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Review

The risk of fever following one dose of trivalent inactivated influenza vaccine in children aged ≥6 months to <36 months: A comparison of published and unpublished studies

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ABSTRACT

There are limited summary data published on the risk of fever and febrile seizures in children following influenza vaccination.

We performed a review of the risk of fever and febrile seizures following receipt of trivalent inactivated influenza vaccine (TIV) in children aged ≥6 months to <36 months, searching PubMED and Google Scholar for English language articles from 2000 onwards, and initiated or ongoing unpublished studies since September 2007 using clinicaltrials.gov. Exclusions included other vaccine co-administration, missing ages or participant numbers, or unmeasured fever. We reviewed articles and collated results using a standard data extraction template.

We identified a total of 909 published papers and unpublished trials from a search conducted on 23 January 2013, 669 from Google Scholar, 114 from PubMed and 126 from the Clinicaltrials.gov online database. After excluding 890 published papers or unpublished trials, 5 published papers and 14 unpublished trials were included in this review. Extracted data on number of events, children at risk and time of follow-up were converted to the risk of fever, which was averaged per week of follow-up (referred to as 'averaged weekly risk').

Following one dose of TIV, the median averaged weekly risk of any fever (≥37.5 °C) was 26.0% (range 10.3–70.0%) in unpublished trials compared to 8.2% (range 5.3–28.3%) in published papers ($p = 0.04$). The median averaged weekly risk of severe fever (≥39.0 °C) was 3.2% (range 0–10.0%) and 2.0% (range 0.6–17.0%), respectively ($p = 0.91$).

Variation in the reporting of fever by participant age groups, time since vaccination and the definition or measurement of fever resulted in a wide range of risk estimates. Reporting of febrile reactions should be standardised to allow comparison between manufacturers and influenza seasons.

Contents

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1. Introduction

Seasonal influenza infection causes a high burden of disease amongst children, in many cases leading to hospitalisations or severe complications, and occasionally resulting in death [1,2]. Although it is not publicly funded in all countries where it is recommended, annual influenza vaccination is recommended for all children aged 6 months and older in Australia, the United States and Canada [3–5]. Across several European countries influenza vaccination is often only recommended for children aged 6 months or older within certain clinical risk groups [6,7]. Influenza vaccination, using a live attenuated vaccine, will be funded for all children aged 2–17 years in the United Kingdom from 2014 following a recommendation by the Joint Committee on Vaccination and Immunisation [8].

Manufacturers are required to demonstrate the safety and tolerability of their vaccines pre and post licensure. Through clinical trials, post-licensure studies, and routine (passive) reporting of adverse events, safety issues may become apparent [9]. Although most adverse events are mild and self-limiting, serious adverse events occur rarely [3,10,11].

During 2010, the risk of fever and febrile seizures in young children following administration of the Southern Hemisphere seasonal trivalent influenza vaccine (TIV) in Australia was higher than expected. This was subsequently shown to be due to vaccines manufactured by CSL Biotherapies (now bioCSL) [12]. Approximately 50% of children vaccinated with CSL TIV experienced fever, which in most cases was relatively mild [11]. However the estimated risk of febrile seizures following CSL 2010 TIV ranged from 3 to 10 per 1000 children vaccinated [12,13].

The incidence of fever and febrile seizures appeared much higher than had been recorded in post-marketing adverse event surveillance in the United States [14] but there was no accepted baseline in Australia by which to judge the evolving data.

By conducting a review of data in the public domain, specifically papers published in English language journals and unpublished clinical trials available online, we aimed to define the risk of fever and febrile seizures following influenza vaccination with TIV in young children. We also aimed to identify any differences in reported risk between published papers and unpublished trials.

2. Methods

2.1. Article search

A review of unpublished clinical trials available online and published papers was conducted to determine the risk of fever associated with influenza vaccination using TIV in children aged at least 6 months to less than 36 months old.

The published literature search used *Google Scholar* and *PubMed* (*MEDLINE*) search engines, while the unpublished literature was searched using only ClinicalTrials.gov, an online database of clinical trials. The search was conducted on 23 January 2013. Terms for each search engine varied slightly (Table 1) and we restricted our search to articles published since 1 January 2000. The ClinicalTrials.gov database includes clinical trials that were ongoing at 27 September 2007, or were initiated since that date. Only data in the public domain were used, and manufacturers were not contacted for safety data on their paediatric influenza vaccines. We did not restrict our search by study design, and allowed for the inclusion of randomised controlled trials, cohort studies and phases I–IV clinical trials.

