contemporary vaccines hence our restriction to this publication period. Both controlled vocabulary and text-word terms were used, including ‘immunization’, ‘influenza vaccines’, ‘influenza, human’, ‘safety’, ‘fever’, ‘seizures, febrile’, ‘adverse event/effect’, ‘product surveillance, post-marketing’, ‘Guillain–Barré syndrome’, together with ‘child’ or ‘infant.’ A listing of the specific databases, search strategy and coverage dates are available from the corresponding author upon request. In addition, a search was performed within ClinicalTrials.gov, a globally used registry, for phase 2, 3 or 4 clinical trials using TIV in a paediatric population.

We included randomised controlled trials (RCTs), non-randomised clinical trials (with or without a control group) and observational studies. Studies were included if they (i) involved the use of inactivated seasonal TIV, administered intramuscularly, in at least one study arm; (ii) involved healthy children up to 17 years of age; and (iii) presented safety data in an extractable format. Studies were excluded if they only involved children younger than six months or only populations with chronic illness and/or immunocompromise. We analysed data by age band, study design, vaccine type and vaccine manufacturer, where possible. Dose 1 and dose 2 data were analysed separately. Febrile convulsion rates and SAEs were noted, if documented.

The quality of RCT studies was assessed by examining bias using the Cochrane Collaboration’s tool for assessing risk of bias [13]; non-randomised clinical trials were assessed by the Effective Public Health Practice Project (EPHPP) Quality Assessment tool, as this better encompassed variation [14,15].

Meta-analysis was conducted on fever data using the Brighton Collaboration case definition of ≥ 38°C from any source (axillary, oral or rectal) [11]. Due to variability in study methods and a lack of placebo-controlled studies, we conducted a proportion meta-analysis of fever rates using similar single-arm data from trials (StatsDirect statistical software version 2.7.9) to calculate pooled fever proportions. This method has been used previously in systematic reviews across different disciplines [16-21]. A random effects model with the DerSimonian–Laird method was used to account for variability in study design and results. The I² statistic was used as a measure of heterogeneity of pooled estimates [13].

We conducted sensitivity analyses of meta-analyses to see if exclusion of high-risk RCTs, or those non-randomised clinical trials rated as weak, reduced heterogeneity. If heterogeneity was unchanged, then all available studies were used for analysis.

**Results**

Of the 4,372 studies initially identified (Figure), 18 RCTs [22-39], 14 non-randomised clinical trials [40-53], and six observational studies [54-59] were eligible for inclusion. The clinical trial registry search yielded 12 additional relevant studies (five RCTs and seven non-randomised trials). We found substantial variation in study methods, fever definitions, age of participants, year of study, length of follow-up for solicited adverse events, vaccine types and brands.

**Characteristics of randomised controlled trials**

In the 18 randomised control trials (Table 1), a total of 22,484 subjects were enrolled, of whom 16,474 received TIV and had safety data collected. Multiple study designs were encountered in terms of comparison groups; for non-adjuvanted TIV, comparison with placebo was only found in one study [33]. Five studies examined adjuvanted vaccines (MF59 or virosomal adjuvant) in at least one study arm [30,31,34,35,39].

Classification of fever varied across studies, but a majority of studies [22,25,27,29-31,34,35,37,38] provided data on fever ≥ 38°C. We used these studies for meta-analysis of fever rate and one additional study [39], where we assumed a fever definition of ≥ 38°C based on two similar studies by the same lead author [31,35].

Study quality varied using the Cochrane Collaboration’s tool for assessing risk of bias. Five studies were assessed as being at low risk of bias [26,31,33-35]. Ten studies had medium risk of bias [22,24,25,27-30,32,38,39], and three studies had high risk [23,36,37]. Sensitivity analyses limited only to low-risk studies were not feasible; there were too few studies, and two did not use a fever definition of ≥ 38°C.

**Characteristics of non-randomised clinical trials**

Fourteen non-randomised trials were identified (Table 2). Of the 8,119 total participants, 7,901 received TIV and had safety data available. Two studies [48,52] were follow-on studies from previous RCTs. Most used within-study age cohorts for comparison and/or had no control group [40,42,44-47,49,50,53]. For fever meta-analysis, we used five studies with fever defined as ≥ 38°C [40,41,48,49,52] and two [47,53] where fever was ≥ 37.5°C axillary or ≥ 38°C orally (still meeting the Brighton Collaboration criteria [11]).

Overall, a high risk of bias was observed due to lack of randomisation and open-label study designs, without blinding in most studies. In addition, many studies were lacking control groups. Five studies [41,43,48,49,51] were assessed as being of ‘moderate’ strength while nine studies were ‘weak’ [40,42,44-47,50,52,53].
Results of literature search for fever, febrile convulsions and serious adverse events following administration of inactivated trivalent influenza vaccine in children, and studies analysed

Studies included:
- 18 randomised controlled trials
- 14 non-randomised clinical trials
  - 5 cohort studies
  - 1 case–control study
- 12 Clinicaltrials.gov studies
  (5 randomised controlled trials, 7 non-randomised clinical trials)

Adapted from PRISMA 2009 Flow Diagram [73].
### Table 1a

Characteristics of randomised controlled trials included for analysis of fever, febrile convulsions and serious adverse events following administration of inactivated trivalent influenza vaccine in children

| Reference | Ages | Comparison groups | Enrolment period and location | TIV recipients evaluable for safety | Vaccines used | Vaccine manufacturer | Antigen dose per strain | Length monitoring solicited AE | Length SAE monitoring | Definition of fever | Method of measurement | Risk of bias assessment | Fever rate recorded |
|-----------|------|-------------------|------------------------------|-----------------------------------|---------------|---------------------|-----------------------|--------------------------|--------------------------|----------------|---------------------|----------------------|----------------------|------------------|
| Englund 2005 [22] | 6 – 23 months | 1. Standard schedule: 2 doses autumn 2. Previous year priming schedule: spring then autumn 3. Non-randomly allocated standard schedule | Apr – Jun 2003 United States | 259 | TIV | Aventis-Pasteur (Sanofi) | 15 µg/0.5mL | 5 days | 6 months | ≥ 38 °C | Axillary | Medium | 6.7–8.0% |
| Hu 2005 [23] | 6 months – 2 years, 6 – 12 years, 16 – 60 years, 60 years | 1. Fluval 2. Vaxigrip | Mar – Sep 2004 China | 785 | Fluval: TIV Vaxigrip: TIV | Fluval: Shire Biologics. Vaxigrip: Aventis-Pasteur (Sanofi) | 15 µg/0.5 mL | 3 days | 3 days | Not stated | Not stated | High | 5.2–6.3% (6 months–2 years) |
| Ashkenazi 2006 [24] | 6–7 months | 1. LAIV 2. Inactivated TIV | Oct 2002 9 European countries | 1,086 | LAIV: 15 µg/0.5 mL | TIV: 15 µg/0.5 mL | 11 days | To end of study | Not stated | ≤ 37.5 °C axillary or ≤ 38.0 °C rectal | Not stated | Average | 21.4% (LAIV) |
| Walter 2006 [25] | 6–23 months | 1. Spring–autumn schedule 2. Standard autumn 2-dose schedule | Apr – Jun 2004 United States | 462 | TIV | Aventis Pasteur (Sanofi) | 15 µg/0.5 mL | 3 days | 6 months post last vaccine | ≥ 38 °C | Axillary | Medium | 3.4% |
| Belshe 2007 [26] | 6–59 months | 1. LAIV 2. Inactivated TIV | Oct 2004 16 countries | 4,173 | Fluzone: TIV Vaxigrip: TIV Flumist: LAIV | Fluzone: Shire Biologics. Vaxigrip: Aventis-Pasteur (Sanofi) | 107 μLf/Strain TIV: not stated | 42 days | Median 219 days (180 days after last vaccine) | > 37.8 °C Oral, axillary or rectal | Not stated | Medium | 7.1% (intramuscular route) |
| Chiu 2007 [27] | 3–18 years | 1. Intradermal TIV 2. Intramuscular TIV | Oct – Nov 2005 Hong Kong | 56 | Fluixiv: TIV | GSK | 15 µg/0.5 mL | 3 days | Not stated | ≥ 38 °C | Not stated | Medium | 4.0–4.4% |
| King 2009 [29] | 6–59 months | 1. Standard TIV 2. Recombinant TIV | Oct – Nov 2006 United States | 156 | Fluixiv: TIV Flublok: recombinant TIV | TIV: Sanofi Flublok: Protein Sciences Corporation | 15 µg/0.5 mL | 7 days | 180 days | ≥ 38 °C | Not stated | Medium | 3.3% |
| Marchisio 2009 [30] | 1–5 years | 1. Virosomal ATIV 2. No treatment | Oct 2006 Italy | 90 | Influvax IV: virosomal ATIV | Bema Biotech | 15 µg/0.5 mL | 7 days | Not stated | ≥ 38 °C | Not stated | Rectal | Medium | 5.3% (standard TIV) |
| Vesikari 2009 [31] | 6–35 months | 1. MF59 ATIV 2. TIV | Nov 2006 – Aug 2007 Finland | 269 | Fluad: MF59 ABIVAX Vaxigrip TIV | Fluad: Novartis Vaxigrip: Sanofi | 15 µg/0.5 mL | 7 days | 6 months | ≥ 38 °C | Not stated | Low | 6.3% TIV 6.9% ATIV |
| Baxter 2010 [32] | 6 months–18 years for safety | 1. Fluarix 2. Fluzone | Nov 2006 – Oct 2007 United States | 3,325 | Fluixiv: TIV Fluzone: TIV | Fluixiv: GSK Fluzone: Sanofi | 15 µg/0.5 mL | 4 days (0–3) | 6 months post first vaccine | > 37.5 °C | Axillary | Medium | 74–75% |
| Cowling 2010 [33] | 6–15 years | 1. Vaccinated household 2. Placebo household | Nov – Dec 2007 Hong Kong | 71 | Vaxigrip: TIV | Sanofi Pasteur | 15 µg/0.5 mL | 4 days | 10 months | ≥ 37.8 °C | Not stated | Low | 1.4% |
| Espital 2010 [34] | 6–35 months | 1. 2 doses of 0.5 mL 2. 2 doses of 0.25 mL | Oct 2008 – May 2009 Italy | 65 | Influvax IV: virosomal ATIV | Crucell | 15 µg/0.5 mL | 15 days | Not stated | ≥ 38 °C | Not stated | Rectal | Low | 7.0–9.1% |
| Vesikari 2010 [35] | 6–35 months; 3–8 years; 9–17 years | 1. H5N1-MF59 ATIV 2. MF59 ATIV | Sep – Nov 2007 Finland | 137 | Aflunov H5N1 Fluad: MF59 ABIVAX | Novartis | 75 µg/0.5 mL 15 µg/0.5 mL TIV | 7 days | Not stated | ≥ 38 °C | Axillary | Low | 12.5% (6–35 months, MF59 ATIV group) |
### Characteristics of randomised controlled trials included for analysis of fever, febrile convulsions and serious adverse events following administration of inactivated trivalent influenza vaccine in children

