Vaccines and febrile seizures

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Vaccine administration is the second leading cause of febrile seizures (FS). FS occurrence in children is a serious concern because it leads to public apprehension of vaccinations. This review discusses the clinical implications of FS, its potential link to vaccinations and its impact on official recommendations for vaccinations in children. Vaccines such as the pertussis antigen-containing vaccine, the measles-containing vaccine and the influenza vaccine have been linked to FS. However, FS events are very rare and are not usually associated with downstream complications or severe neurologic diseases. Considering their significant health benefits, vaccinations have not been restricted in the pediatric population. Nevertheless, vaccine-induced FS could be a problem, particularly in genetically predisposed children. Therefore, post-marketing surveillance studies are required to accurately assess the incidence of FS and identify individuals who are particularly susceptible to FS after vaccination.

KEYWORDS: febrile seizures • influenza vaccine • measles-containing vaccines • pertussis vaccines • prevention • vaccines • varicella vaccine

According to the American Academy of Pediatrics, febrile seizures (FS) occur in febrile children (6–60 months old) who do not have intracranial infection, metabolic disturbance or history of afebrile seizures [1]. FS affect 2–5% of children with a threefold higher risk in children between the ages of 6 and 16 months [1]. In addition to age, genetics [2,3], co-morbidities (e.g., premature birth and fetal growth retardation) [4,5] and environmental risk factors (in utero exposure to smoking or antihistamine use) [6,7] may further increase the risk of fever-induced seizures. FS have also been known to occur as a consequence of a sudden increase in body temperature to 39°C or higher. In the majority of cases, FS are defined as simple because they last for less than 15 minutes, are generalized without a focal component, and occur once in a 24-h period [1]. A small fraction of FS is complex because they are prolonged (>15 min), involve focal signs and recur during the same febrile episode [1]. Contrary to complex FS, which may be indicative of a pre-existing neurologic problem, simple FS are benign even if they occur frequently. Children with simple FS exhibit normal neurologic and mental growth, and usually do not have increased risk of developing epilepsy [8]. Only those who have had several FS, are younger than 1 year at the time of their first FS and have a family history of epilepsy can have a negative prognosis with generalized afebrile seizures in 2.5% of the cases by 25 years of age [9].

Infections, particularly those involving the respiratory tract, are the most common cause of FS [10]. Vaccine administration is the second most common medical event associated with FS [1]. In children, fever is the most reported adverse effect following vaccination; however, the available data probably overestimates the impact of vaccines since many studies have included fevers that occurred in days after the vaccination had generated a biological response [11]. For instance, for a complication to be linked to vaccination, an event must occur no later than 72 h from inactivated vaccine administration and between 7 and 14 days from injection with live, attenuated vaccines [12]. Moreover, in almost all of the studies regarding safety and tolerability of vaccines, no comparison was included using a control group of unvaccinated children was included [12]. Consequently, the possibility remains that part of the observed febrile episodes considered to be caused by vaccine administration were due to other unidentified and confounding reasons. This idea was confirmed in a randomized, double-blind, placebo-controlled trial of measles, mumps and rubella (MMR) vaccines showing that 6% of children receiving placebo had developed fevers and that 88% of the fevers ≥38.5°C were unrelated to vaccination [13]. A possible explanation for this is that infections, extremely common in young children [14], may have contributed to higher fever rates in previous studies that did not control for infections occurring in the first days after vaccine administration.
Overall, most reported cases of fevers accompanying vaccine administration are generally well tolerated. Problems tend to arise when high fever is reported, thereby increasing the possibility of FS. Notably, this has been reported for the pertussis antigen– and measles-containing vaccines and, more recently, for influenza vaccines. Despite its low health risks, emergence of FS following vaccine administration could be considered a serious event by parents and some physicians and could result in negative attitudes toward vaccinating children. A questionnaire study found that witnessing an FS was a frightening experience for parents and that parental fear of FS was a major problem with several negative consequences for daily family life [15]. Moreover, physicians themselves have problems in this regard and generally prefer to administer vaccines with a lower risk of FS than products with a supposed increased risk [16]. Here, we discuss the association of FS with vaccine administration and how this relationship has impacted vaccination regimens in children.

