Systematic review of fever, febrile convulsions and serious adverse events following administration of inactivated trivalent influenza vaccines in children

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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systematically reviewed the rates of fever, FC and serious adverse events (SAEs) after TIV, focussing on published and unpublished clinical trial data from 2005 to 2012, and performed meta-analysis of fever rates.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5.1% with Sanofi or GlaxoSmithKline vaccines; bioCSL vaccines were used in two non-randomised clinical trials and one unpublished RCT and were associated with fever in 22.5–37.1% for children aged 6–35 months.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

is a common respiratory viral infection with a substantial disease burden in children younger than five years, of whom between nine and 45 per 10,000 need hospital admission each year in developed countries [1-4]. Vaccination is the leading strategy to combat influenza. The recommendations for influenza vaccination have been progressively expanded and now include all healthy children aged six months and older in the United States (US) and several European countries [5,6]. The United Kingdom's (UK) Joint Committee on Vaccination and Immunisation (JCVI) recommended vaccination of all children two to 17 years of age with live attenuated influenza vaccine (LAIV) from the 2013/14 season onwards, although implementation was being staggered, commencing with two and three year-old children in the first year [7]. In Australia, TIV is funded nationally for any child older than six months with medical conditions predisposing to severe influenza, and in one state (Western Australia) also for healthy children aged six to 59 months [8].

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). Influenza vaccination for children five years and younger was briefly suspended. The increase in FC (estimated to be between five and seven events per 1,000 vaccinated children) was related only to one brand of TIV, manufactured by bioCSL (Fluvax and Fluvax Junior) [9]. 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

(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 I^2 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.

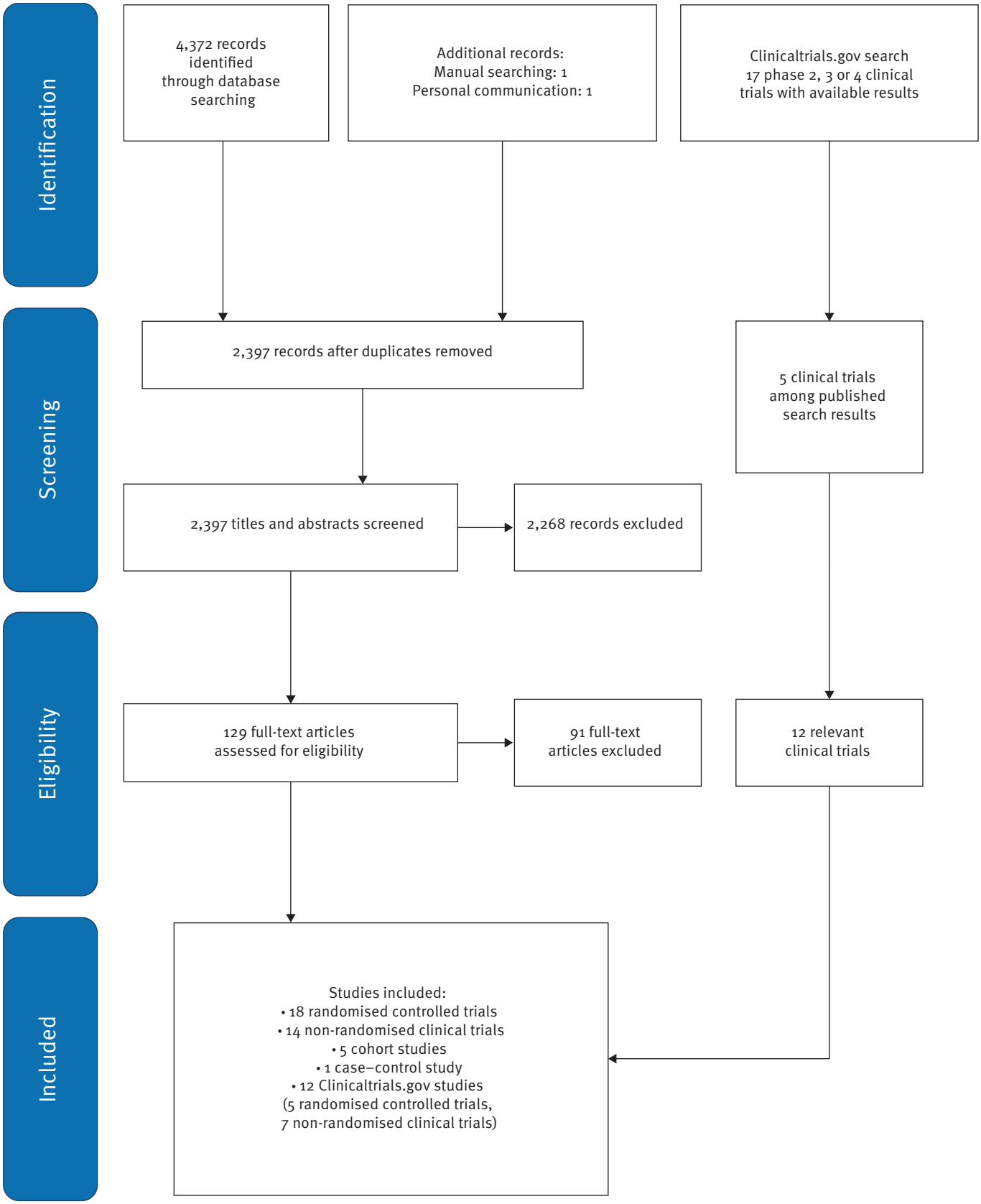
Characteristics of non-randomised clinical trials