| Reference       | Ages                  | Comparison groups                                                                 | Enrolment period and location | TIV recipients evaluable for safety | Vaccines used | Vaccine manufacturer | Antigen dose per strain | Length monitoring solicited AE | Length SAE monitoring | Definition of fever | Method of measurement | Risk of bias assessment | Fever rate recorded |
|-----------------|-----------------------|-----------------------------------------------------------------------------------|-------------------------------|-----------------------------------|---------------|----------------------|-------------------------|----------------------------|------------------------|---------------------|----------------------|----------------------|----------------------|----------------------|
| Hoft 2011 [36] | 6–35 months           | 1. TIV/TIV 2. LAIV/LAIV 3. TIV/LAIV 4. LAIV/TIV                                   | 2005 – 2007 United States     | 14                                | Fluzone: TIV  | Sanofi Pasteur       | 15 µg/0.5mL             | 14 days                   | 7 months               | > 37.5 °C           | Axillary            | High                 | 7.1%                 |
| Kang 2011 [37] | 6 months – 17 years   | 1. Green Cross TIV 2. Fluarix TIV                                                 | Sep – Nov 2008 Korea          | 282                               | Green Cross: TIV | Green Cross: GSK     | 15 µg/0.5mL            | 7 days                     | Not stated              | ≥ 38 °C             | Axillary            | High                 | 0–3.1%               |
| Skowronski 2011 | 6–23 months           | 1. Full dose 0.5 mL x 2 2. Half dose 0.25 mL x 2                                 | Sep – Dec 2008 Canada         | 252                               | Vaxigrip: TIV | Sanofi Pasteur       | 15 µg/0.5mL             | 4 days (0–3)               | 45 days                | ≥ 38 °C             | Axillary            | Medium               | 2.3% (half dose group) |
|                 |                       | 2008–09: Fluad and Influsplit SSW TIV                                              |                              |                                    | Influsplit SSW: GSK | Fluad: Novartis Agrippal S1 TIV |
|                 |                       |                                                                                   | 15 µg/0.5mL                   | 7 days                             | Year 1: 6 months Year 2: 12 months |

Adj: adjuvanted; AE: adverse event; ATIV: adjuvanted trivalent influenza vaccine; FFU: fluorescence focus assay units; GSK: GlaxoSmithKline; LAIV: live attenuated influenza vaccine; SAE: serious adverse event; TIV: non-adjuvanted trivalent influenza vaccine.

Where multiple doses were administered, fever is listed for the first dose. Rates are for the youngest age group within the study unless otherwise stated.
Adverse events following immunisation

Fever
Pooled estimates of fever obtained using proportion meta-analysis of studies are shown in Table 3 and Table 4.

Non-adjuvanted vaccines in children six to 35 months of age
The pooled proportion estimate of fever was 6.7% (95% confidence interval (CI): 3.0–11.8) after first dose of TIV based on five eligible RCTs [22,29,31,38,39]. None of these RCTs had a high risk of bias. Analysis of five non-randomised clinical trials [40,41,47,49,53] provided higher first-dose fever estimates of 17.7% (95% CI: 11.3–25.2), largely due to the inclusion of two studies of bioCSL vaccines [47,53] that reported higher rates of post-vaccination fever. Rates after second doses are listed in Table 3 and Table 4.

Non-adjuvanted vaccines in children three to 17 years of age
There were only two eligible two-dose RCTs in this age group [29,39]. The pooled proportion estimate of fever for children three years and older was 6.9% (95% CI: 5.2–8.7) for dose 1. Meta-analysis of non-randomised clinical trials revealed more fever, 15.1% (95% CI: 13.3–17.0), again due to the inclusion of studies using bioCSL vaccines [47,53]. Second doses caused lower rates of fever.

Adjuvanted vaccines
Three RCTs used Fluarix (Novartis), an MF59-adjuvanted vaccine which remains investigational and unlicensed in the paediatric age group, and included children aged from six months to 17 years [31,35,39]. Two of these studies [31,35] had low risk of bias and one was medium risk [39]. Point estimates of fever were higher than corresponding values for non-adjuvanted vaccines; however confidence intervals were wide due to the limited number of subjects. For children six to 35 months of age, first-dose pooled fever estimates were 11.9% (95% CI: 6.8–18.3). Data were more limited on children three years and older with pooled fever rates of 10.3% (95% CI: 1.1–27.0). Again, second doses elicited less fever. A small single non-randomised clinical trial reported fever rates of 16.0% for age 16–35 months, and 11.1% for age 36–48 months [48].

Direct within-study comparison between MF59-ATIV and non-adjuvanted TIV fever rates in two RCTs [31,39] showed significantly higher fever rates only in the subset of children aged 36–71 months in the ATIV group compared with the TIV group in one study (17.5% and 6.7%, respectively, for dose 1, p < 0.001) [39]. Two small studies of Inflexal V (Berna Biotech) virosomal-adjuvanted vaccine [30,34] showed pooled fever rates of 5.5% (95% CI: 1.3–12.3) (Table 3).

Post-vaccination fever, analysis by vaccine manufacturer
Fever estimates were calculated for Sanofi Pasteur, GlaxoSmithKline (GSK), Novartis, and bioCSL vaccines. Studies were grouped together, despite some variation in definition of fever, to maximise the number of studies evaluated. Data were analysed within age bands of six to 35 months and three to 17 years; data for dose 1 and 2 were analysed separately where possible. Data presented below covers non-adjuvanted vaccines. As MF59-adjuvanted (Novartis) and virosomal-adjuvanted (Berna Biotech) vaccines were produced by single manufacturers, corresponding data for adjuvanted vaccines are listed within the adjuvanted sections of Table 3 and Table 4.