**Pertussis antigen-containing vaccines**

For many years the whole cell pertussis (wcP) vaccine had been the only vaccine available for pertussis infection. Immediately after its introduction to the market, it was found that its administration seemed to correlate with local and systemic reactions in a subset of children. These complications included a very severe clinical picture with high fever, FS and epileptic encephalopathy (referred to as Dravet syndrome) [17]. These negative and neurologic events were highly publicized, which led to the reduction of pertussis vaccinations in many countries and, consequently, pertussis epidemics [18]. Later it was shown that Dravet syndrome is not directly associated with wcP vaccination and depends on a genetic defect involving a mutation in the SCN1A sodium channel gene. Fever, due to vaccination, may have been a factor simply triggered by the onset of disease [19]. This conclusion is further supported by evidence that the late onset of Dravet syndrome in children did not differ significantly between vaccinated and unvaccinated FS patients [20]. However, an association between wcP vaccination and an increased risk of developing FS was considered a valid and well-documented phenomenon. Reports concerning the administration of wcP vaccine in combination with diphtheria and tetanus vaccines and the occurrence of FS have been documented [21–23]. A complete evaluation of all studies regarding the use of wcP-containing vaccines showed that the overall risk of FS was relatively uncommon [21]. However, these reports were limited to the period immediately following vaccination and follow-up reports of neurological complications were not documented. A meta-analysis on earlier studies regarding DTwcP vaccines found that the relative risk (RR) of FS was 1.8 (95% CI: 1.2–2.7) [21]. Higher RR of FS up to 3 days after DTwcP injection was later reported by Farrington et al. (RR: 3.0; 95% CI: 1.5–6.2), although this was correlated with only the third dose of the vaccine [22]. Finally, in a study by Barlow et al., it was shown that receiving the DTwcP vaccine was associated with an increased risk of FS only on the day of vaccination (RR: 5.70; 95% CI: 1.98–16.42) without any significant risk of subsequent seizures or neurodevelopmental disorders [23]. The number of FS attributable to the use of this vaccine was estimated to vary from 6 to 9 per 100,000 children. Collectively, these findings explain why health authorities, lacking safer pertussis vaccines continued to recommend wcP-containing vaccines. On the other hand, the severity of pertussis in infants and the efficacy of wcP-containing vaccines largely justified the mild risks associated with vaccine administration [24].

More recently, the less reactogenic acellular pertussis vaccine (aP) has been introduced and has become widely available in most of the industrialized countries. However, the DTwcP vaccine is still in use in many developing countries because it is significantly cheaper [25]. Several studies involving DTaP were performed to test its safety and tolerability, including the occurrence of FS. In the first set of studies there was no significant difference in FS incidence between patients receiving aP vaccines and those who received wcP [26–29]. However, these studies had limits because they were not powered to assess rare adverse events. Moreover, two of the three studies indicated that certain preparations of the aP vaccine may confer increased risk of FS. They found that on the day of vaccination, children receiving diphtheria–tetanus toxoids–aP-inactivated polio–Haemophilus influenzae type b (DTaP-IPV-Hib) [30] or DTaP vaccine [31] had a twofold and 30% higher risk of seizures, respectively, although these estimates did not reach statistical significance. Moreover, the studies did not distinguish between afebrile seizures and FS. Only one study clearly showed a potential negative effect of aP [32]. In this cohort study, 378,834 children were followed up for several years and it was found that incidence of FS was more frequent after vaccine administration than in other periods of time. In particular, it was reported that despite the pertussis component of the vaccine used (DTaP-IPV-Hib vaccine) being made by only one antigen instead of three antigens as in other studies, RR of FS was increased on the day of the first and the second vaccinations even if not on the day of the third vaccine administration. However, it was calculated that the absolute risk was low (<four per 100,000 vaccinations). Moreover, the overall risk of FS was not increased within 0–7 days after vaccinations, as it was the risk of recurrent FS or subsequent epilepsy. In conclusion, aP-containing vaccines have a marginal role, if any, in causing FS. This is in agreement with the very low local and systemic reactogenicity reported for these preparations [33].