Following the search, the titles and abstracts of all articles identified were reviewed to determine their relevance. Articles assessed as not relevant, based on the title or abstract, or published in a language other than English, were excluded.

Citations for all remaining articles were entered into EndNote, and duplicate articles were removed.

All articles were then retrieved and reviewed to assess whether they met the inclusion criteria. To be included, the study needed to have reported the administration of non-adjuvanted TIV to children aged ≥6 months to <36 months, with vaccine details (vaccine type, manufacturer, formulation, doses), age group and study size clearly defined. In addition, vaccine safety (adverse event) data needed to have been included as raw number of events with time since vaccination, and febrile reactions needed to have been measured with a thermometer (either oral, axillary or rectal measurement). Any studies that co-administered TIV with other childhood vaccines were excluded.

2.2. Data extraction and analysis

Using a standard template (available on request), data were extracted from articles satisfying the inclusion criteria. Data

Table 1
Search terms used to identify published papers and unpublished trials.

Search engine	Search terms	Limits
Google scholar	*With all of the words*: influenza vaccine fever safety *With the exact phrase*: adverse event *With at least one of the words*: newborn infant child children *Without the words*: haemophilus Hib H5N1 pregnancy yellow	*Anywhere in article* *Articles between*: 2000 and 2013 *Search only in* [*subject areas*]: 'Biology, Life Sciences, and Environmental Science'; 'Medicine, Pharmacology, and Veterinary Science'
PubMed	Influenza vaccine AND fever AND adverse ((“influenza vaccines” [MeSH Terms] OR (“influenza” [All Fields] AND “vaccines” [All Fields]) OR “influenza vaccines” [All Fields] OR (“influenza” [All Fields] AND “vaccine” [All Fields]) OR “influenza vaccine” [All Fields]) AND (“fever” [MeSH Terms] OR “fever” [All Fields])) AND adverse[All Fields]	*Publication date*: 01/01/2000–23/01/2013 *Age groups*: 'All Infant: birth–23 months'; 'All Child: 0–18 years'; 'Newborn: birth–1 month'; 'Infant: 1–23 months'; 'Preschool child: 2–5 years'; 'Child: 6–12 years'; 'Adolescent: 13–18 years'
ClinicalTrials.gov	Influenza AND vaccine	*Age group*: Child (birth-17) *Study results*: Studies with results

extraction focused on the percentage of children experiencing a febrile reaction following receipt of TIV, but also included vaccine manufacturer and type (split or sub-unit), age at vaccination, duration of follow-up and severity of reaction. All eligible studies were reviewed independently by two authors (MK, UD) and results recorded in a Microsoft Excel spread sheet. No adjustment was made for temperature measured at different sites (oral, axillary or rectal measurement).

Extracted data were grouped by the severity of febrile reaction ('any': reported fever with any measurement ≥37.5 °C, or 'severe': measured fever ≥39.0 °C) and data source (unpublished trial or published paper). Where multiple doses of TIV were given, we considered only the risk after the first dose. We extracted raw data on the number of events, the number of children at risk and the time of follow-up from each study and derived the risk of fever, which was averaged per week of follow-up (referred to as 'averaged weekly risk'). We grouped results by severity and data source. We tested for heterogeneity using the chi-squared test, and when estimates derived from individual studies were sufficiently homogeneous, a weighted (pooled) estimate of fever risk was calculated using a weighted average of study-specific confidence limits. The equality of the median averaged risk comparing published papers and unpublished trials was tested using the Wilcoxon rank-sum test in Stata version 10 (StataCorp, College Station, TX).

A sensitivity analysis was conducted to determine whether a similar range of fever was observed in excluded papers. This was done by extracting the same data from all published papers and unpublished trials that had been excluded because fever was not defined (either not measured/parental report only or temperature cut-offs not defined) or because the study used an adjuvanted TIV. In addition, we extracted reports of any febrile seizures following vaccination. We did not analyse fever or febrile seizures according to vaccine manufacturer.

3. Results

3.1. Studies identified and included in the review

The search identified a total of 909 published papers and unpublished trials on Google Scholar (n = 669), PubMed (n = 114), and the Clinicaltrials.gov online database (n = 126). After excluding 890 studies, based on pre-defined inclusion criteria, 5 published papers and 14 unpublished trials were included in the review (Fig. 1).