Randomised studies
RCTs using Sanofi Pasteur products (Vaxigrip, Fluzone) [22-26,29,31-33,36,38], GSK’s Fluarix [27,32,37], and Novartis’s Agrippal [28] were examined (Table 3). Overall, fever rates were comparable between these brands of vaccine. For Sanofi products, in the age bands six to 35 months and three to 17 years, pooled first-dose fever rates were 5.1% and 4.4% respectively. Fever estimates were 4.7% (95% CI: 0.9–11.1) for GSK’s vaccine and 4.0% (95% CI: 1.5–10.5) for Novartis’s vaccine (analysis by age bands was not possible). Where applicable, high-risk studies were excluded, but this did not change heterogeneity.

Non-randomised studies
Fever rates were relatively high in Sanofi studies after the first dose in young children aged six to 35 months (16.9%; 95% CI: 12.6–21.6), but lower in those aged eight to 17 years (6.9%; 95% CI: 4.3–9.8). GSK studies do not allow analysis by these age bands; the average childhood fever rate was 5.6% (95% CI: 2.9–9.1).

In contrast, markedly higher fever rates were reported in the two studies of bioCSL vaccine [47,53]. Both were uncontrolled clinical trials and had different age cohorts. Pooled estimates of fever were elevated after the first dose in children aged six to 35 months (26.4%; 95% CI: 21.0–32.3 and 18.8%; 95% CI: 15.9–21.9, respectively). Children nine years and older had a considerably lower fever rate (5.0%; 95% CI: 3.3–7.7). For second doses, fever rates were high for children aged six to 35 months (19.4%; 95% CI: 15.3–23.9) and were elevated, to a lesser extent, for three to eight-year-old children (9.7%; 95% CI: 7.7–11.9). Second-year booster doses of bioCSL vaccine with two vaccine strain changes, described in one study [47], showed even higher rates of fever, both in those aged six to 35 months (39.5%; 95% CI: 28.4–51.4) and in those aged three to eight years (27.0%; 95% CI: 21.0–33.8) (Table 4).

Serious adverse events (SAEs)
‘Serious adverse events’ were not routinely defined in studies but we assumed them to be the standard definition commonly used in clinical trials [12].
Randomised Studies
Among 15 RCTs of adjuvanted and non-adjuvanted vaccines [22,24-26,28-35,37-39] with 14,668 vaccinated individuals, 14 possibly or probably related SAEs were documented. Proportion meta-analysis yielded a pooled SAE rate of 1.2 per 1,000 vaccinated children. SAEs, where specifically described, included suspected allergic reactions to the vaccine, febrile and afebrile seizures after vaccination, new-onset diabetes, gait disorder, pneumonia, wheezing and viral gastroenteritis. A death was reported in one TIV recipient [26], deemed unrelated to the vaccination.

Non-randomised studies
Eight related SAEs were reported in non-randomised clinical trials among 7,655 vaccinated children (pooled estimate: 1.85 events per 1,000) [40,41,43-53]. SAEs described included post-vaccination fever requiring hospitalisation, bronchial hyperreactivity, bronchopneumonia, dysentery diarrhoea and distension of the abdomen, increased respiratory secretions, fever and vomiting or one FC and vomiting. One unrelated death was reported [51].

Febrile convulsions
Randomised studies
Using similar proportion meta-analysis of vaccinated study arms, we calculated an FC rate of 1.1 per 1,000 (95% CI: 0.51–1.9) using three large RCTs [26,32,39] (n = 7,439 children up to 59 or 71 months of age) that specifically reported FC as adverse events, and six RCTs (1,207 children aged up to 59 months) [22,25,29,31,34,38] that reported no related SAEs and by assumption, no FC. One of the three studies that reported on FC [32] included one vaccine-related seizure within a subset of 1,496 children aged 6–59 months (0.67 events per 1,000 children). Another study [26] reported two vaccine-related FCs among 4,173 children aged six to 59 months following TIV administration (0.48 events per 1,000). A third study [39], the only one incorporating a non-TIV control group, found similar FC rates in three study arms of non-adjuvanted TIV (2.82 per 1,000; n = 1,770), MF59 ATIV (2.59/1,000; n = 1,934) and active control vaccine (4.05/1,000; n = 988) in children six to 71 months of age. However, no comment was made if these FCs were causally related to vaccination.

Non-randomised studies
Two vaccine-related FCs were recorded in two non-randomised clinical trials (in total 2,269 evaluable children, 854 aged between six months and three years) [47,53]. Both studies used bioCSL TIV and had high rates of fever, particularly in younger vaccine recipients, compared with other non-randomised study results. Rates were not calculated due to the unavailability of denominator data within the susceptible age range.

Estimates of fever from unpublished clinical trial data
Results from unpublished clinical trials are summarised in Table 5 and Table 6. Insufficient information on study methodology precluded detailed comparisons between studies. Temperature definitions were largely unavailable. There were five RCTs, of which three were double-blind RCTs (NCT04046472, NCT00764790, NCT00959049). One of these, an RCT (NCT00959049) which was unpublished at the time of our literature search [60], directly compared Afluria (bioCSL) with Fluzone (Sanofi) across several age bands. It was conducted in the US between September 2009 and May 2010 and defined fever as either ≥ 37.5 °C axillary or ≥ 38 °C oral. Afluria was associated with significantly higher rates of fever compared with Fluzone for first doses in children aged six to 35 months (37.1% vs 13.6%, respectively, p < 0.0001) and three to eight years (21.8% vs 9.4%, respectively, p = 0.0001). There were no significant differences in fever following second doses or after single doses in children aged nine to 17 years.

Fever rates in other RCTs ranged from 6.2 to 10.7% for children aged six to 35 months, 0–11.0% in children aged three to eight or nine years, and 0–3.8% in children aged nine or 10 to 17 years. Seven small non-randomised clinical trials were identified, all using Sanofi vaccine. Age ranges were variable, precluding detailed comparison. Fever rates varied widely (Table 6).

Observational studies: cohort studies and case-control studies
The six included observational studies [54-59] are summarised in Table 7. A study of inactivated virosomal-adjuvanted TIV (Inflexal V) in 966 vaccinated children reported fever in 0.52%, without comparison data from the unvaccinated cohort [54]. One retrospective case-control study assessed safety outcomes within 42 days after TIV in 13,383 children (3,697 vaccinated children aged six to 23 months, with three age- and sex-matched controls) from a US medical group patient database [55]. No significant associations were detected for any condition, including fever or seizures, except for pharyngitis and second TIV doses.