**Measles-containing vaccines**

The relationship between the MMR vaccine administration and the development of FS has been extensively studied [22,34,35]. It has been documented that seizures can occur in children 1–2 years of age during the second week following the first vaccination. FS are ascribed to the measles component of the trivalent vaccine. Barlow et al. examined medical records of 137,457 MMR vaccine recipients and reported that its administration was associated with seizures at an RR of 2.83 (95% CI: 1.44–5.55) from 8 to 14 days after vaccination. No elevated risk was found in the first week or 15–30 days following vaccination [23]. The same authors used background rates of seizures derived from different data sources and found that MMR vaccine administration increased the number of FS cases by 25.0 to 34.2 per 100,000 children [23].
The second dose of the MMR vaccine to 4- to 6-year-old children has not been linked to febrile neurologic problems [36]. Follow-up cohort studies have shown that children experiencing their first FS after MMR vaccination were equally prone to recurrent seizures than unvaccinated children who suffered from FS [23,34]. Moreover, none of the patients experienced nonfebrile seizures or were diagnosed with epilepsy. In addition, risk of FS was greater in those who had previously experienced episodes of FS and in those with a family history of seizures, regardless of vaccination [37]. On the basis of these findings, it was concluded that the potential risk of developing FS after the first MMR vaccination was not sufficient to dismiss the use of MMR vaccine. Therefore, this vaccine has been widely recommended to children. However, as a precaution, American health authorities have recommended that parents of children receiving MMR vaccine should remain vigilant and informed of appropriate actions if fever ensues [38].

With the approval of the tetravalent measles, mumps, rubella and varicella (MMRV) vaccine in the USA (2005), new problems regarding FS and vaccinations occurred. The pre-licensed studies of the vaccine, ProQuad®, showed an increased occurrence of fever at 5–12 days and 0–42 days after the first dose compared to the MMR vaccine and varicella (V) vaccine [39]. Moreover, post-licensure observational studies not only confirmed the increased occurrence of fever, but also showed that FS were significantly more common. Jacobsen et al. reported that among 31,298 children between the ages of 12–60 months who received either MMRV or MMR+V vaccination for the first time, 22 (0.70/1,000) and ten (0.32/1,000) cases (RR: 2.20; 95% CI: 1.04–4.65), respectively, suffered from febrile seizures 5–12 days following vaccination [40]. Klein et al. with a cohort study assessed seizures and fever visits among children aged 12–23 months after MMRV and separate MMR+V vaccines and found that among the 83,107 MMRV vaccine recipients seizure risk during days 7–10 after vaccination was higher than among 376,354 children given MMR+V (RR: 1.98 [95% CI: 1.43–2.73]) with an excess risk of 0.43 per 1000 doses (95% CI: 2.6–5.6) [40].

Despite these previous findings, American health authorities initially (2008) concluded that the use of vaccines containing multiple antigens could maximize vaccination coverage and showed no preference between MMRV or MMR+V vaccines [42]. However, their stance changed when a more complete analysis of epidemiological data was performed confirming that the first dose of MMRV vaccine was more reactogenic than that of MMR+V vaccines, whereas a second dose of the tetravalent vaccine was not associated to increased health risks in children [43]. Starting from these data, the Advisory Committee on Immunization Practice of the USA stated that for the first vaccination MMRV vaccine or MMR+V vaccines might be administered to 1–2 year olds, and that, after discussion between the provider and parents, families without a strong preference for MMRV vaccine should receive MMR+V vaccines [44]. On the contrary, MMRV could be used for the second dose. Similar conclusions were reached in Germany with a different formulation of MMRV (Priorix-Tetra®) [101]. This stemmed from meta-analyses reports on clinical studies of Priorix-Tetra®, which showed that combined vaccine was more reactogenic than MMR+V vaccines and fever was more frequently associated with seizures. Although the incidence of FS in this case was not statistically significant, this result was considered sufficient to warn about the use of MMRV. The Standing Committee on Vaccination at the Robert Koch Institute in Germany, following consultations with the EMA decided to revise the technical information on Priorix-Tetra® and include a sentence declaring that the MMR and V vaccines have to be preferred for the first tetravalent vaccination and MMRV vaccine could be used for the second dose [101].

Vaccination against MMRV is widely available for children, and while health authorities show a preference for separate MMR and V vaccinations, the option to use MMRV vaccine is still available for parents and physicians. This could potentially limit vaccine coverage in children for MMR and/or V vaccines. A recent survey, carried out in a period of time during which MMRV vaccine was on the market, assessing knowledge, beliefs, attitudes, and intended practices regarding the MMRV vaccine and its relationship to FS found that, after reading an informational statement, only 20% of pediatricians and 7% of family physicians would recommend the MMRV vaccine to a healthy 12–15-month-old child [16]. These findings indicate that, in most cases, separate injections of MMR and V vaccines were chosen despite requiring more deferrals or injections.