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].

Figure

Results of literature search for fever, febrile convulsions and serious adverse events following administration of inactivated trivalent influenza vaccine in children, and studies analysed



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 recordeda
Englund 2005 [22]	6 – 23 months	1. Standard schedule: 2 doses autumn 2. Previous year priming schedule: spring then autumn dose 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 – 3 years, 6 – 12 years, 16 – 60 years, › 60 years	1. Fluviral 2. Vaxigrip	Mar – Sep 2004 China	785	Fluviral: TIV Vaxigrip: TIV	Fluviral: 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–3 years)
Ashkenazi 2006 [24]	6–71months	1. LAIV 2. Inactivated TIV	Oct 2002 9 European countries	1,086	LAIV TIV	LAIV: Wyeth Pharmaceuticals TIV: Aventis Pasteur	15 µg/0.5mL	11 days	To end of study	≥ 37.5 °C axillary or ≥ 38 °C Rectal	Axillary or rectal	Medium	21.4% (TIV) 23.5% (LAIV)
Walter 2006 [25]	6–23months	1. Spring–autumn schedule 2. Standard autumn 2-dose schedule	Apr – Jun 2004 United States	462	TIV	Aventis Pasteur (Sanofi)	15 µg/0.5mL	5 days 3 days for fever	6 months post last vaccine	≥ 38 °C	Axillary	Medium	3.8%
Belshe 2007 [26]	6–59 months	1. LAIV 2. Inactivated TIV	Oct 2004 16 countries	4,173	Fluzone: TIV Vaxigrip: TIV Flumist: LAIV	Fluzone and Vaxigrip: Aventis-Pasteur (Sanofi) LAIV: Medimmune	LAIV: 107 FFU/antigen TIV: not stated	42 days	Median 219 days (180 days after last vaccine)	› 37.8 °C	Oral, axillary or rectal	Low	2% (TIV measured Day 2 only) 5.4% (LAIV measured Day 2 only)
Chiu 2007 [27]	3–18 years	1. Intradermal TIV 2. Intramuscular TIV	Oct – Nov 2005 Hong Kong	56	Fluarix: TIV	GSK	15 µg/0.5mL	3 days	Not stated	› 38 °C	Not stated	Medium	7.1% (intramuscular route)
Zhu 2008 [28]	3–12 years; 18–59 years; › 60 years	1. Influvac 2. Agrippal	2005 China	300	2005–2006: Influvac TIV; 2005–2006: Agrippal TIV	Influvac:Solvay / Abbott Agrippal: Novartis	15 µg/0.5mL	3 days	4 weeks	Not stated	Not stated	Medium	4.0–4.5%
King 2009 [29]	6–59 months	1. Standard TIV 2. Recombinant TIV:	Oct – Nov 2006 United States	156	Fluzone: TIV FluBlok: recombinant TIV	TIV: Sanofi FluBlok: Protein Sciences Corporation	TIV: 15 µg/0.5mL	7 days	180 days	≥ 38 °C	Not stated	Medium	5.3% (standard TIV)
Marchisio 2009 [30]	1–5 years	1. Virosomal-ATIV 2. No treatment	Oct 2006 Italy	90	Inflexal V: virosomal ATIV	Berna Biotech	15 µg/0.5mL	7 days	Not stated	≥ 38 °C	Rectal	Medium	3.3%
Vesikari 2009 [31]	6–35 months	1. MF59 ATIV 2. TIV	Nov 2006 – Aug 2007 Finland	269	Fluad: MF59 ATIV Vaxigrip TIV	Fluad: Novartis Vaxigrip: Sanofi	15 µg/0.5mL	7 days	6 months	≥ 38 °C	Not stated	Low	4.3% 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	Fluarix: TIV Fluzone: TIV	Fluarix: GSK Fluzone: Sanofi	15 µg/0.5mL	4 days (0–3)	6 months post first vaccine	≥ 37.5 °C	Axillary	Medium	7.4–7.5%
Cowling 2010 [33]	6–15 years	1. Vaccinated household 2. Placebo household	Nov – Dec 2008 Hong Kong	71	Vaxigrip: TIV	Sanofi Pasteur	15 µg/0.5mL	4 days	10 months	≥ 37.8 °C	Not stated	Low	1.4%
Esposito 2010 [34]	6–35 months	1. 2 doses of 0.50 mL 2. 2 doses of 0.25 mL	Oct 2008 – May 2009 Italy	65	Inflexal V: virosomal ATIV	Crucell	15 µg/0.5mL	14 days	Not stated	≥ 38 °C	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 ATIV	Novartis	7.5 µg/0.5 mL H5N1 15 µg/0.5 mL TIV	7 days	Not stated	≥ 38 °C	Axillary	Low	12.5% (6–35 months, MF59 ATIV group)

