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**TITLE**

# Active surveillance of 2017 seasonal influenza vaccine safety in individuals aged 6 months and older in Australia

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**ABSTRACT**

**Objective:** To actively solicit adverse events experienced in the days following immunisation with quadrivalent inactivated influenza vaccine using Australia's near real-time, participant-based vaccine safety surveillance system, AusVaxSafety.

**Design and setting:** Observational cohort study conducted in 194 sentinel surveillance immunisation sites (primary care, hospital, and community-based clinics) across Australia.

**Participants:** Individuals aged ≥6 months who received a routine seasonal influenza vaccine at a participating site (N=102,911) and responded to a survey (via Short Message Service or email) sent 3 days post-vaccination about adverse events experienced (N =73,892; 71.8%).

**Main Outcome Measure:** Near real-time and cumulative participant-reported rates of any adverse event, fever or medical attendance experienced within 3 days post-vaccination overall, by brand, age, pregnancy status, and concomitant vaccine receipt.

**Results:** Participant median age was 57 years (range: 6 months–102 years); 58.1% (N=42,869) were female and 2.7% (N=2,018) were pregnant. Near real-time fast initial response cumulative summation and Bayesian analyses of weekly event rates did not demonstrate a safety signal. Children aged 6 months–4 years had higher event rates (522/6,180; 8.4%) compared to older ages; participants aged ≥65 years reported fewer events (1,695/28,154; 6.0%). There were no clinically significant differences in safety between brands, by age group or overall. Cumulative data analysis demonstrated that concomitant vaccination was associated with increased rates of fever (2.1% versus 0.8%) and medical attendance (0.8% versus 0.4%), although all rates were low and did not exceed expected levels.

**Conclusions:** Novel, post-marketing AusVaxSafety surveillance demonstrated comparable and expected safety outcomes for the 2017 quadrivalent inactivated influenza vaccines brands used in

Australia. These near real-time, participant-reported data are expected to encourage confidence in vaccine safety and promote uptake.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- A large number of vaccinated individuals of all ages across Australia participated, leading to a greater ability to detect serious adverse events.
- Comprehensive data enabled analysis of adverse events with respect to age, pregnancy, vaccine brand, and concomitant vaccination with a wide variety of vaccines.
- Safety signal detection was conducted in near real time using multiple statistical methods, with results reported to the public each week.
- Individuals participating in active surveillance may be less inclined to report common and expected reactions, limiting the ability to compare reported adverse event rates with those from clinical trials.
- Some outcomes of vaccine safety, such as participant-reported fever, are subjective and have not been verified.

## FUNDING

AusVaxSafety surveillance was funded under a contract with the Australian Government Department of Health.

## COMPETING INTERESTS

All authors are either located at organisations that hold the AusVaxSafety contract from the Australian Government Department of Health or are subcontract holders. None of the authors has any other conflicts of interest to declare.

## INTRODUCTION

Influenza vaccines are given to hundreds of millions of people within short, fixed periods of time worldwide each year.[1] This widespread use, coupled with the high degree of influenza vaccine variability, including multiple vaccine types (live, inactivated, subunit, or adjuvanted), manufacturing processes (in eggs, cell lines, or with recombinant techniques), and strain compositions (trivalent or quadrivalent, with the potential for vaccine viruses to change twice yearly across the Southern and Northern Hemisphere seasons), underscores the need for timely post-marketing vaccine safety surveillance. The European Medicines Agency (EMA) now requires manufacturers to address the paucity of clinical trial safety data available for vaccine changes by conducting enhanced post-marketing safety surveillance for seasonal influenza vaccines.[2]

AusVaxSafety, an automated, active vaccine safety surveillance system, reports near real-time, brand-specific data independently of manufacturers using participant-reported outcomes. AusVaxSafety was established to improve vaccine safety monitoring following recommendations of an independent inquiry into the unprecedented increase in febrile seizures observed in young Australian children in 2010, ultimately determined to be associated with one influenza vaccine brand (Fluvax/Afluria; bioCSL).[3] This incident, which led to temporary nationwide suspension of paediatric influenza immunisation, resulted in a loss of confidence in influenza vaccines among consumers and immunisation providers and decreased influenza vaccine uptake.[4 5]