A large population-based retrospective cohort study investigated the safety of TIV in children six to 23 months of age [56]. It examined the risk of medically attended events (MAE) after TIV in 45,356 children (69,359 vaccinations) from 1991 to 2003. Using a case-crossover method, MAE in four risk windows post vaccination was compared with two control periods, one before and one after receiving TIV. No significant associations between TIV vaccination and any MAE, including FCs, were found. Another retrospective cohort study examined children aged 24 to 59 months in the US Vaccine Safety Datalink (VSD) over four influenza seasons (2002–06) [57]. Risk of fever and SAEs was examined in 66,283 children (91,692 doses). Similar case-crossover analysis showed no SAEs associated
| Reference | Study design | Ages | Comparison groups | Enrolment period and location | TIV recipients evaluable for safety | Vaccines used | Vaccine manufacturer | Antigen dose per strain | Length monitoring solicited AE | Length SAE monitoring | Definition of fever | Method of measurement | EPHPP quality assessment tool rating | Fever rate recorded |
|-----------|--------------|------|-------------------|-----------------------------|-----------------------------------|-----------------|---------------------|------------------------|--------------------------|--------------------------|----------------|----------------------|-------------------------------|---------------------|---------------------|
| Mitchell 2005 [40] | Uncontrolled prospective study | 6–35 months | 1. 6–23 months 2. 24–36 months | 2005/06 season United States | 31 | Fluzone: TIV | Sanofi-Pasteur | 15 µg/0.5mL | 3 days | Not stated | ≥ 38°C | Rectal | Weak | 10.4% (6–23 months) |
| Englund 2006 [41] | Open-label clinical trial | 6–24 months | 1. Vaccine primed 2. Vaccine naive | Sep – Oct 2004 United States | 100 | Not stated | Aventis-Pasteur (Sanofi) | Not stated | 5 days | 6 months | ≥ 38°C | Axillary | Moderate | 2.8 – 10.3% |
| Neuzil 2006 [42] | Uncontrolled prospective open label study | 5–8 years | 1. Healthy unvaccinated children | 2004/05 season United States | 232 | Not stated | Sanofi-Pasteur | 15 µg/0.5mL | 5 days | Not stated | ≥ 37.8°C | Not stated | Weak | 0.4% |
| Avila Aguero 2007 [43] | Controlled open-label trial | 6–35 months | 1. Healthy children 2. High-risk children, unvaccinated 3. High-risk, previously vaccinated | 2001/02 Costa Rica | 218 | Inovac Grippe (Vaxigrip): TIV | Sanofi-Pasteur | 15 µg/0.5mL | 30 days | Throughout study | ≥ 37.1°C | Axillary | Moderate | 17.3% (healthy children) |
| Schmidt-Ott 2007 [44] | Uncontrolled open-label prospective phase IV study | 6–13 years | 1. Subjects 6–9 years: 2 vaccine doses 2. Subjects 10–13 years: 1 vaccine dose | Nov 2005 – Mar 2006 Germany | 226 | Influsplit SW or Fluarix: TIV | GSK | 15 µg/0.5mL | 4 days | Not stated | ≥ 37.5°C | Axillary | Weak | 2.7% (6–19 years) |
| Chai 2008 [45] | Uncontrolled clinical trial | > 6 months | 1. 6 months–3 years 2. 6–13 years 3. 18–60 years 4. > 60 years | 2005/06 season China | 764 | TIV | Chinese manufacturer | 15 µg/0.5mL | 3 days | 3 days | ≥ 37.6°C | Not stated | Weak | 9.0% (6 months–3 years) |
| Kunz 2009 [46] | Uncontrolled clinical trial | 6 months–6 years | 1. Children 6 months–6 years | 2006/07 season Germany | 405 | Inflexal IV: Virosomal ATIV | Crucell, Berna Biotech | 15 µg/0.5mL | 4 days | Not stated | Not stated | Not stated | Weak | 5.3% |
| Nolan 2009 [47] | Uncontrolled prospective open label clinical trial | 6 months–8 years | 1. 6 months–<3 years 2. ≥ 3 years–<9 years | Mar 2005 – June 2006 Australia | 293 | Fluvax: TIV | bioCSL | 15 µg/0.5mL | 7 days (0–6) | 6 months after last vaccine | ≥ 37.5°C axillary or ≥ 38°C oral | Oral or axillary | Weak | 22.5% (6 months – 3 years) |
### Table 2b

Characteristics of non-randomised clinical trials included for analysis of fever, febrile convulsions and serious adverse events following administration of inactivated trivalent influenza vaccine in children

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Ages</th>
<th>Comparison groups</th>
<th>Enrolment period and location</th>
<th>TIV recipients evaluable for safety</th>
<th>Vaccine manufacturer</th>
<th>Antigen dose per strain</th>
<th>Length monitoring solicited AE</th>
<th>Length SAE monitoring</th>
<th>Definition of fever</th>
<th>Method of measurement</th>
<th>EPHPP quality assessment tool rating</th>
<th>Fever rate recorded*</th>
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<tbody>
<tr>
<td>Vesikari 2009</td>
<td>Observer-blind follow-on study from previous RCT</td>
<td>16–47 months</td>
<td>1. Previous MF59 x 2. ATIV booster 2. Previous Split TIV x 2. TIV booster</td>
<td>2007/08 season Finland</td>
<td>89</td>
<td>Fluad: MF59 ATIV Vaxigrip: TIV</td>
<td>15 µg/0.5mL</td>
<td>7 days</td>
<td>6 months</td>
<td>≥ 38 °C</td>
<td>Axillary</td>
<td>Moderate</td>
<td>8.7% (TIV, 16–35 months)</td>
</tr>
<tr>
<td>Walter 2009</td>
<td>Controlled clinical trial</td>
<td>6–12 weeks; 6 months</td>
<td>1. 6–12 week-old infants 2. 24–36 week-old infants</td>
<td>Apr–Aug 2009</td>
<td>393</td>
<td>Fluzone: TIV</td>
<td>15 µg/0.5mL</td>
<td>7 days</td>
<td>6 months</td>
<td>≥ 38 °C</td>
<td>Not stated</td>
<td>Moderate</td>
<td>18.0% (ATIV, 16–35 months)</td>
</tr>
<tr>
<td>Wang 2009</td>
<td>Uncontrolled clinical trial</td>
<td>&gt;6 months</td>
<td>1. 6–35 months 2. 3–11 years 3. 12–17 years 4. 18–60 years 5. 160 years</td>
<td>2005/06 season China</td>
<td>2,794</td>
<td>Anflu: TIV</td>
<td>15 µg/0.5mL</td>
<td>7 days</td>
<td>7 days</td>
<td>≥ 37.6 °C</td>
<td>Not stated</td>
<td>Weak</td>
<td>5.3% (6–35 months)</td>
</tr>
<tr>
<td>D’Angio 2011</td>
<td>Controlled clinical trial</td>
<td>6–17 months</td>
<td>1. Full-term birth 2. Premature birth</td>
<td>2006/07, 2007/08 United States</td>
<td>83</td>
<td>Fluzone: TIV</td>
<td>15 µg/0.5mL</td>
<td>3 days (72 hours)</td>
<td>4–6 weeks after last vaccine</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Moderate</td>
<td>11.2% (full-term group)</td>
</tr>
<tr>
<td>Walker 2012</td>
<td>Controlled open-label follow-on study</td>
<td>17 months Adj: adjuvanted; 13 years</td>
<td>1. Original study: non-ad H1N1 vaccine; given 1x TIV 2. Original study: adj H1N1 vaccine; given 1x TIV</td>
<td>Nov–Dec 2010 United Kingdom</td>
<td>295</td>
<td>Fluarix: TIV</td>
<td>GSK 15 µg/0.5mL</td>
<td>Not stated</td>
<td>≥ 38 °C</td>
<td>Not stated</td>
<td>Axillary</td>
<td>Weak</td>
<td>13.6% (67 months – 15 years)</td>
</tr>
<tr>
<td>Lambert 2013</td>
<td>Uncontrolled prospective, multicentre, open-label clinical trial</td>
<td>6–17 years</td>
<td>1. 6–35 months 2. 3–8 years 3. 9–12 years</td>
<td>Mar–Jul 2009 Australia</td>
<td>1,976</td>
<td>Fluovax / Fluovax Junior: TIV</td>
<td>bioCSL 15 µg/0.5mL</td>
<td>7 days (0–6)</td>
<td>180 days after last vaccine</td>
<td>≥ 37.5 °C axillary oral or axillary</td>
<td>Oral or axillary</td>
<td>Weak</td>
<td>28.6% (6–35 months)</td>
</tr>
</tbody>
</table>

Adj: adjuvanted; AE: adverse event; ATIV: adjuvanted trivalent influenza vaccine; EPHPP: effective public health practice project; GSK: GlaxoSmithKline; LAIV: live attenuated influenza vaccine; RCT: randomised controlled trial; SAE: serious adverse event; TIV: non-adjuvanted trivalent influenza vaccine.