**Influenza vaccines**

Since its approval for use in children, the trivalent inactivated influenza vaccine (TIV) has been considered safe and well tolerated without any known risk of acute neurological events. In the years after its release, no increases in the occurrence of seizures were reported the week following vaccination [45–48]. Moreover, no increase in the incidence of influenza vaccine-related FS was reported in the 2009–2010 influenza season, despite the increased number of vaccinations in young children with a monovalent vaccine designed to prevent pandemic influenza [49,50]. Despite these reassuring outcomes, a safety alert for FS associated with influenza vaccination was issued in April 2010. In Australia, it was reported that an increase in the number of children less than 5 years of age (median age 1.5 years) had suffered from fever and FS after having received the 2010 Southern Hemisphere TIV formulation (Fluvax® and Fluvax® junior) [51]. In the majority of cases, seizures occurred within 12 h of vaccination at a rate of 3.3 cases per 1000 TIV doses. This rapid onset of fever and seizures, together with immediate recovery, supported the hypothesis that seizures were induced by high fevers in predisposed children as opposed to being provoked by vaccine-related neurological or metabolic toxicities [52]. This resulted in a temporary suspension of all influenza vaccinations in Australian children [53]. Furthermore, it was recommended that Fluvax and Fluvax junior vaccines not be used in children aged 6 months to 8 years in the USA [54]. An observational study carried out in New Zealand investigated four TIVs manufactured by different companies for children between the ages of 6 months and 5 years. It was confirmed that Fluvax had higher reactogenicity and despite having similar antigenic compositions, the other TIVs had significantly...
lower risk of febrile reactions and seizures [55]. Additionally, it was reported that FS occurred only after Fluvax administration in addition to higher frequency of fevers. However, Influvax® had higher rates of febrile reactions (OR: 0.54; 95% CI: 0.36–0.81) than Vaxigrip® (OR: 0.21; 95% CI: 0.16–0.27) and Fluarix® (OR: 0.10; 95% CI: 0.05–0.20).

Because β-propiolactone was used to make Fluvax instead of formaldehyde as in the other influenza vaccines, it was believed that this manufacturing process led to incomplete disruption of virion particles and enhanced pyrogenicity of Fluvax [56,57]. On the other hand, with an in vitro model, Blyth et al. were able to demonstrate that Fluvax injections, in comparison to other TIVs, led to higher induction of IFN-α, IL-6 and IL-1β [52,58]. This response resembled the effect of treatment with inactivated influenza A virus in vitro (59) or infection with natural influenza (59,60). However, what happened in the USA during the 2010–2011 influenza season supports the hypothesis that the problem of vaccination-associated FS could not be ascribed only to Fluvax [61,62].

During that influenza season, the Centers for Disease Control and Prevention and the US FDA conducted enhanced vaccine safety monitoring for possible febrile seizures in all TIV products in the USA using the vaccine adverse event reporting system (VAERS) [61]. Empirical Bayesian data mining techniques were used to assess disproportionate reporting after TIV and febrile seizure reports in children aged <5 years were reported. On 23 November 2010 the combination of the coding term ‘febrile convolution’ and the Fluzone® TIV product exceeded a predetermined threshold in the VAERS database. By 10 December, 43 reports of febrile seizure following TIV in children aged 6–23 months were confirmed. Moreover, a study with a cohort of 206,174 children aged 6–59 months demonstrated that Fluzone vaccinations significantly increased the risk of FS [62]. The highest risk was demonstrated in children who had received TIV together with 13-valent pneumococcal conjugate vaccine (PCV13), although single influenza and pneumococcal vaccinations were also associated with increased risk of FS. The incidence rate ratio (IRR) for TIV adjusted for concomitant PCV13 was 2.4 (95% CI: 1.2–4.7), PCV13 adjusted for concomitant TIV was 2.5 (95% CI: 1.3–4.7) and concomitant TIV and PCV13 was 5.9 (95% CI: 3.1–11.3), suggesting that the concomitant administration of both vaccines could be significantly more dangerous. Moreover, RR varied as a function of age with the highest estimates occurring at 16 and the lowest at 59 months (45 and four per 100,000 doses for TIV with concomitant PCV13, respectively) with a trend quite similar to that demonstrated for febrile seizures associated with infectious diseases [62].