From 2014–2016 AusVaxSafety conducted influenza vaccine safety surveillance in 8,184 children aged 6 months–4 years.[6 7] A retrospective analysis comparing safety profiles of trivalent inactivated influenza vaccine (TIIV) and quadrivalent inactivated influenza vaccine (QIIV) brands in 2015 and 2016 demonstrated that concomitant vaccine administration in young children was associated with increased fever and medical attendance (MA) rates post-vaccination, although rates were low and within expected ranges.[7] Importantly, detailed follow-up data on the small number of children who

sought medical attention showed no serious or unexpected vaccine-associated adverse events following immunisation (AEFI).

In 2017, AusVaxSafety surveillance expanded to include influenza vaccine recipients of all ages. Here we provide an overview of AusVaxSafety's weekly surveillance and a detailed analysis of cumulative (end of vaccine season) safety data by QIIV brand, age, pregnancy status and concomitant vaccine receipt.

## METHODS

### AusVaxSafety active vaccine safety surveillance

Surveillance included individuals aged ≥6 months who received a 2017 seasonal influenza vaccine between 1 April–31 August 2017 at one of 194 participating immunisation providers across Australia, including general practices, hospitals, community-based clinics and Aboriginal Medical Services. Most individuals were enrolled using the opt-out, computer-based monitoring platform SmartVax, which integrates with immunisation provider management software to issue automated surveys to vaccine recipients or their caregivers via SMS, as previously described.[8] A minority of AusVaxSafety sites (n=30) utilised one of two alternative computer-based monitoring platforms—Vaxtracker[9] (recipients aged 6 months–4 years only) or STARSS (Stimulated Telephone-Assisted Rapid Safety Surveillance)[10]—to solicit influenza vaccine adverse events following opt-in enrolment.

Vaccinated individuals/caregivers received an SMS from their medical provider 3 days post-vaccination inquiring about AEFI ("We would like to know if there were any reactions to the vax. Please reply with JUST a Y or N."). Those who responded "Y" or "N" were classified as participants, and those who responded "Y" were then asked whether or not the event was medically attended. "Yes" responders were asked to detail the adverse event(s) and/or medical attention in a short online survey, which listed a range of symptoms and asked participants to tick all symptoms experienced. As children aged 6 months–8 years and immunocompromised individuals of any age

are recommended to receive two vaccine doses at least four weeks apart when first immunised, some may have been represented by more than one record.

Primary outcomes surveyed were reports of any event (yes or no), fever (solicited in the online survey), and MA (yes or no). Secondary outcomes (solicited in the online survey) were injection site (IS) pain, swelling and/or redness; tiredness/fatigue; headache; sleep pattern change; irritability; rash; vomiting; diarrhoea; rigors; non-responsiveness/loss-of-consciousness; and convulsions/seizures. Unsolicited symptoms were detailed by participants in free text.

Detailed clinical data from MAs were sought using additional information from participants' immunisation providers and/or by a public health authority, who attempted to contact participants/caregivers.

**Ethics**

The AusVaxSafety surveillance system and its data monitoring platforms operate nationally under human research ethical approval obtained from the Sydney Children's Hospital Network (HREC/16/SCHN/19) and the Royal Australian College of General Practitioners National Research and Evaluation Ethics Committee (NREEC15-007).

**Patient involvement**

The AusVaxSafety surveillance system does not specifically recruit patients but does rely on community participation. The AusVaxSafety surveillance system Advisory Committee includes a consumer/patient representative. The data monitoring platforms were piloted and developed with feedback from users. Surveillance results are uploaded to the AusVaxSafety website (www.ausvaxsafety.org.au) weekly and available to the public.