*Where multiple doses were administered, fever is listed for the first dose. The youngest age group is shown unless otherwise stated.
### Table 3
Pooled estimates of fever proportions from randomised controlled trials of inactivated trivalent influenza vaccine in children

<table>
<thead>
<tr>
<th>Fever in randomised controlled trials</th>
<th>Age</th>
<th>Dose (study numbers)</th>
<th>Number of children</th>
<th>Single study fever proportion (%)</th>
<th>Overall fever estimate (%)</th>
<th>95% CI</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-adjuvanted vaccines</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>6–35 months</td>
<td>Dose 1 [22,29,31,38,39]</td>
<td>1,543</td>
<td>NA</td>
<td>6.7</td>
<td>3.0–11.8</td>
<td>87.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 [22,29,31,38,39]</td>
<td>1,501</td>
<td>NA</td>
<td>7.6</td>
<td>3.5–13.0</td>
<td>87.6</td>
</tr>
<tr>
<td></td>
<td>3–17 years</td>
<td>Dose 1 [29,39]</td>
<td>795</td>
<td>NA</td>
<td>6.9</td>
<td>5.2–8.7</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 [29,39]</td>
<td>775</td>
<td>NA</td>
<td>5.4</td>
<td>1.2–12.1</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Adjuvanted vaccines</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>MF59 adjuvanted</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>6–35 months</td>
<td>Fluad Dose 1 [31,35,39]</td>
<td>1,286</td>
<td>NA</td>
<td>11.9</td>
<td>6.8–18.3</td>
<td>74.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluad Dose 2 [31,35,39]</td>
<td>1,261</td>
<td>NA</td>
<td>10.4</td>
<td>4.2–18.9</td>
<td>86.4</td>
</tr>
<tr>
<td></td>
<td>3–17 years</td>
<td>Fluad Dose 1 [35,39]</td>
<td>913</td>
<td>NA</td>
<td>10.3</td>
<td>1.1–27.0</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluad Dose 2 [35,39]</td>
<td>894</td>
<td>NA</td>
<td>9.0</td>
<td>0.3–27.2</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Virosomal adjuvanted</strong></td>
<td>6 months–5 years</td>
<td>Inflexal V Dose 1 [30,34]</td>
<td>112</td>
<td>NA</td>
<td>5.5</td>
<td>1.3–12.3</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inflexal V Dose 2 [30,34]</td>
<td>112</td>
<td>NA</td>
<td>5.5</td>
<td>1.3–12.3</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Vaccine manufacturers</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Sanofi (Vaxigrip, Fluzone)</strong></td>
<td>6–35 months</td>
<td>Dose 1 [22,29,31,36,38]</td>
<td>558</td>
<td>NA</td>
<td>5.1</td>
<td>2.8–8.1</td>
<td>42.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 [22,29,31,36,38]</td>
<td>548</td>
<td>NA</td>
<td>4.3</td>
<td>2.8–6.2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3–17 years</td>
<td>Dose 1 [23,29,33]</td>
<td>162</td>
<td>NA</td>
<td>4.4</td>
<td>1.2–9.2</td>
<td>32.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 [29]</td>
<td>18</td>
<td>0</td>
<td>NA</td>
<td>0–18.5</td>
<td>NA</td>
</tr>
<tr>
<td><strong>GSK (Fluarix)</strong></td>
<td>6 months–17 years</td>
<td>Combined doses [27,32,37]</td>
<td>2,151</td>
<td>NA</td>
<td>4.7</td>
<td>0.9–11.1</td>
<td>79.7</td>
</tr>
<tr>
<td><strong>Novartis (Agrippal)</strong></td>
<td>3–12 years</td>
<td>Dose 1 [28]</td>
<td>100</td>
<td>4.0</td>
<td>NA</td>
<td>1.1–9.3</td>
<td>NA</td>
</tr>
</tbody>
</table>

CI: confidence interval; NA: not applicable.

a Overall fever estimate calculated from studies using 38°C fever definition for non-adjuvanted and adjuvanted vaccine analyses. Analysis by vaccine manufacturer used any fever definition. Random-effects proportion meta-analysis performed.

b I² not calculated due to low numbers of studies.

c Calculated confidence interval of a single proportion.

d Single study data. No meta-analysis performed.

e Only combined dose data available.
<table>
<thead>
<tr>
<th>Fever in non-randomised clinical trials</th>
<th>Age</th>
<th>Dose</th>
<th>Number of children</th>
<th>Single study fever proportion (%)</th>
<th>Overall fever estimate(^a) (%)</th>
<th>95% CI</th>
<th>(I^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-adjuvanted vaccines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6–35 months</td>
<td>Dose 1 [40,41,47,49,53]</td>
<td>1,253</td>
<td>NA</td>
<td>17.7</td>
<td>11.3–25.2</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 [40,41,47,49,53]</td>
<td>1,046</td>
<td>NA</td>
<td>11.7</td>
<td>5.4–19.9</td>
<td>89.9</td>
</tr>
<tr>
<td></td>
<td>3–17 years</td>
<td>Dose 1 [47,53]</td>
<td>1,420</td>
<td>NA</td>
<td>15.1</td>
<td>13.3–17.0</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 [47,53]</td>
<td>781</td>
<td>NA</td>
<td>9.7</td>
<td>7.7–11.9</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Adjuvanted vaccines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>16–35 months</td>
<td>Fluad [48](^c)</td>
<td>25</td>
<td>16.0</td>
<td>NA</td>
<td>4.5–36.1</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>36–48 months</td>
<td>Fluad [48](^c)</td>
<td>18</td>
<td>11.1</td>
<td>NA</td>
<td>1.4–34.7</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Vaccine manufacturer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6–35 months</td>
<td>Dose 1 [40,41,49]</td>
<td>287</td>
<td>NA</td>
<td>16.0</td>
<td>12.6–21.6</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 [40,41,49]</td>
<td>280</td>
<td>NA</td>
<td>6.2</td>
<td>0.0–21.0</td>
<td>90.9</td>
</tr>
<tr>
<td></td>
<td>3–8 years</td>
<td>Dose 1 [42](^c)</td>
<td>232</td>
<td>0.4</td>
<td>NA</td>
<td>0–2.4  (^a)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 [42](^c)</td>
<td>232</td>
<td>1.3</td>
<td>NA</td>
<td>0.3–3.7  (^a)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>17 months–13 years</td>
<td>Combined doses [44,52](^e)</td>
<td>627</td>
<td>NA</td>
<td>5.6</td>
<td>2.9–9.1</td>
<td>65.3</td>
</tr>
<tr>
<td></td>
<td>6–35 months</td>
<td>Dose 1 [47,53]</td>
<td>854</td>
<td>NA</td>
<td>26.4</td>
<td>21.0–32.3</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 [47,53]</td>
<td>768</td>
<td>NA</td>
<td>19.4</td>
<td>15.3–23.9</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Booster dose [47](^c)</td>
<td>76</td>
<td>39.5</td>
<td>28.4–51.4 (^a)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3–8 years</td>
<td>Dose 1 [47,53]</td>
<td>1,022</td>
<td>NA</td>
<td>18.8</td>
<td>15.9–21.9</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 2 [47,53]</td>
<td>781</td>
<td>NA</td>
<td>9.7</td>
<td>7.7–11.9</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Booster dose [47](^c)</td>
<td>196</td>
<td>27.0</td>
<td>NA</td>
<td>21.0–33.8</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>9–17 years</td>
<td>Dose 1 [53](^c)</td>
<td>398</td>
<td>5.0</td>
<td>NA</td>
<td>3.3–7.7</td>
<td>NA</td>
</tr>
</tbody>
</table>

CI: confidence interval; NA: not applicable.

\(^a\) Overall fever estimate calculated from studies using 38°C fever definition for non-adjuvanted and adjuvanted vaccine analyses. Analysis by vaccine manufacturer used any fever definition. Random-effects proportion meta-analysis performed.

\(^b\) \(I^2\) not calculated due to low numbers of studies.

\(^c\) Single study data. No meta-analysis performed.

\(^d\) Calculated confidence interval of a single proportion.