Of the excluded 890 published papers and unpublished trials, many were reports of other influenza vaccines (primarily monovalent pandemic H1N1 and live-attenuated influenza vaccines), other vaccines (*Haemophilus influenzae* (Hib) and other routine childhood vaccinations), involved the co-administration of influenza vaccine

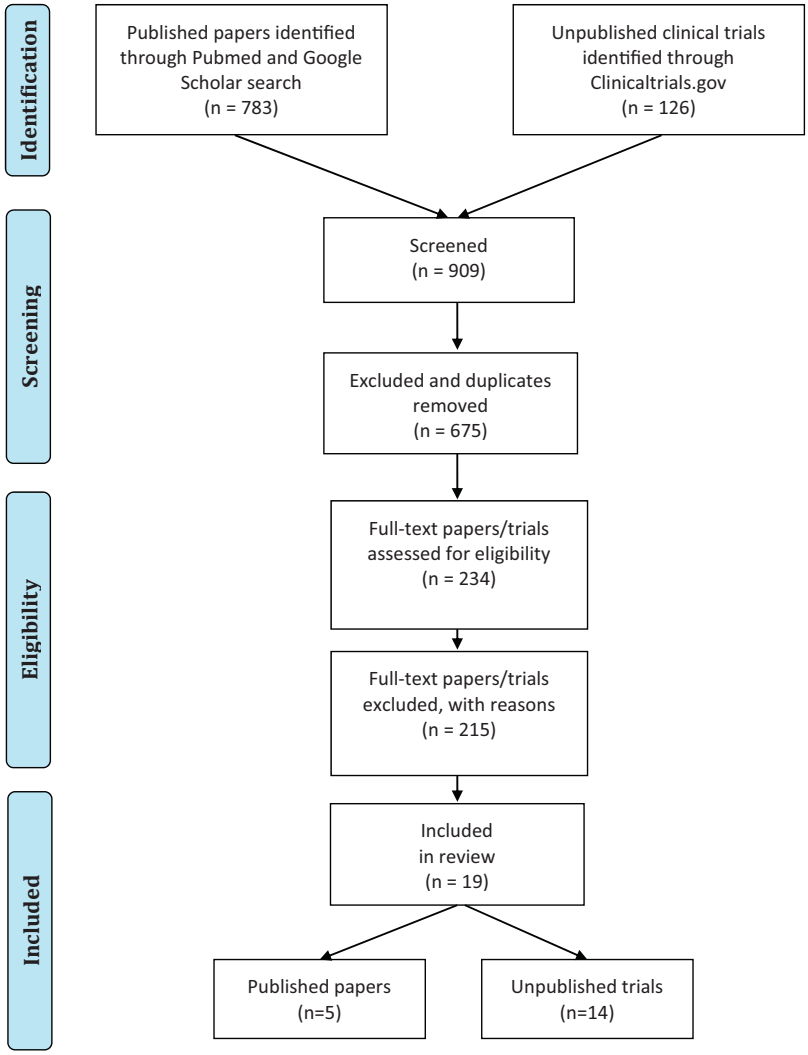

Fig. 1. Flow chart of study identification, screening and inclusion.

with other vaccines, did not include or report separately on children aged ≥6 months and <36 months, or were in a language other than English.

The published papers (Table 2) and unpublished trials (Table 3) included in the review varied by study location, study type, vaccine manufacturer, definition of fever (minimum temperature threshold), and follow up period (from 0–1 days to 0–30 days post vaccination). Published papers included randomised controlled trials and cohort studies and were conducted in a range of countries. Unpublished trials (phases ranging from I to IV) were more homogenous, with 10 of 14 located in the United States, and 11 of 14 reporting results for Sanofi Pasteur vaccines. Only one study had results reported in both a published paper and an unpublished trial [15,16]. One unpublished trial has been published since the search was conducted, but only the results from the unpublished trial were included in this review [17,18].

3.2. The risk of fever after first-dose of TIV

Fourteen unpublished trials (2520 participants) and five published papers (1163 participants) reported on any fever (defined as ≥37.5 °C), while 13 unpublished trials (2270 participants) and three published papers (903 participants) reported on severe fever (defined as ≥39.0 °C). No study contained a placebo control arm, so meta-analysis could not be performed.