**Near real-time reporting and analysis**

De-identified records (including demographic, immunisation visit, and SMS/survey response data) were uploaded to the computer-based monitoring systems and exported weekly to the AusVaxSafety coordinating centre for aggregation and analysis. MA reports triggered clinical follow-up by designated public health authorities each weekday. Weekly analysis of cumulative data (received up to 5 days prior) for age- and pregnancy-specific AEFI rates and participant demographic characteristics were reported in detail to the Australian Department of Health and summary results published online each Friday (www.ausvaxsafety.org.au) from week three of surveillance for the duration of the surveillance period.

**Weekly signal detection**

Participant-reported rates of fever (for those aged 6 months–4 years) and MA (for all participants, grouped by age: 6 months–4 years, 5–64 years, and ≥65 years; and pregnant participants) as a surrogate for serious adverse events (SAE)[7] were considered the most objective outcome measures of vaccine safety and were monitored weekly using signal detection methods.

Fast initial response cumulative summation (FIR CUSUM) control charts monitored log-likelihood ratios of each event rate being at a maximum acceptable level versus expected level.[11] Expected and maximum acceptable rates were set based on syntheses of clinical trial data and previous surveillance results.[6 7 9 12-14] The expected MA rate was set at 1%, and the expected fever rate at 3%. Maximum acceptable rates were set at 3% and 10% for MA and fever, respectively. A safety signal is generated if the log-likelihood ratio (a measure of the degree to which the data are more consistent with an event rate equal to the maximum acceptable rate versus the expected rate) rises above a predetermined threshold. The threshold log-likelihood ratio was selected such that across 10,000 simulated vaccination seasons there would be ≥80% probability of signal generation within 3 weeks

of commencement if the event rate is at the maximum acceptable level, and ≤2% probability of (false) signal generation over the entire season when the event rate is at the expected level.

Bayesian analysis was also performed weekly for robust, optimal estimation of the 95% credibility interval (CI) for true cumulative event rates. Beta distributions with means derived from 2016 surveillance data and literature review (MA: 1% for participants aged 6 months–4 years; 0.3% for participants aged 5–64 years and ≥65 years; 1% for pregnant participants; and fever: 3% for participants aged 6 months–4 years)[7] were used as priors at the start of the 2017 season. Priors were updated with each week's observed data and credibility intervals from the posterior beta distribution were reported weekly.

**End-of-surveillance cumulative analysis**

Cumulative data were reported by epidemiological week and demographic information including age (6 months–4 years, 5–14 years, 15–39 years, 40–64 years, and ≥65 years), sex, pregnancy status (available for SmartVax participants only), Aboriginal and/or Torres Strait Islander (hereafter referred to as Indigenous) status, and concomitant vaccine administration (defined as any additional vaccine(s) received at the same visit as influenza vaccine).

For any adverse event, fever, and MA, rates were calculated for each age group and pairwise proportion tests with Holm adjustment for multiple comparisons were performed to compare AEFI rates between pairs of age groups using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). AEFI rates in pregnant women were compared to those of non-pregnant female SmartVax participants of the same age range (15–49 years) using Pearson's chi-square test in Stata version 14.2 (Statacorp LLC, College Station, TX, USA). Rates of primary and secondary outcomes were calculated by brand, and secondary outcomes were calculated for each age group and pregnant women.

Primary outcome AEFI rates were also calculated for age groups and pregnant women by vaccine brand and concomitant vaccine receipt (yes or no). The relative risk of each adverse event was compared for those receiving influenza vaccine plus any concomitant vaccine(s) versus influenza vaccine alone, and for those receiving FluQuadri verus Fluarix Tetra, using a generalised linear model with a log link and binomial distribution in Stata version 14.2.

## RESULTS

### Weekly signal detection throughout 2017

No safety signals were detected by the FIR CUSUM method (eFigure 1). Weekly and cumulative Bayesian rates of fever and MA remained well below their respective maximum acceptable rates over the surveillance period: the cumulative (end-of-season) fever rate in children aged 6 months–4 years was 2.3% (95% posterior CI: 2.0, 2.7), while cumulative MA rates were 1.0% (95% CI: 0.73, 1.21) in children aged 6 months–4 years, 0.5% (95% CI: 0.41, 0.55) in participants aged 5–64 years, 0.3% (95% CI: 0.22, 0.34) in participants aged ≥65 years and 0.5% (95% CI: 0.26, 0.87) in pregnant women.