\(^e\) Dose 1 and 2 treated as separate groups within analysis.
**Table 5a**

Unpublished clinical trials from Clinicaltrials.gov included for analysis of fever, febrile convulsions and serious adverse events following administration of inactivated trivalent influenza vaccine in children

<table>
<thead>
<tr>
<th>Reference</th>
<th>Phase</th>
<th>Study design</th>
<th>Ages</th>
<th>Comparison groups</th>
<th>Study period and location</th>
<th>TV recipients evaluable for safety</th>
<th>Vaccine type (whole, split, subunit)</th>
<th>Vaccine manufacturer</th>
<th>Length monitoring solicited AE</th>
<th>Length monitoring unsolicited AE</th>
<th>Length SAE monitoring</th>
<th>Definition of fever</th>
<th>Method of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00391391</td>
<td>2</td>
<td>RCT – open-label</td>
<td>6–35 months; 3–8 years</td>
<td>1. Fluzone intradermal 2. Fluzone IM</td>
<td>Oct 2006 – Oct 2007 United States</td>
<td>517 Split vaccine Sanofi Pasteur</td>
<td>7 days</td>
<td>6 months after last vaccination</td>
<td>6 months after last vaccination</td>
<td>6 months after last vaccination</td>
<td>≥ 37.5 °C oral or ≥ 38 °C rectal (exclusion criteria)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>NCT00764790a</td>
<td>3</td>
<td>RCT, double-blind</td>
<td>6–35 months</td>
<td>1. Fluarix 2. Fluarix, half dose 3. Fluzone</td>
<td>Oct 2008 – Mar 2009 5 countries</td>
<td>3,256 Fluarix split; Fluzone split GSK: Fluarix Sanofi Pasteur</td>
<td>4 days</td>
<td>28 days post vaccination</td>
<td>6 months</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00943202</td>
<td>2</td>
<td>RCT, open-label</td>
<td>Primed 6–35 months; primed 3–9 years; 10–18 years</td>
<td>1. Day 0: H1N1; Day 21: H1N1; Day 42: TIV 2. Day 0: H1N1 + TIV; Day 21: H1N1 3. Day 0: H1N1; Day 21: H1N1 + TIV 4. Day 0: TIV; Day 21: H1N1; Day 42: H1N1</td>
<td>Aug 2009 – May 2010 United States</td>
<td>262 Licensed seasonal trivalent influenza vaccine Sanofi Pasteur: H1N1</td>
<td>8 days</td>
<td>21 days post last vaccination</td>
<td>8 months post first vaccination</td>
<td>13.7 °C axillary or 38.3 °C oral</td>
<td>Axillary or oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00959049</td>
<td>3</td>
<td>RCT, double-blind</td>
<td>6 months–18 years</td>
<td>1. bioCSL: Afluria in 3 age cohorts 2. Sanofi: Fluzone in 3 age cohorts</td>
<td>Sep 2009 – May 2010 United States</td>
<td>1,468 Afluria split Fluzone split BioCSL: Afluria Sanofi: Fluzone</td>
<td>7 days post vaccination</td>
<td>30 days</td>
<td>6 months after last vaccination</td>
<td>≥ 37.5 °C axillary or ≥ 38 °C oral</td>
<td>Axillary or oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Phase</td>
<td>Study design</td>
<td>Ages</td>
<td>Comparison groups</td>
<td>Study period and location</td>
<td>TIV recipients evaluable for safety</td>
<td>Vaccine type (whole, split, subunit)</td>
<td>Vaccine manufacturer</td>
<td>Length monitoring solicited AE</td>
<td>Length monitoring unsolicited AE</td>
<td>Length SAE monitoring</td>
<td>Definition of fever</td>
<td>Method of measurement</td>
</tr>
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<tr>
<td>NCT00831675</td>
<td>4</td>
<td>Non-randomised, open-label, parallel assignment</td>
<td>6–&lt;36 months</td>
<td>1. 6–112 months, healthy</td>
<td>Sep 20 04 – Apr 2006 United States</td>
<td>30</td>
<td>Split Sanofi Fluzone</td>
<td>4 days (day 0–3)</td>
<td>42 days post vaccination</td>
<td>42 days post vaccination</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>NCT00253847</td>
<td>4</td>
<td>Non-randomised, open-label, parallel assignment</td>
<td>6–&lt;36 months</td>
<td>1. Vaccine naïve, 2 doses</td>
<td>Oct 2005 – Aug 2007 United States</td>
<td>30</td>
<td>Split Sanofi Fluzone</td>
<td>4 days (day 0–3)</td>
<td>2 weeks after last vaccine</td>
<td>2 weeks after last vaccine</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>NCT00389857</td>
<td>4</td>
<td>Non-randomised, open-label, parallel assignment</td>
<td>6–&lt;36 months</td>
<td>1. Vaccine naïve, 2 doses</td>
<td>Oct 2006 – July 2008 United States</td>
<td>31</td>
<td>Split Sanofi Fluzone</td>
<td>4 days (day 0–3)</td>
<td>2 weeks after last vaccine</td>
<td>2 weeks after last vaccine</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>NCT00561002</td>
<td>4</td>
<td>Non-randomised, open-label, parallel assignment</td>
<td>6–&lt;36 months</td>
<td>1. Vaccine naïve/adequately primed 2 previous doses; given 1 dose now</td>
<td>Oct 2007 – Jun 2008 United States</td>
<td>32</td>
<td>Split Sanofi Fluzone</td>
<td>4 days (day 0–3)</td>
<td>2 weeks after last vaccine</td>
<td>2 weeks after last vaccine</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>NCT00753274</td>
<td>4</td>
<td>Non-randomised, open-label, parallel assignment</td>
<td>6–&lt;159 months</td>
<td>1. Vaccine primed 2 previous doses; given 2 doses now</td>
<td>Sep 2008 – Jan 2009 United States</td>
<td>32</td>
<td>Split Sanofi Fluzone</td>
<td>4 days (day 0–3)</td>
<td>2 weeks after last vaccine</td>
<td>2 weeks after last vaccine</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>NCT0085105</td>
<td>3</td>
<td>Non-randomised, open-label, parallel assignment</td>
<td>6–&lt;11 months</td>
<td>1. Previous study 2x Fluzone at 2 months; given 2 doses Fluzone</td>
<td>Oct 2005 – Sep 2007 United States</td>
<td>242</td>
<td>Split Sanofi Fluzone</td>
<td>8 days (day 0–7)</td>
<td>6 months post vaccination</td>
<td>6 months post vaccination</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>NCT0039084</td>
<td>4</td>
<td>Non-randomised, open-label, parallel assignment</td>
<td>11–14 months</td>
<td>1. Fluzone primed; previous study Fluzone 2 doses; given 2 doses Fluzone</td>
<td>Oct 2006 – Sep 2008 United States</td>
<td>173</td>
<td>Split Sanofi Fluzone</td>
<td>8 days (day 0–7)</td>
<td>2 months post vaccination</td>
<td>2 months post vaccination</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

AE: adverse event; GSK: GlaxoSmithKline; NR: not recorded; RCT: randomised controlled trial; SAE: serious adverse event; TIV: non-adjuvanted trivalent influenza vaccine.

* Studies published after our literature search and review.
with TIV in healthy children, however, fever was significantly associated with TIV within the window between Day 1 and 14 (incidence rate ratio (IRR) = 1.71; 95% CI: 1.64–1.80).

One retrospective observational cohort study in children in Western Australia (WA) from 2010 reported on the rate of fever seen with bioCSL TIV [58]. Data linkage of TIV-associated FC cases and vaccine exposure recorded in the Australian Childhood Immunisation Register, was added to data obtained from vaccine providers or primary caregivers. A high rate of FC, 3.3 per 1,000 vaccine doses, was documented during the 49-day vaccination programme, with 62 of 63 FC associated with bioCSL TIV, all occurring after a first dose, with a median time of 7 hours from vaccination to symptom onset. In children younger than five years, FCs were significantly more associated with bioCSL TIV than with Solvay’s Influvac (p < 0.0001).

Subsequent to the reporting of excess FC rates post TIV in Australia, another VSD study was conducted in the US during the 2010/11 influenza season, examining Day 0 to 1 after TIV administration and examined 206,174 children aged six to 59 months who received at least one dose of vaccine [59]. None received bioCSL vaccine as its recommendation had been removed. While the main finding was of increased FC with concurrent TIV and 13-valent pneumococcal conjugate vaccine (PCV13), adjustment for PCV 13 still yielded a statistically significant increase in seizures following TIV by itself (IRR = 2.4; 95% CI: 1.2–4.7). The risk difference estimate was maximal at 16 months of age with 12.5 vaccine-attributable seizures per 100,000 doses.

**Discussion**

Our study summarises fever and FC data from multiple clinical trials, reporting group (not individual) safety outcomes following TIV receipt. Using published RCT data, we have found a reassuringly low pooled rate of fever >38 ºC after non-adjuvanted TIV, which was similar to most non-bioCSL vaccines in observational studies conducted during 2010 when safety concerns arose due to bioCSL TIV [61-63].