Table 1b

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 recordeda
Hoft 2011 [36]	6–35months	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 Fluarix: TIV	Green Cross Fluarix: GSK	15 µg/0.5mL	7 days	Not stated	≥38 °C	Axillary	High	0–3.1%
Skowronski 2011 [38]	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)
Vesikari 2011 [39]	6–71 months	1. MF59 ATIV 2. TIV 3. Active placebo -MenC or tickborn encephalitis vaccine	2007 – 2009 Germany and Finland	4,692	2007–08: Fluad MF59 ATIV and Agrippal S1 TIV. 2008–09: Fluad and Influsplit SSW TIV	Fluad: Novartis Agrippal S1: Novartis Influsplit SSW: GSK	15 µg/0.5mL	7 days	Year 1: 6 months Year 2: 12 months	Not stated	Not stated	Medium	13.3% (TIV) 15.3% (ATIV) 13.3% (control)

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.

[a] 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 Fluad (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 three to eight year-old children (0.4%; 95% CI: 0–2.4). GSK studies did 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 and three to eight years (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 was 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 (Clinicaltrials.gov)

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 (NCT00464672, 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

Table 2a

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

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[a]
Mitchell 2005 [40]	Uncontrolled prospective study	6–35 months	1. 6–23 months 2. 24–36 months	2003/04 season United States	31	Fluzone: TIV	Sanofi-Pasteur	15 µg/0.5mL	3 days	Not stated	›38 °C	Rectal	Weak	10.5% (6–23 months)
Englund 2006 [41]	Open-label clinical trial	6–24 months	1. Vaccine primed 2. Vaccine naïve	Sep – Oct 2004 United States	100	Not stated	Aventis-Pasteur (Sanofi)	Not stated	5 days	6 months	≥38 °C	Axillary	Moderate	2.8 – 10.9%
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 (0–4)	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	Imovax 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	224	Influsplit SSW or Fluarix: TIV	GSK	15 µg/0.5mL	4 days	Not stated	≥37.5 °C	Axillary	Weak	2.7% (6–‹9 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)
Kunzi 2009 [46]	Uncontrolled clinical trial	6 months–6 years	1. Children 6 months-6 years	2006/07 seasonGermany	405	Inflexal V: 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. 6months–‹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