### End-of-surveillance analysis

Over the surveillance period, 73,892 of 102,911 enrollees (71.8%) responded to the post-vaccination SMS. Participants received one of four available QIIVs: Fluarix Tetra (GlaxoSmithKline; 45.3%), FluQuadri (Sanofi-Aventis; 42.3%), FluQuadri Junior (Sanofi-Aventis; 5.6%), or Afluria Quad (Seqirus; 6.8%); less than 1.0% received a vaccine whose brand could not be determined. Half of all vaccines were administered within 5 weeks of starting surveillance, with older participants (≥65 years) receiving vaccines earlier compared to young children (6 months–4 years old) and pregnant women (Figure 1).

Among all participants, 58.1% were female and the median age was 57 years (range: 6 months–102 years). Two percent (1,156/58,145 with data available) were Indigenous, which is representative of

the Australian national Aboriginal and/or Torres Strait Islander population (2.8%) (Table 1). Among female participants aged 15–49 years for whom pregnancy status was available (98.6%), 15.2% (2,018/13,242) were pregnant. Individuals aged ≥65 years represented the largest proportion of participants (38.1%; 33.6% aged 65–79 years and 4.5% aged ≥80 years). Approximately 14% of participants (10,428/73,892) received a concomitant vaccine, of which 86.6% received only one. The most commonly received concomitant vaccines are listed in Table 1.

Compared to other age groups, children aged 6 months–4 years were reported as having significantly higher rates of any adverse event, while participants aged ≥65 years reported events less often (Table 2). Pregnant women reported significantly lower rates of any adverse event compared to non-pregnant women of the same age range (15–49 years; p=.019, data not shown). Rates of more subjective secondary outcomes surveyed showed similar trends across age groups and by pregnancy status (eTable 1).

Participants who received concomitant vaccine(s) had an elevated risk of reporting any adverse event and fever compared to participants who received influenza vaccine alone (Table 3). This pattern was seen for all age groups, with the exception of fever in participants aged 15–39 years and pregnant women. Participants aged ≥40 years who received concomitant vaccine(s) reported MA at a significantly higher rate than those who received only an influenza vaccine.

Brand-specific AEFI rates were similar, particularly for FluQuadri and Fluarix Tetra, the brands administered to the majority of participants (Table 4, eTable 2).

**DISCUSSION**

AusVaxSafety surveillance utilised almost 74,000 actively solicited participant-reported outcomes to demonstrate that the four brands of QIIV used in Australia in 2017 were safe and had low and comparable adverse event rates within expected ranges for all age groups and pregnant women.[9 12-

[14] This novel system provided reassuring, locally-derived feedback on vaccine safety in near real time to the public and immunisation providers as influenza vaccination was rolled out across Australia.[15]

Consistent with data published from vaccine clinical trials, the most common participant-reported event following influenza immunisation was IS pain (1.7% overall). IS pain was also commonly reported in clinical trials, but at higher rates than those demonstrated in this post-marketing surveillance. Clinical trials in children reported IS pain in approximately two-thirds of those aged 3–17 years[16] with similarly high rates (up to 72.4%) in adults aged 18–60 years.[17,18] This difference is likely due to more active solicitation of AEFI in clinical trials via daily diary cards, resulting in more complete reporting. Also, as AusVaxSafety participants may be informed of expected common vaccine reactions by their clinicians, these symptoms may be less likely to be reported. By comparison, data from both this post-marketing surveillance and clinical trials confirmed low rates of SAEs (0.4% for AusVaxSafety compared with 0.0–2.3% for the clinical trials), despite differences in SAE definitions. Equally reassuring, both IS pain rates and SAEs among pregnant women in our surveillance were low and consistent with rates reported among participants of all ages.