Limited pooled data on investigational MF59-ATIV showed higher fever rates compared with non-adjuvanted vaccines. However in the two RCTs [31,39] with direct comparison of MF59-ATIV and TIV, fever rate differences were non-significant between adjuvanted and non-adjuvanted vaccine groups, apart from a subset of children aged 36 to 71 months in one study where the MF59-ATIV recipients had higher fever [39]. The same RCT [39] found no differences in fever rate between MF59-ATIV and TIV in younger children aged six to 35 months. However, it also recorded the highest fever rates in the non-adjuvanted arm for this age group (13.3% and 13.4% for doses 1 and 2, respectively) relative to all other non-adjuvanted vaccine study arms in our meta-analysis; this may have contributed to the absence of observable difference in fever between MF59-ATIV and TIV. In addition, the European Medicines Agency (EMA) raised concerns, after site inspections, that this study was not conducted in accordance with guidelines on good clinical practice (GCP), and therefore did not grant marketing approval for the Novartis MF59-ATIV used [64,65].

Non-randomised clinical trials were of lower quality, often being uncontrolled. Pooled fever estimates for non-adjuvanted vaccines were higher than those from RCTs, probably due in part to the inclusion of reactogenic bioCSL vaccines [47,53], although other manufacturers’ vaccines also recorded higher fever rates than in RCT studies.

A recent systematic review of fever by Kaczmarek et al. following dose 1 of inactivated TIV, reported a similar rate (8.0%) for any fever in children aged six to <36 months after non-adjuvanted TIV, using weighted average weekly risk [66]. However, our study, by using a proportion meta-analysis method, allowed inclusion of a broader range of studies. We used the Brighton Collaboration’s fever definitions (≥38 ºC) and analysed fever in a number of additional settings: adjuvanted vaccine studies, older children (36 months and older), fever after second doses of vaccine and by vaccine manufacturer.

Most non-bioCSL brand TIVs had low rates of fever in RCT analyses. However, bioCSL TIVs had significantly higher fever after first doses in children aged six months to eight years, across three studies conducted from March 2005 through to May 2010, particularly in an RCT (NCT00959049) comparing bioCSL’s Afluria and a comparator TIV [60], subsequently published after our literature search and review (Table 6). Observational studies from 2010 in Australia and New Zealand documented similar findings comparing bioCSL TIV to other manufacturers [58,62].

Our findings on SAE and FC rates are considerably limited by the absence of studies using within-study placebo controls, which precludes calculation of true vaccination-related rates. However, analysing TIV-vaccinated arms, we found that vaccination-related SAEs were uncommon. Our calculated FC rate from published RCT data (no bioCSL studies available) was 1.1 per 1,000 children six to <72 months-old and vaccinated with non-adjuvanted TIV. However, it was unclear in one study if all FC reported were causally related to TIV [39]; the actual rate may be lower. The same study showed no difference in FC rates between TIV and the non-TIV, active control arm [39]. We could not calculate FC rates in the clinical trials with bioCSL vaccine, but two observational studies conducted since 2010 reported FC rates of 3.5–4.4/1,000 doses for bioCSL Fluvax/Fluvax Junior compared with no FCs after 4,720 doses of Solvay vaccine (Influvac) or 3,213 doses of non-bioCSL TIV [58,62]. Furthermore, a 2010 investigation by the Therapeutics Goods Administration (TGA)
Table 6
Fever estimates from unpublished trials identified at Clinicaltrials.gov following administration of inactivated trivalent influenza vaccine in children

<table>
<thead>
<tr>
<th>Study code</th>
<th>Fever definition</th>
<th>Age</th>
<th>Dose</th>
<th>Fever rate study vaccine % (denominator)</th>
<th>Fever rate comparator vaccine % (denominator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised controlled trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00391391a</td>
<td>&gt; 37.5 °C</td>
<td>6–35 months</td>
<td>Dose 1</td>
<td>10.3% (97)</td>
<td>10.3% (97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–35 months</td>
<td>Dose 2</td>
<td>9.3% (97)</td>
<td>6.2% (97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–8 years</td>
<td>Dose 1</td>
<td>11.0% (163)</td>
<td>6.3% (160)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–8 years</td>
<td>Dose 2</td>
<td>8.6% (163)</td>
<td>10.0% (160)</td>
</tr>
<tr>
<td>NCT00464672</td>
<td>ND</td>
<td>3–8 years</td>
<td>Dose 1</td>
<td>3.0% (426)</td>
<td>1.5% (199)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–8 years</td>
<td>Dose 2</td>
<td>2.5% (396)</td>
<td>2.5% (197)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9–17 years</td>
<td>Dose 1</td>
<td>0.3% (400)</td>
<td>2.0% (199)</td>
</tr>
<tr>
<td>NCT00764790b</td>
<td>ND</td>
<td>6–35 months</td>
<td>Any dose</td>
<td>6.2% (1,080)</td>
<td>6.6% (1,090)</td>
</tr>
<tr>
<td>NCT00943202c</td>
<td>≥ 37.8 °C</td>
<td>6–35 months</td>
<td>Dose 1</td>
<td>10.7% (28)</td>
<td>9.4% (32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–35 months</td>
<td>Dose 2</td>
<td>2.0% (51)</td>
<td>0.0% (49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–17 years</td>
<td>Dose 1</td>
<td>3.8% (53)</td>
<td>0.0% (49)</td>
</tr>
<tr>
<td>NCT00959049[60]</td>
<td>≥ 37.5 °C or ≥ 38 °C oral</td>
<td>6–35 months</td>
<td>Dose 1</td>
<td>37.1% (229)</td>
<td>13.6% (228)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–35 months</td>
<td>Dose 2</td>
<td>14.6% (96)</td>
<td>13.6% (110)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–8 years</td>
<td>Dose 1</td>
<td>21.8% (252)</td>
<td>9.4% (255)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–8 years</td>
<td>Dose 2</td>
<td>5.9% (68)</td>
<td>6.4% (78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9–17 years</td>
<td>Dose 1</td>
<td>6.3% (254)</td>
<td>4.0% (250)</td>
</tr>
<tr>
<td>Non randomised studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00831675</td>
<td>ND</td>
<td>6–11 months</td>
<td>Dose 1</td>
<td>0.0% (12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–11 months</td>
<td>Dose 2</td>
<td>8.3% (12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12–35 months</td>
<td>Dose 1</td>
<td>16.7% (18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12–35 months</td>
<td>Dose 2</td>
<td>16.7% (18)</td>
<td></td>
</tr>
<tr>
<td>NCT00258817</td>
<td>≥ 38 °C</td>
<td>6–35 months</td>
<td>Dose 1</td>
<td>6.7% (15)</td>
<td>13.3% (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–35 months</td>
<td>Dose 2</td>
<td>33.3% (15)</td>
<td></td>
</tr>
<tr>
<td>NCT00389857</td>
<td>ND</td>
<td>6–35 months</td>
<td>Dose 1</td>
<td>0.0% (14)</td>
<td>5.9% (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–35 months</td>
<td>Dose 2</td>
<td>7.1% (14)</td>
<td></td>
</tr>
<tr>
<td>NCT00561002</td>
<td>ND</td>
<td>6–35 months</td>
<td>Dose 1</td>
<td>17.4% (23)</td>
<td>22.2% (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–35 months</td>
<td>Dose 2</td>
<td>13.0% (23)</td>
<td></td>
</tr>
<tr>
<td>NCT00755274</td>
<td>ND</td>
<td>6–59 months</td>
<td>Dose 1</td>
<td>25.0% (8)</td>
<td>8.3% (24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–59 months</td>
<td>Dose 2</td>
<td>25.0% (8)</td>
<td></td>
</tr>
<tr>
<td>NCT00885105</td>
<td>ND</td>
<td>6–10 months</td>
<td>Dose 1</td>
<td>25.0% (130)</td>
<td>25.0% (112)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–10 months</td>
<td>Dose 2</td>
<td>14.0% (130)</td>
<td>14.0% (112)</td>
</tr>
<tr>
<td>NCT00390884</td>
<td>ND</td>
<td>11–14 months</td>
<td>Dose 1</td>
<td>10.5% (57)</td>
<td>15.5% (116)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11–14 months</td>
<td>Dose 2</td>
<td>15.8% (57)</td>
<td>17.2% (116)</td>
</tr>
</tbody>
</table>

ND: not defined; TIV: trivalent influenza vaccine.