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[a]
Vesikari 2009 [48]	Observer-blind follow-on study from previous RCT	16–47 months	1. Previous MF59 x 2. ATIV booster 2. Previous Split TIV x 2. TIV booster	2007/08 season Finland	89	Fluad: MF59 ATIV Vaxigrip: TIV	Fluad: Novartis Vaxigrip: Sanofi-Pasteur	15 µg/0.5mL	7 days	6 months	≥ 38 °C	Axillary	Moderate	8.7% (TIV, 16–35 months) 16.0% (ATIV, 16–35 months)
Walter 2009 [49]	Controlled clinical trial	6–12 weeks; 6 months	1. 6–12 week-old infants 2. 24–36 week-old infants	Apr – Aug 2005	393	Fluzone: TIV	Sanofi-Pasteur	15 µg/0.5mL	7 days	6 months	≥ 38 °C	Not stated	Moderate	18.2% (24–36 weeks)
Wang 2009 [50]	Uncontrolled clinical trial	› 6 months	1. 6–35 months 2. 3–11 years 3. 12–17 years 4. 18–60 years 5. › 60 years	2005/06 season China	2,794	Anflu: TIV	Chinese manufacturer	15 µg/0.5mL	7 days	7 days	≥ 37.6 °C	Not stated	Weak	5.3% (6–35 months)
D'Angio 2011 [51]	Controlled clinical trial	6–17 months	1. Full-term birth 2. Premature birth	2006/07, 2007/08 United States	83	Fluzone: TIV	Sanofi-Pasteur	15 µg/0.5mL	3 days (72 hours)	4–6 weeks after last vaccine	Not stated	Not stated	Moderate	14.7% (term group)
Walker 2012 [52]	Controlled open-label follow-on study	17 month-sAdj: adjuvanted; 13 years	1. Original study: non-adj H1N1 vaccine; given 1x TIV 2. Original study: adj H1N1 vaccine; given 1x TIV	Nov– Dec 2010 United Kingdom	295	Fluarix: TIV	GSK	15 µg/0.5mL	7 days	Not stated	≥ 38 °C	Axillary	Weak	13.6% (17 months – ‹ 5 years)
Lambert 2013 [53]	Uncontrolled prospective, multicentre, open-label clinical trial	6–17 years	1. 6–35 months 2. 3–8 years 3. 9–17 years	Mar– Jul 2009 Australia	1,976	Fluvax / Fluvax Junior: TIV	bioCSL	15 µg/0.5mL	7 days (0–6)	180 days after last vaccine	≥ 37.5 °C axillary or ≥ 38 °C oral	Oral or axillary	Weak	28.6% (6–35 months)

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.

[a] 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

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

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] Calculated confidence interval of a single proportion.

[d] Single study data. No meta-analysis performed.

[e] Only combined dose data available.

Table 4

Pooled estimates of fever proportions from non-randomised clinical trials of inactivated trivalent influenza vaccine in children*

Fever in non-randomised clinical trials	Age	Dose	Number of children	Single study fever proportion (%)	Overall fever estimate[a] (%)	95% CI	I^2
Non-adjuvanted vaccines							
	6–35 months	Dose 1 [40,41,47,49,53]	1,253	NA	17.7	11.3–25.2	85
		Dose 2 [40,41,47,49,53]	1,046	NA	11.7	5.4–19.9	89.9
	3–17 years	Dose 1 [47,53]	1,420	NA	15.1	13.3–17.0	NA[b]
		Dose 2 [47,53]	781	NA	9.7	7.7–11.9	NA[b]
Adjuvanted vaccines							
MF59 adjuvanted	16–35 months	Fluad [48][c]	25	16.0	NA	4.5–36.1[d]	NA[c]
	36–48 months	Fluad [48][c]	18	11.1	NA	1.4–34.7[d]	NA[c]
Vaccine manufacturer							
Sanofi (Fluzone, Vaxigrip, Imovax Grippe)	6–35 months	Dose 1 [40,41,49]	287	NA	16.9	12.6–21.6	4.3
		Dose 2 [40,41,49]	280	NA	6.2	0.0–21.0	90.9
	3–8 years	Dose 1 [42][c]	232	0.4	NA	0–2.4[d]	NA[c]
		Dose 2 [42][c]	232	1.3	NA	0.3–3.7[d]	NA[c]
GSK (Influsplit SSW / Fluarix)	17 months–13 years	Combined doses [44,52][e]	627	NA	5.6	2.9–9.1	65.3
bioCSL (Fluvax / Fluvax Junior)	6–35 months	Dose 1 [47,53]	854	NA	26.4	21.0–32.3	NA[b]
		Dose 2 [47,53]	766	NA	19.4	15.3–23.9	NA[b]
		Booster dose [47][c]	76	39.5		28.4–51.4[d]	NA[c]
	3–8 years	Dose 1 [47,53]	1,022	NA	18.8	15.9–21.9	NA[b]
		Dose 2 [47,53]	781	NA	9.7	7.7–11.9	NA[b]
		Booster dose [47][c]	196	27.0	NA	21.0–33.8[d]	NA[c]
	9–17 years	Dose 1 [53][c]	398	5.0	NA	3.3–7.7[d]	NA[c]