Adverse event rates were similar for Fluarix Tetra (GlaxoSmithKline) and FluQuadri (Sanofi-Aventis), the two most utilised QIIVs in Australia in 2017. Though small and variable differences in AEFI rates between brands were reported, this is likely attributable to factors such as age and uncontrolled confounding, and is not of clinical significance. Ongoing brand-specific surveillance will provide valuable safety data in future years, especially as two new, more immunogenic vaccine types—the high dose TIIV (Fluzone High Dose, Sanofi-Aventis) and the MF-59 adjuvanted influenza vaccine (Fluad, Seqirus)—are being included on the Australian National Immunisation Program (NIP) for adults aged ≥65 years from 2018.[19]

We previously observed that AusVaxSafety participants aged 6 months–4 years who received influenza vaccine and another vaccine concomitantly (in particular diphtheria-tetanus-acellular pertussis-inactivated poliovirus (DTPa-IPV) or meningococcal B vaccines) had significantly increased

AEFI rates (especially fever) compared to those receiving influenza vaccine alone.[6 7] The present analysis showed that AEFI were more common with concomitant vaccination among participants of all ages, including increased fever rates in both children and older adults and an increased risk of MA among those aged ≥40 years. The most commonly received concomitant vaccines were 23-valent pneumococcal vaccine, reduced antigen pertussis-containing vaccine (dTpa) and live attenuated zoster vaccine, which are reactogenic when administered individually.[20-26] It has been shown that concomitant receipt of influenza and 13-valent pneumococcal vaccines results in increased local and systemic events, including fever among children[27-29], while such differences in AEFI rates were not observed with concomitant receipt of influenza and pertussis or zoster vaccines.[30-33] Importantly, the increased risks of AEFI occurring with concomitant vaccination reported by AusVaxSafety—including those requiring MA—were low and likely not of clinical importance. This information may help providers to reassure patients who are receiving more than one vaccine at the same time that although they may have a slightly higher rate of side effects, the absolute rate is low overall. As more vaccines become available, assessment of adverse events associated with concomitant vaccination using surveillance like AusVaxSafety has the potential to contribute valuable detail to post-marketing pharmacovigilance.

To the best of our knowledge, AusVaxSafety is a unique post-marketing vaccine safety surveillance system in its high level of automation, patient and provider engagement and ability to provide data on vaccine brand-specific AEFI rates in near real time. However, since the EMA recommendation to provide annual brand-specific safety data, there has been an increase in pilot and feasibility studies of influenza vaccine safety surveillance methods and systems. [34-38] Several are enhanced passive surveillance systems relying on patients returning adverse events reports via cards or telephone.[34 36] Such systems are limited by potential under-reporting of events and are likely slower and more resource-intensive as staff must enter AEFI details or conduct interviews. The Canadian National Vaccine Safety (CANVAS) Network has conducted a small pilot of a mobile phone app for reporting adverse events.[38] Eighty-six percent of those replying to questions about the usability of an app for

reporting AEFI said they would prefer an app to visiting a website. Nevertheless, investigators acknowledged that the app was limited by download requirements and low survey completion rates. The Centers for Disease Control and Prevention's Vaccine Safety Datalink, which utilises large linked databases from health care organisations, conducts Rapid Cycle Analysis to report AEFI rates in near real time but may be limited by delays between AEFI occurrence and electronic reporting to administrative datasets.[39 40] AusVaxSafety surveys vaccine recipients directly and can thus quickly estimate the number of vaccine recipients who are (or are not) experiencing an AEFI without relying on complex analytical methods.

There are several limitations of AusVaxSafety surveillance and the analysis in this report. Firstly, self- or parent/carer-reports of outcomes gathered through participant-based feedback may be less accurate for common and expected reactions than those solicited from clinical trial participants. Secondly, though we have attempted to adjust for potential biases by reporting the more objective outcomes of MA and fever, it should be noted that participant-reported fever is subjective and has not been confirmed. Also, should a very serious event, such as death, occur post-immunisation, an individual may not be capable of participating in AusVaxSafety surveillance; the system may therefore not identify the most serious adverse events. Thirdly, not all adverse events are vaccine-attributable, and AEFI rates may be affected by other illnesses with similar outcomes, e.g. fever from intercurrent viral illness. Finally, in this report, data did not allow for comparisons of the reactogenicity of each non-influenza vaccine administered alone, and therefore conclusions made about increased adverse event rates associated with concomitant vaccination must be tempered. As AusVaxSafety expands to include safety surveillance for more vaccines, the system's capacity to make such comparisons and provide data on the reactogenicity of more and varied vaccines will be enhanced.