The median averaged weekly risk of any fever was 26.0% (range 10.3–70.0%) in unpublished trials compared to 8.2% (range 5.3–28.3%) in published papers ($p = 0.04$). The median averaged weekly risk of severe fever were 3.2% (range 0–10.0%) and 2.0% (range 0.6–17.0%), respectively ($p = 0.91$). For both outcomes, the results from unpublished trials were too heterogeneous to combine as a weighted (pooled) risk estimate, while published trials had a weighted (pooled) averaged weekly risk of 8.0% (95% CI: 5.9–10.6%) for any fever and 2.8% (95% CI: 1.3–5.1%) for severe fever. Febrile seizures were reported in two unpublished trials. Three febrile seizures in one participant among 703 participants in one week follow-up were reported by one unpublished trial [19], while the other reported one seizure among 192 participants in one week follow-up [17]. The weighted (pooled) averaged weekly risk of a febrile seizure following TIV in an infant aged under 36 months was 0.22% (95% CI: 0–1.24%)

The sensitivity analysis, examining the risk of fever following TIV in published papers and unpublished trials excluded from our review because fever had not been defined, identified only three published papers and one unpublished trial. The published papers reported averaged weekly risk of any fever (not specifically defined) as: 13.3% [20], 26.3% [21], and 26.7% [22]. The unpublished trial reported averaged weekly risk of any fever (not specifically defined) following administration of two different vaccines as 11.0% and 11.6% [23].

Two studies reporting fever following administration of an adjuvanted TIV in children <36 months were also noted. One study reported averaged weekly risk of any fever as 20.4% and severe fever as 7.1% [24], while the second study reported averaged weekly risk of any fever as 4.0% [25].

4. Discussion

Our review found more recent unpublished than published estimates of the risk of fever following the receipt of one dose of TIV alone in children aged ≥6 to <36 months, with two to three times more subjects in the unpublished studies, depending on the outcome. We estimated a median averaged weekly risk of any fever after TIV of 26.0% from unpublished trials and 8.2% from published studies, with the median averaged weekly risk of severe fever of 3.2% and 2.0%, respectively. The median averaged weekly risk of

Table 2
Summary of reviewed published papers.

Authors	Influenza season	Study location	Study type	Vaccine manufacturer	Comparison arms	Participant ages (range included in review)	Total participants/ doses[a] (*n*)	Any fever (≥37.5 °C) n (%)	Severe fever (≥39 °C) n (%)	Adverse event follow up period
Gonzalez et al. [32]	1995–1996	Uruguay	Cohort	Aventis Pasteur	N/A	6 months to 35 months	65	4 (6.2)[b]	Not reported	0–30 days
Aguero et al. [26]	2000–2001 2001–2002	Costa Rica	Cohort	Sanofi Pasteur	N/A	6 months to 35 months	195	44 (22.6)	Not reported	0–30 days
Delore et al. [33]	Various between 1991 and 2002	France, Belgium, UK, Australia, Uruguay, Colombia, Costa Rica	Review of 28 RCTs	Sanofi Pasteur	Group 1: Tween-ether split formulation Group 2: TritonX-100 split formulation	6 months to 99 years (6 months to 35 months)	4599 (406)	80 (19.7)	7 (1.7)	0–21 days
Englund et al. [31]	2002–2003 2003–2004	USA	RCT	Aventis Pasteur	Group 1: early[#] Group 2: standard[#] Group 3: non-randomised standard[#] ([#] refers to timing of vaccination relative to influenza season)	6 months to 23 months	247	30 (12.3)	18 (7.2)	0–3 days
Skowronski et al. [15]	2008–2009	Canada	RCT	Sanofi Pasteur	Group 1: 2 × 0.5 mL doses Group 2: 2 × 0.25 mL doses	6 months to 23 months	250	25 (10.0)	5 (2.0)	0–7 days

[a] Where more than one dose was given to participants, only the first dose is reported here.
[b] This result has not been included for the median estimate calculation as it has been reported within Delore et al. [32].

Table 3
Summary of reviewed unpublished trials (clinicaltrials.gov).