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

Reference	Phase	Study design	Ages	Comparison groups	Study period and location	TIV recipients evaluable for safety	Vaccine type (whole, split, subunit)	Vaccine manufacturer	Length monitoring solicited AE	Length monitoring unsolicited AE	Length SAE monitoring	Definition of fever	Method of measurement
Randomised studies													
NCT00391391	2	RCT – open-label	6–35 months; 3–8 years	1. Fluzone intradermal 2. Fluzone IM	Oct 2006 – Oct 2007 United States	517	Split vaccine	Sanofi Pasteur	7 days	6 months after last vaccination	6 months after last vaccination	≥ 37.5 °C oral or ≥ 38 °C rectal (exclusion criteria)	NR
NCT00464672	3	RCT, double-blind	3–8 years; 9–17 years	1. Novartis vaccine 2. Comparator	Apr 2007 – Dec 2007 Argentina	1,200	Subunit	Novartis	7 days	Day 21–216 post vaccination	Until Day 216	NR	NR
NCT00764790[a] [74]	3	RCT, double-blind	6–35 months	1. Fluarix 2. Fluarix, half dose 3. Fluzone	Oct 2008 – Mar 2009 5 countries	3,256	Fluarix split; Fluzone split	GSK : Fluarix Sanofi-Pasteur: Fluzone	4 days	28 days post vaccination	6 months	NR	NR
NCT00943202[a] [75]	2	RCT, open-label	Primed 6–35 months; primed 3–9 years; 10–18 years	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	Aug 2009 – May 2010 United States	262	Licensed seasonal trivalent influenza vaccine	Sanofi Pasteur: H1N1	8 days	21 days post last vaccination	8 months post first vaccination	› 37.8 °C axillary or 38.3 °C oral	Axillary or oral
NCT00959049 [60]	3	RCT, double-blind	6 months–18 years	1. bioCSL: Afluria in 3 age cohorts 2. Sanofi: Fluzone in 3 age cohorts	Sep 2009 – May 2010 Unites States	1,468	Afluria split Fluzone split	BioCSL: Afluria Sanofi: Fluzone	7 days post vaccination	30 days	6 months after last vaccination	≥ 37.5 °C axillary or ≥ 38 °C oral	Axillary or oral

Table 5b

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

Reference	Phase	Study design	Ages	Comparison groups	Study period and location	TIV recipients evaluable for safety	Vaccine type (whole, split, subunit)	Vaccine manufacturer	Length monitoring solicited AE	Length monitoring unsolicited AE	Length SAE monitoring	Definition of fever	Method of measurement
Non-randomised studies													
NCT00831675	4	Non-randomised, open-label, parallel assignment	6–<36 months	1. 6–<12 months, healthy 2. 12 months–<36 months, healthy	Sep 20 04 – Apr 2006 United States	30	Split	Sanofi: Fluzone	4 days (day 0–3)	42 days post vaccination	42 days post vaccination	NR	NR
NCT00258817	4	Non-randomised, open-label, parallel assignment	6 months–<36 months	1. Vaccine naïve, 2 doses 2. Vaccine primed, 1 dose	Oct 2005 – Aug 2007 United States	30	Split	Sanofi: Fluzone	4 days (day 0–3)	2 weeks after last vaccine	2 weeks after last vaccine	≥ 38 °C	NR
NCT00389857	4	Non-randomised, open-label, parallel assignment	6 months–<36 months	1. Vaccine naïve, 2 doses 2. Vaccine primed, 1 dose	Oct 2006 – July 2008 United States	31	Split	Sanofi: Fluzone	4 days (day 0–3)	2 weeks after last vaccine	2 weeks after last vaccine	NR	NR
NCT00561002	4	Non-randomised, open-label, parallel assignment	6 months–<36 months	1. Vaccine-naïve/inadequately primed ≤ 1 previous dose: given 1 dose now 2. Vaccine-primed 2 previous doses: given 1 dose now	Oct 2007 – Jun 2008 Unites States	32	Split	Sanofi: Fluzone	4 days (day 0–3)	2 weeks after last vaccine	2 weeks after last vaccine	NR	NR
NCT00755274	4	Non-randomised, open-label, parallel assignment.	6–<59 months	1. Vaccine primed ≥ 2 previous doses: given 1 dose now 2. Vaccine-naïve/inadequately primed ≤ 1 previous dose: given 2 doses now	Sep 2008 – Jan 2009 United States	32	Split	Sanofi: Fluzone	4 days (day 0–3)	2 weeks after last vaccine	2 weeks after last vaccine	NR	NR
NCT00885105	3	Non-randomised, open-label, parallel assignment	6–<11 months	1. Previous study 2x Fluzone at 2 months: given 2 doses Fluzone 2. Fluzone naïve: given 2 doses Fluzone	Oct 2005 – Sep 2007 United States	242	Split	Sanofi: Fluzone	8 days (day 0–7)	6 months post vaccination	6 months post vaccination	NR	NR
NCT00390884	4	Non-randomised, open-label, parallel assignment	11–14 months	1. Fluzone primed: previous study Fluzone 2 doses; given 2 doses Fluzone 2. Fluzone naïve: previous study placebo 2 doses; given 2 doses Fluzone	Oct 2006 – Sep 2008 United States	173	Split	Sanofi: Fluzone	8 days (day 0–7)	2 months post vaccination	2 months post vaccination	NR	NR