## CONCLUSIONS

Approximately 74,000 influenza vaccine recipients reported low adverse event rates following immunisation with the four brands of QIIV used in Australia in 2017. Concomitant vaccination was associated with an increased AEFI risk, but rates were still low and within expected ranges. Our novel participant-based post-marketing vaccine safety surveillance system is a valuable tool for monitoring immunisation, especially for annually changing influenza vaccines.

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All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafted the work or revised it critically for important intellectual content; had final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Figure 1. Enrollees and participants by epidemiological week and age group**

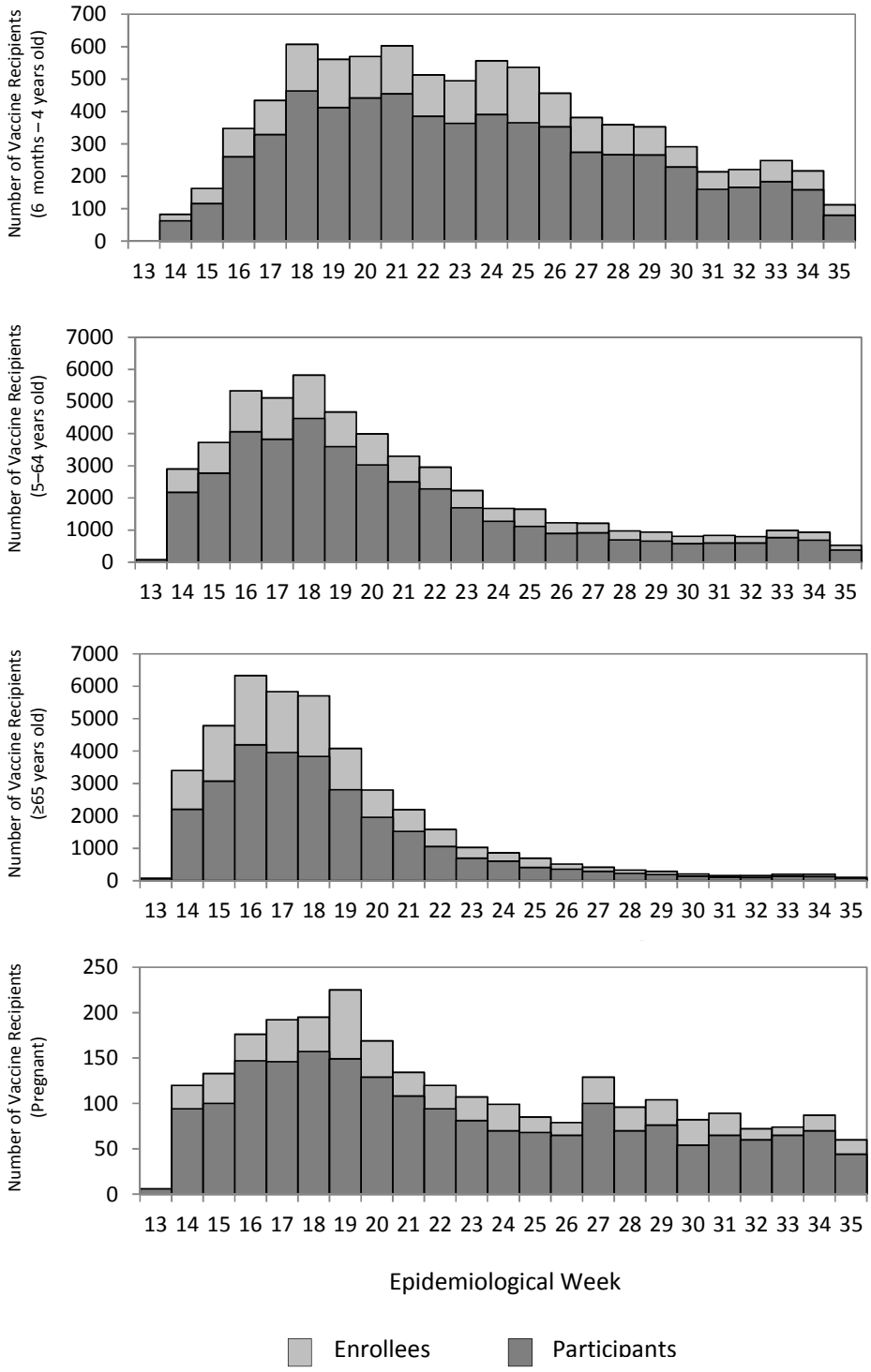


**Table 1. Descriptive variables of 73,892 participants in AusVaxSafety's 2017 influenza vaccine safety surveillance**

| Variable | Description | n (%) |
|---|---|---|
| *Sex*[a] | Male | 30,968 (41.9) |
| | Female | 42,869 (58.1) |
| *Indigenous status*[b] | Aboriginal | 1,000 (1.7) |
| | Torres Strait Islander | 32 (0.1) |
| | Both | 124 (0.2) |
| | Total | 1,156 (2.0) |
| *Pregnant*[c] | 2,018 (2.8) | |
| *Age* median (IQR; range) | 57 years (31–69 years; 6 months–102 years) | |
| *Age group* | 6 months–4 years | 6,180 (8.4) |
| | 5–14 years | 4,415 (6.0) |
| | 15–39 years | 13,434 (18.2) |
| | 40–64 years | 21,709 (29.4) |
| | ≥65 years | 28,154 (38.1) |
| Number of participants receiving concomitant vaccine(s) | 10,428 (14.1) | |
| *Most common concomitant vaccines by group*[d,e] | | |