NCBI trial number	Influenza season	Study location	Study phase	Vaccine manufacturer	Comparison arms	Participant ages (range included in review)	Total participants/ doses[a] (*n*)	Any fever (≥37.5 °) n (%)	Severe fever (≥39 °) *n* (%)	Adverse event follow up period
NCT00836953 [34]	2003–2004	US	IV	Sanofi Pasteur	None	6 months to 35 months	33	6 (18.2)	2 (6.1)	0–7 days
NCT00858468 [19]	2004–2005	US	I–II	Sanofi Pasteur	Group 1: 6–12 weeks* Group 2: 24–36 weeks* (*at enrolment)	2 months & 6 months (6 months)	393 (192)	50 (26.0)	4 (2.1)	0–7 days
NCT00831675 [44]	2004–2005	US	IV	Sanofi Pasteur	Group 1: aged 6–12 months* Group 2: aged 12–36 months* (*at enrolment)	6 months to 35 months	30	3 (10.0)	0 (0)	0–3 days
NCT00885105 [45]	2005–2006	US	III	Sanofi Pasteur	Group 1: vaccine-primed Group 2: vaccine-naive	6 months to 11 months	242	80 (33.1)	4 (1.7)	0–7 days
NCT00390884 [29]	2005–2006	US	IV	Sanofi Pasteur	Group 1: vaccine-primed Group 2: vaccine-naive	11 months to 14 months	173	27 (15.6)	0 (0)	0–7 days
NCT00258817 [28]	2005–2006	US	IV	Sanofi Pasteur	Group 1: vaccine-primed Group 2: vaccine-naive	6 months to 35 months	30	3 (10.0)	0 (0)	0–3 days
NCT00389857 [30]	2006–2007	US	IV	Sanofi Pasteur	Group 1: vaccine-primed Group 2: vaccine-naive	6 months to 35 months	31	2 (6.5)	0 (0)	0–3 days
NCT00391391 [27]	2006–2007	US	II	Sanofi Pasteur	Group 1: investigational formulation Group 2: licensed formulation	6 months to 8 years (6 months to 35 months)	520 (194)	20 (10.3)	1 (0.5)	0–7 days
NCT00561002 [35]	2007–2008	US	IV	Sanofi Pasteur	Group 1: vaccine-primed Group 2: vaccine-naive	6 months to 35 months	32	6 (18.7)	1 (3.1)	0–3 days
NCT00710866 [16]	2008–2009	Canada	III	Sanofi Pasteur	Group 1: 2 × 0.5 mL doses Group 2: 2 × 0.25 mL doses	6 months to 23 months	250	23 (9.2)	not reported	0–3 days
NCT00825162 [17]	2009	Australia	IV	CSL Limited	Group 1: 1 × 0.25 mL dose Group 2: 2 × 0.25 mL doses	6 months to 18 years (6 months to 35 months)	1992 (710)	201 (28.6)	13 (1.9)	0–7 days
NCT00959049 [36]	2009–2010	US	III	CSL[A] & Sanofi Pasteur[B]	Group 1: vaccine A Group 2: vaccine B	6 months to 17 years (6 months to 3 years)	1474 (229[A] & 228[B])	[A] 85 (37.1) [B] 31 (13.6)	[A] 6 (2.6) [B] 0 (0)	0–7 days
NCT01096056 [46]	2010–2011	Spain	I	GSK	Group 1: vaccine formulation A Group 2: vaccine formulation B	6 months to 35 months	40 ([A]20 & [B]20)	[A] 14 (70.0) [B] 12 (60.0)	[A] 2 (10.0) [B] 1 (5.0)	0–7 days
NCT01196026 [47]	2010–2011	Netherlands Sweden	IV	GSK (Fluarix[A] & Havrix Junior[B])	Group 1: vaccine A Group 2: vaccine B	6 months to 10 years (6 months to 35 months)	162 ([A]53 & [B]53)	[A] 19 (35.8) [B] 14 (26.4)	[A] 2 (3.8) [B] 0 (0)	0–7 days

Where a study compared two different vaccines, [A] and [B] have been used to differentiate between results for each vaccine

[a] Where more than one dose was given to participants, only the first dose is reported here.

any fever was lower in published papers compared to unpublished trials but this may have reflected the longer follow-up periods in the published papers. Since fever due to vaccination is most likely to occur within 24 h of vaccination, the averaged weekly risk for studies with longer follow-up periods will underestimate the post-vaccination risk. If all studies had identical follow-up periods the difference in averaged weekly risk would likely be much smaller.

Our review focussed only on febrile reactions after the first dose of vaccine, where more than one dose was administered, for three reasons. Firstly, not all studies administered more than one dose to all participants. Secondly, across studies where multiple doses were administered, adverse event risks were variable, with one published paper [26] and four clinical trials [27–30] reporting increased risk of fever after a second dose, while the remaining studies reported decreased risk with subsequent doses [15,17,27,31–36]. Finally, children who react severely to an initial dose of any vaccine may be less likely to return for or be offered successive doses [37].