a Only data on intramuscularly administered vaccine group was used.
b Only groups with full dose were examined. Data from groups with half dose are not presented.
c Only groups with TIV administered alone are listed.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Study period</th>
<th>Location</th>
<th>Number of participants</th>
<th>Intervention</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salleras 2009 [54]</td>
<td>Prospective cohort study</td>
<td>2004/05 season</td>
<td>Barcelona, Spain</td>
<td>1951 children 3–14 years-old; 966 received TIV</td>
<td>TIV Viro-somal adjuvanted vaccine</td>
<td>Only vaccinated cohort findings presented. Fever ≥ 38 °C recorded in 0.52% of vaccinated cohort. Local redness in 4%. Systemic malaise in 0.72%. SAE not documented.</td>
</tr>
<tr>
<td>Goodman 2006 [55]</td>
<td>Retrospective case–control study</td>
<td>2002/03 and 2003/04 seasons</td>
<td>United States</td>
<td>13,383 including 3,697 TIV recipients aged 6–23 months at vaccination</td>
<td>TIV</td>
<td>Safety outcomes assessed within 42 days of TIV. Pharyngitis associated with dose 2 of TIV. No other associations detected including for fever or seizures.</td>
</tr>
<tr>
<td>Hambidge 2006 [56]</td>
<td>Retrospective cohort using self-control analysis</td>
<td>1991–2003</td>
<td>United States</td>
<td>45,356 children aged 6–23 months with 69,359 vaccinations</td>
<td>TIV</td>
<td>13 diagnoses less likely to occur within two weeks after TIV compared with control periods before and after this period. Positive association detected for limb soreness, fever, and gastrointestinal tract symptoms associated with vaccination.</td>
</tr>
<tr>
<td>Armstrong 2011 [58]</td>
<td>Three-part study: 1. Descriptive case–control study</td>
<td>Mar–Apr 2010</td>
<td>Western Australia</td>
<td>63 TIV-associated FC presentations related to TV</td>
<td>TIV</td>
<td>1. 3.3 FC/1,000 doses of TV. All occurred after first dose, with median onset 7 h post vaccine. CSL TIV 14.8 × higher risk of febrile reaction compared with alternative brand.</td>
</tr>
<tr>
<td>Tse 2012 [59]</td>
<td>Near real-time surveillance study using self-controlled risk interval and current vs historical vaccine study designs</td>
<td>2010 (in influenza season)</td>
<td>United States</td>
<td>206,174 children aged 6–59 months from the Vaccine Safety Datalink</td>
<td>TIV</td>
<td>Among children 6–59 months of age, the incidence rate ratio for TIV adjusted for concomitant PCV3 was 2.4 (95% CI: 1.4–4.7). Risk difference estimates were highest at 16 months (12.5/100,000 doses for TIV without concomitant PCV3) and younger age (p = 0.024) associated with higher risk of “significant febrile adverse events” in logistic regression model.</td>
</tr>
</tbody>
</table>
Proposed explanations for higher fever rates with bioCSL vaccines have included 2010 TIV strain changes and manufacturing methods. Investigations by bioCSL concluded that their method of manufacture retained more virus components due to less splitting of virus, compared with other manufacturers, and that characteristics of the three viruses included in the 2010 vaccine elicited an excessive immune response in young children [69,70]. However, all manufacturers used the same new strains in formulating the 2010 southern hemisphere vaccine without eliciting increased fever or FCs.

These results highlight the differences in the propensity to febrile events that may exist between different companies’ TIVs. The single RCT (NCT00959049) comparing bioCSL TIV with a comparator vaccine in children most clearly demonstrates these important differences. This study was conducted in 2009/10 but only recently published in 2014 [60]. It was not yet completed when the bioCSL TIV problem emerged in April 2010. Access to individual level data of this study would offer valuable insights into fever following receipt of TIV.

The lack of clearly presented, publicly available, comparable data regarding the safety of influenza vaccines, particularly in young children, has been emphasised in a previous systematic review of influenza vaccination [71]. Few of the studies we examined were eligible for that systematic review due to the lack of placebo controls. Without such placebo-controlled studies, the true rate of adverse events due solely to TIV is difficult to ascertain accurately. Such studies are difficult to justify ethically as more and more countries recommend universal influenza vaccination of healthy children. Our study addressed as much data as possible, with sensitivity analyses, to provide the most comprehensive information by which to compare vaccines.

Limitations of this study are acknowledged, including the difficulty of comparing studies that have different methodology. By examining studies involving healthy children, we have maximised the comparability of studies, but the findings may not apply to children with chronic illness for whom TIV is specifically recommended. The majority of fever analyses showed substantial heterogeneity; I2 values ranged from 0% to 95.6% with most being larger than 50%. Bias assessment revealed that the majority of randomised studies had low to moderate risk of bias. A random-effects model for pooled fever estimates was used to provide an accurate estimate across variable studies. Our sensitivity analysis was not able to identify specific sources of heterogeneity based on assessments of study quality, but underlying study variability is the most likely cause.

Our analysis did not specifically take into account differing follow-up periods. Solicited AE follow-up periods longer than 48 hours result in the possibility of unrelated fever being captured. This highlights the need for consistent reporting in studies of post-vaccination fever rates occurring within specific timeframes, particularly the first 24 hours. Lastly, most pooled fever estimates involved overlapping confidence intervals, meaning that the point estimates of fever must be compared cautiously. However, where possible, we have compared similar types of vaccines, within set age ranges, and included studies that used Brighton Collaboration definitions of fever.

Conclusions and recommendations

This review provides a generally reassuring assessment on the safety of most TIVs which have low rates of fever or serious adverse events. There is, however, evidence that the bioCSL brand vaccines have been associated with higher rates of fever than comparable vaccines. This cannot be ascribed to the change in vaccine strains alone as the 2010 TIV made by other manufacturers was not highly reactogenic.

Although Tse et al. [59] found an association between early post-vaccination FCs and US 2010/11 non-bioCSL TIVs, containing strains identical to the 2010 southern hemisphere TIV, the risk was low and comparable to other routine immunisations.

We advocate prompt reporting and publication of clinical trial safety data for influenza vaccines. This is even more pertinent with the impending adoption of quadrivalent influenza vaccines (QIV) containing an additional influenza B strain, to ensure that reactogenicity is not increased. Closer scrutiny of the safety of each new season’s vaccine formulations in children, for example through a period of active surveillance after TIV release each season, may facilitate the early detection and rapid response to any future safety signals.
to minimise future impacts on the health of vaccinees and maintain confidence in immunisation programmes. The EMA is heading in this direction with requirements from 2014 to 2015 for vaccine manufacturers to implement systems for yearly enhanced safety surveillance to rapidly detect clinically significant changes in the frequency or severity of expected reactogenicity of influenza vaccines [72,73].

Furthermore, we believe public availability of individual-level data (of precise levels of fever over time) from both past and future vaccine trials as well as the use of standardised study methods, through stricter adherence to Brighton Collaboration case definitions and reporting recommendations for adverse events, is essential to enable effective comparison both between vaccines and over time.

Erratum *

The statement of conflict of interest was omitted in the original publication and added on 25 June 2015. In Table 4, a line was added between the data for GSK and BioCSE.

Conflict of interest *

J. K. Yim received an educational grant from Sanofi Pasteur for influenza economic research in 2012. R. Booy has received funding from bioCSE, Roche, Sanofi, GlaxoSmithKline (GSK), Novartis, and Pfizer to conduct sponsored research or attend and present at scientific meetings; any funding received is directed to a research account at the Children’s Hospital at Westmead. C. Jones has received funding from GlaxoSmithKline (GSK) to attend and present at the New Zealand Infection and Immunisation Special Interest group in 2013.

Authors’ contributions

Jean Li-Kim-Moy conceived and designed the study, was involved in screening of relevant studies, data collection, data analysis, data interpretation and writing of the manuscript. Jihkeu Kevin Yim conceived and designed the study, was involved in screening of relevant studies, data collection, assisted in writing all sections of the paper, and revision of the manuscript. Harunor Rashid conceived and designed the study, was involved in screening of relevant studies, data collection, data analysis, and revision of the manuscript. Gulam Khandaker assisted with design of the study, was involved in screening of relevant studies, and revised the manuscript. Catherine King conducted the electronic literature search, assisted in writing the methods section, and revised the manuscript. Nicholas Wood, Kristine Macartney, and Cheryl Jones revised the manuscript and assisted in writing all sections of the manuscript. Robert Booy conceived, designed, and supervised the study; he was involved in data interpretation, writing of all sections of the paper, and revision of the manuscript.

References