A number of hypotheses have been advanced to explain the recent emergence of vaccine-induced FS after influenza vaccine administration. It was supposed that the risk of FS in children had not been initially discovered due to its low incidence in children [62]. Moreover, it was thought that differences in incidence of TIV-related FS between older and more recent epidemiological studies could simply be due to the changes in the definition of risk interval [62]. In older studies, occurrence of FS was monitored for up to 1 week, whereas in recent studies only events in the first 24 h are recorded. A re-calculation of older data using the first day risk interval did not reveal increased risk of FS, suggesting that TIV injection was not an underlying cause. Another explanation, which was likely wrong, was that the presence of pandemic virus in the TIV used for the 2010–2011 season could have modified the reactogenicity of the vaccine although the methods used for the preparation of the vaccine were exactly the same as for previous influenza vaccines [62], which were not associated with increased risk of FS [63–65]. Finally, it was suggested that the host-specific factors may play a role in the development of seizures. In New Zealand, it was found that patients of European decent were more likely to develop a fever within 24 h of vaccination [55]. Ethnic origin has been implicated in variable immunogenicity to hepatitis B [65] and reactogenicity to the anthrax vaccine [66]. However, genetic characteristics can underlie the immune response and reactogenicity to TIV, but they do not explain the emergence of influenza vaccine–related seizures in a population that had previously been exposed to the same vaccine.

Despite not being solved, the problem of the increased risk of febrile seizures after TIV administration in younger children has led to several practical consequences. In the USA, vaccination against influenza with approved TIV was not discouraged, although the risk of FS was obvious. However, particular attention was paid not only to TIV but also to the simultaneous administration of TIV and PCV13, since co-injection conferred higher risk of FS [67]. However, since both vaccines were considered to be essential for children by the American health authorities, co-injection was still recommended. ACIP highlighted the need for education of providers and parents on the risks and benefits of vaccines [67]. Moreover, the labels for Fluzone and for PCV13 warned users of the associated risk of FS [67]. In Europe, when it was shown that virosomal-adjuvanted influenza vaccine, approved for use in younger children, could cause a fever of ≥38°C in approximately 15% of recipients and >39°C in approximately 5% of the cases, although not accompanied by FS [68], warnings in the package insert were included [102].

Because the origin of TIV-related FS and whether its effects are brand-specific is not known, further studies on the immediate effects of TIV administration are mandatory. These have to include the live attenuated influenza vaccine, despite the fact that this vaccine has a very low risk of fever and adverse neurologic events [69].

Expert commentary
For some vaccines, such as pertussis antigen-containing vaccines, measles-containing vaccines and influenza vaccines, there exists an association between vaccination and increased risk of FS. However, the risk of severe consequences is very low since associated FS are not usually followed by any further neurologic disorders. Considering the efficacy of these vaccines in reducing the risk of disease with significant clinical, social and economic impact, the benefits of vaccination outweigh its risks. This explains why health authorities have not restricted the use of these vaccines in the pediatric population although they have clearly indicated that when different preparations of the same vaccine are
available, it is recommendable to administer the preparation or to use the schemes of administration with the lowest documented risk of FS. Acellular pertussis vaccine has to be preferred to the whole cell pertussis vaccine, whereas at least for the first administration, MMR and V vaccine have to be administered separately. Despite less common than the episodes associated with measles containing vaccines or wcP vaccines, further studies are needed to understand the mechanism of influenza vaccine–induced FS and whether co-administration with other vaccines increases the risk of FS. The yearly use of influenza vaccines universally recommended in children today justifies particular attention to this kind of prevention.

**Five-year view**

Although vaccine-induced FS is a rare phenomenon that does not lead to deleterious outcomes, it could impact patient and physician attitude toward the safety of vaccination. For this reason, the incidence and timing of vaccine-induced fever and FS has to be precisely quantified. Moreover, genetic factors associated with risk need to be identified. In this way, children most susceptible to vaccine-induced FS can be treated with antipyretics, which reduce fever, prior to vaccination [70,71]. Indeed, ibuprofen and acetaminophen can reduce the possibility of fever following DTaP immunization in children with a history of febrile seizures [72]. Vaccine-induced FS is a rare phenomenon that occurs mainly in genetically predisposed children. Moreover, as reported for the simultaneous administration of influenza and pneumococcal vaccines, the associated risks could be enhanced when vaccines are administered in combination. Moreover, even if recently performed studies on vaccine safety and tolerability have included tens of thousands of participants, adverse but rare events such as FS can be missed. Finally, because most immunizations are administered in the first months of life, an accurate estimation of FS-prone children is not possible since detailed clinical history is frequently missed in infants. Only an extensive and thorough post-marketing study can accurately address these problems. This is particularly important for those vaccines that have caused fever in pre-marketing studies and that are frequently administered with other vaccines. The recent multicompontent, recombinant meningococcal serogroup B (4CMenB) vaccine is an example. A recent study has showed that increased reactogenicity is associated with this vaccine when it is administered concomitantly with routine vaccines (DTaP-IPV-HBV-Hib and PCV7) [73]. Seventy seven percent (1912 out of 2478) of infants had a fever of 38.5°C or higher after 4CMenB injection, compared to only 45% (295 out of 659) after routine vaccinations alone and 47% (228 out of 490) with Neisseria meningitidis group C co-vaccination [73]. Although only two FS events were associated with 4CMenB injections, this problem deserves particular attention and requires further studies.