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

[a] 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 °C 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 °C) 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

Study code	Fever definition	Age	Dose	Fever rate study vaccine % (denominator)	Fever rate comparator vaccine % (denominator)
Randomised controlled trials					
NCT00391391[a]	>37.5 °C			Fluzone intramuscular	Fluzone intradermal
		6–35 months	Dose 1	10.3% (97)	10.3% (97)
		6–35 months	Dose 2	9.3% (97)	6.2% (97)
		3–8 years	Dose 1	11.0% (163)	6.3% (160)
		3–8 years	Dose 2	8.6% (163)	10.0% (160)
NCT00464672	ND			Novartis vaccine	Comparator vaccine
		3–8 years	Dose 1	3.0% (402)	1.5% (199)
		3–8 years	Dose 2	2.5% (396)	2.5% (197)
		9–17 years	Dose 1	0.3% (400)	2.0% (199)
NCT00764790[b]	ND			Fluarix – GSK	Fluzone – Sanofi Pasteur
		6–35 months	Any dose	6.2% (1,080)	6.6% (1090)
NCT00943202[c]	≥ 37.8 °C			TIV as first vaccine	TIV as third vaccine
		6–35 months	Fever after TIV	10.7% (28)	9.4% (32)
		3–9 years	Fever after TIV	2.0% (51)	0.0% (49)
		10–17 years	Fever after TIV	3.8% (53)	0.0% (49)
NCT00959049 [60]	≥ 37.5 °C axillary or ≥ 38 °C oral			Afluria – BioCSL	Fluzone – Sanofi
		6–35 months	Dose 1	37.1% (229)	13.6% (228)
		6–35 months	Dose 2	14.6% (96)	13.6% (110)
		3–8 years	Dose 1	21.8% (252)	9.4% (255)
		3–8 years	Dose 2	5.9% (68)	6.4% (78)
		9–17 years	Dose 1	6.3% (254)	4.0% (250)
Non randomised studies					
NCT00831675	ND	6–11 months	Dose 1	0.0% (12)	
		6–11 months	Dose 2	8.3% (12)	
		12–35 months	Dose 1	16.7% (18)	
		12–35 months	Dose 2	16.7% (18)	
NCT00258817	≥ 38 °C			Vaccine naïve	Vaccine primed
		6–35 months	Dose 1	6.7% (15)	13.3% (15)
		6–35 months	Dose 2	33.3% (15)	
NCT00389857	ND			Vaccine naïve	Vaccine primed
		6–35 months	Dose 1	0.0% (14)	5.9% (17)
		6–35 months	Dose 2	7.1% (14)	
NCT00561002	ND			Vaccine naïve	Vaccine primed
		6–35 months	Dose 1	17.4% (23)	22.2% (9)
		6–35 months	Dose 2	13.0% (23)	
NCT00755274	ND			Vaccine naïve	Vaccine primed
		6–59 months	Dose 1	25.0% (8)	8.3% (24)
		6–59 months	Dose 2	25.0% (8)	
NCT00885105	ND			Fluzone (Sanofi) naïve	Fluzone (Sanofi) primed
		6–10 months	Dose 1	25.0% (130)	25.0% (112)
		6–10 months	Dose 2	14.0% (130)	14.0% (112)
NCT00390884	ND			Fluzone (Sanofi) naïve	Fluzone (Sanofi) primed
		11–14 months	Dose 1	10.5% (57)	15.5% (116)
		11–14 months	Dose 2	15.8% (57)	17.2% (116)