It is important to note that, although there were no placebo comparison groups in the reviewed published studies and unpublished clinical trials, febrile reactions can also be reported in children who receive placebo vaccines. In one excluded study that used cold-adapted live intranasal trivalent influenza vaccine (CAIV-T), the reported averaged weekly risk of fever ≥37.5 °C in children ≥6 to <36 months was comparable between the vaccine group (20.6%) and placebo group (17.7%) [38]. This vaccine formulation was not included in our review, and as it may have a different adverse event profile, these results are not directly comparable with our review results. However this result highlights the difficulties in determining the cause of fever in this young age group, particularly in studies where a placebo group is not used. Indeed the risk of fever following one dose of TIV may be similar to the background risk in many instances.

Severe fever or a sudden rise in body temperature can cause febrile seizures, especially in children under 3 years old, and can occasionally lead to hospital admission and serious outcomes [39]. In this review we found very few studies that reported febrile seizures as an outcome. However febrile seizures were reported in seven published papers that did not meet the review inclusion criteria: three reported febrile seizures only (the risk of fever was not reported), two had no denominator (the number of vaccinated children), one did not measure fever, and one reported febrile reactions in ≥6 month to <5 year old children as a single group [12,14,21,40–43]. Among these studies, the risk of febrile seizures was much higher than found in our review.

Although it is possible that this review could have underestimated the risk of febrile seizures following TIV, it is more likely that other factors lead to an increased risk estimate in the seven excluded studies that reported febrile seizures. Three of the seven papers reported febrile reactions following the CSL 2010 southern hemisphere TIV, which is known to have had a higher risk of febrile reactions than comparator vaccines [12,42,43]. Another three were database studies that may have overestimated the risk of febrile seizures associated with influenza vaccine, as it has been estimated that at least one febrile seizure from any cause occurs in 2–5% of children before the age of five years [42]. Only one of the seven studies, which was excluded from our review as fever-related temperature cut-offs were not defined, reported a febrile seizure following a booster TIV vaccination in a 3 year old child [21].

4.1. Limitations

Influenza vaccines used across the reviewed studies were produced by different pharmaceutical companies, using different manufacturing processes. Due to non-standard design and reporting across the 19 studies, there was considerable variation in the estimates of risk.

Our literature search strategy and inclusion/exclusion criteria are likely to be a substantial source of publication bias. By limiting studies to those that were published in English, we may have excluded studies from manufacturers such as those based in Asian and South American countries, if these studies were published in another language. In addition, the clinical trials search results were heavily dominated by US-based studies, skewing our results towards one particular vaccine manufacturer.

We tried to minimise measurement bias by requiring that fever (temperature) had been quantified. This led to three published studies and one clinical trial being excluded as they did not define fever within a precise temperature range or reports of fever were subjective and unmeasured [20–23], but the risk estimates in the excluded studies were within the range reported for included studies. The two published studies that used adjuvanted TIV also reported risks of any fever following vaccination within the range for included studies [24,25].

In addition, there were differences in the post vaccination follow up methods, cut off temperatures for the definition of fever, temperature measurement methods (oral, rectal, axillary), and participant age ranges, that hindered uniform data extraction. We made no attempt to adjust for site of temperature measurement, and this may have led to an over or underestimation of fever by category. Seasonal changes in vaccine antigen content over the review period (2000–2012), may also have led to variability in reactogenicity.

4.2. Conclusions and recommendations

Variation in the reporting of fever by participant age groups, time since vaccination and the definition or measurement of fever resulted in a wide range of risk estimates. Data on febrile reactions, including febrile seizures, in children following vaccination with TIV and other routine childhood vaccines, should be collected and reported using a standard format. We suggest standardised reporting items should include: vaccine type, vaccine manufacturer, vaccine batch number (for post-marketing studies), vaccine dose, a record of adjuvants and preservatives, recorded fever (temperature), method of temperature measurement (oral, rectal, axillary), and time between vaccine administration and febrile reaction. Special attention should be given to capturing data in the first 24 h after vaccination. Age should be reported in exact years, allowing the assessment of risk by various age groups.

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Sanofi Pasteur. His institute has received honoraria from Merck for talks he has given on rotavirus epidemiology and vaccines. He was principal investigator for a Clinical Trial of influenza vaccine the results of which were included in this paper [17].

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