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**Key issues**

- Notwithstanding the obvious health benefits of vaccination, occurrence of febrile seizures (FS) following injections could be considered by parents and some physicians as a relevant clinical problem.
- FS events could act as a deterrent for public support of vaccinations.
- Administration of some vaccines such as pertussis antigen-containing vaccines, measles-containing vaccines and influenza vaccines confer a low risk of FS.
- For those vaccines for which different preparations exist (e.g., in the case of pertussis and measles-containing vaccines), it is reasonable to use those preparations (acellular instead of whole cell pertussis vaccine) or those schemes of administration (measles, mumps and rubella + varicella instead of measles, mumps, rubella and varicella) that carry a significantly lower risk of FS.
- In the case of influenza vaccines, further studies are needed to evaluate various brands and whether co-administrations with other vaccines significantly increase the risk of FS.
- Considering that FS events are rare, only post-marketing surveillance can accurately assess the risk of vaccination.

**References**

Papers of special note have been highlighted as:

- **of considerable interest**
- **of considerable interest**


- A well-conducted study showing that diphtheria–tetanus toxoids–aP–inactivated polio–Haemophilus influenzae type b vaccination was associated with an increased risk of febrile seizures but not of epilepsy on the day of the first two vaccinations given at 3 and 5 months, although the absolute risk was small.


• This study provides reassurance that MMRV and MMR+V were not associated with increased risk of febrile seizures among 4- to 6-year-olds.


• A well-performed surveillance showing that no major safety problems following H1N1 or seasonal influenza vaccines were detected in the 2009–2010 season in weekly sequential analyses.


• The effort to vaccinate the USA population against the 2009 H1N1 influenza virus improved monitoring of 2009 H1N1 vaccine safety, holding promise for enhancing future national monitoring of vaccine safety, and helping improve public confidence in vaccines.


• Numerous febrile adverse events (including febrile seizures) were observed following Fluvax® or Fluvax® jr junior in 2010. Clear differences in cytokine production were observed when peripheral blood mononuclear cells were stimulated with Fluvax compared with alternate TIV preparations. Increased awareness of these potential adverse events is required to ensure earlier detection and prevention in the future.


55 Petousis-Harris H, Poole T, Turner N, Reynolds G. Febrile events including convulsions following the administration of four brands of 2010 and 2011 inactivated seasonal influenza vaccine in NZ infants and children: the importance of routine active safety surveillance. Vaccine 30(33), 4945–4952 (2012).

• A study showing that influenza vaccines have different rates of reactogenicity in children, which varies between ethnic groups. High rates of febrile convulsions and reactions in children receiving Fluvax and to a lesser extent the higher fever rates in those receiving Influvax® compared with the other two brands of influenza vaccines in this study suggest that reactogenicity profiles need to be considered prior to national policy advice each season.


57 Maraskovsky E, Rockman S, Dyson A et al. Scientific investigations into febrile reactions observed in the paediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine. Vaccine 30(51), 7400–7406 (2012).


Demonstrates that incidence rate ratio and risk difference estimates were lower for children receiving TIV without concomitant PCV13 or PCV13 without concomitant TIV. Because of the importance of preventing influenza and pneumococcal infections and associated complications, the authors concluded that their findings should be placed in a benefit-risk framework to ensure that population health benefits are maximized.

A comprehensive evaluation showing that 4CMenB is immunogenic in infants and children aged 12 months with no clinically relevant interference with routine vaccines, but increases reactogenicity when administered concomitantly with routine vaccines.

**Websites**