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 7

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

Reference	Study design	Study period	Location	Number of participants	Intervention	Main findings
Salleras 2009 [54]	Prospective cohort study	2004/05 season	Barcelona, Spain	1951 children 3–14 years-old; 966 received TIV	Inflexal V Virosomal adjuvanted vaccine	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.
Goodman 2006 [55]	Retrospective case–control study	2002/03 and 2003/04 seasons	United States	13,383 including 3,697 TIV recipients aged 6–23 months at vaccination	TIV	Safety outcomes assessed within 42 days of TIV. Pharyngitis associated with dose 2 of TIV. No other associations detected including for fever or seizures.
Hambidge 2006 [56]	Retrospective cohort using self-control analysis	1991–2003	United States	45,356 children aged 6–23 months with 69,359 vaccinations	TIV	13 diagnoses less likely to occur within two weeks after TIV compared with control periods before/after this period. Positive association with non-infectious gastroenteritis in Emergency Department setting. No association with convulsions detected.
Glanz 2011 [57]	Self-controlled screening study	Oct 2002–Mar 2006	United States	66,283 children aged 24–59 months with 91,692 vaccinations from the Vaccine Safety Datalink	TIV	No association between any serious medically attended events to TIV post-vaccination period. Non serious associations detected for limb soreness, fever, and gastrointestinal tract symptoms
Armstrong 2011 [58]	Three-part study: 1. Descriptive/case–control study 2. Incidence study 3. Retrospective cohort study of AE after three brands TIV	1. Mar–Apr 2010 2. 2008–2010 3. 2010	Western Australia	1. 63 TIV-associated FC 2. Coded public hospital presentations for FC temporally related to TIV 3. Three groups of 120 children each who had received a different brand of TIV	TIV	1. 3.3 FC/1,000 doses of TIV. 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. 2. Pattern of elevated post-TIV FC not seen in years before 2010. 38 TIV temporally associated FC coded in 2010, one in 2009, nil in 2008 3. CSL-branded TIV (OR 8.9; 95%CI 3.1 to 25.7, p<0.0005) and younger age (p=0.024) associated with higher risk of "significant febrile adverse events" in logistic regression model.
Tse 2012 [59]	Near real-time surveillance study for FC using self-controlled risk interval and current vs historical vaccinee study designs	2010/11 influenza season	United States	206,174 children aged 6–59 months from the Vaccine Safety Datalink	TIV (not CSL brand)	Among children 6–59 months of age, the incidence rate ratio for TIV adjusted for concomitant PCV13 was 2.4 (95% CI: 1.2–4.7). Risk difference estimates were highest at 16 months (12.5/100,000 doses for TIV without concomitant PCV13) due to varying age-related baseline risk for seizures in young children.

AE: adverse event; CI: confidence interval; FC: febrile convulsion; OR: odds ratio; PCV13: 13-valent pneumococcal vaccine; TIV: trivalent influenza vaccine.

into bioCSL vaccine found FC rates of 5–7 per 1,000 doses [9].

Based on one study, MF59-ATIV was associated with 2.59 FCs per 1,000 vaccinated children aged six to 71 months, but this was not significantly different to control groups (non-adjuvanted TIV or active control vaccine) [39]. Further study of adjuvanted vaccines is warranted to investigate their safety profile, in terms of fever and FC.

Despite an observational study reporting a link between the 2010/11 US non-bioCSL TIV and FC on Day 0 to 1 [59] (mostly with concurrent PCV13), the absolute risk of TIV-related FC appeared low overall (a maximum of 12.5/100,000 doses), less than the risk seen after measles-mumps-rubella (MMR) vaccine (33/100,000) and similar to the risk after 13-valent PCV (13.7/100,000) [59,67]. A subsequent study of the 2011/12 US influenza season confirmed elevated fever after concurrent TIV and PCV13 on Day 0 to 1 and listed fever rates after TIV alone similar to our findings at 7.5% in children aged six to 23 months [68].

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 BioCSL.

Conflict of interest *

J. K. Yin received an educational grant from Sanofi Pasteur for influenza economic research in 2012. R. Booy has received funding from bioCSL, 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. Jiehui Kevin Yin 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.

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