| Overall (N = 10,428) | 23vPPV | 2,756 (26.4%) |
| | dTpa /dTpa-IPV | 2,504 (24.0%) |
| | Zoster | 1,708 (16.4%) |
| 6 months–4 years (N = 1,295) | DTPa-IPV | 268 (20.7%) |
| | HibMenCCV + MMR | 235 (18.1%) |
| | MenBV | 206 (15.9%) |
| | DTPa + MMRV | 205 (15.8%) |
| 5–14 years (N = 295) | HPV | 46 (15.6%) |
| | Typhoid + Hepatitis A | 43 (14.6%) |
| | Hepatitis A | 39 (13.2%) |
| | MenBV | 34 (11.5%) |
| 15–39 years (N = 2,612) | dTpa /dTpa-IPV | 1,743 (66.7%) |
| | Typhoid-Hepatitis A | 94 (3.6%) |
| | Hepatitis A | 85 (3.3%) |
| 40–64 years (N = 1,516) | dTpa /dTpa-IPV | 534 (35.2%) |
| | 23vPPV | 311 (20.5%) |
| | Typhoid | 87 (5.7%) |
| ≥65 years (N = 4,710) | 23vPPV | 2,403 (51.0%) |
| | Zoster | 1,699 (36.1%) |
| | dTpa /dTpa-IPV | 220 (4.7%) |
| Pregnant[f] (N = 634) | dTpa /dTpa-IPV | 633 (99.8%) |
| | dTpa /dTpa-IPV + Hepatitis B | 1 (0.2%) |

[a] Sex available for N = 73,837 participants.
[b] Indigenous status available for N = 58,145 participants.
[c] Pregnancy status available for N = 72,951 participants (SmartVax only).
[d] The percentages listed under "concomitant vaccines" are the percentage of all concomitant vaccine(s) administered per group.

[e] + indicates two separate vaccines administered concomitantly.

[f] Pregnant participants are also included in their respective age categories (age range: 15–49 years).

Abbreviations: IQR: interquartile range; MMR: measles mumps rubella; 23vPPV: 23-valent pneumococcal polysaccharide vaccine. DTPa: Diphtheria tetanus acellular pertussis (for children aged <10 years); DTPa-IPV: DTPa-inactivated polio vaccine (for children aged <10 years); dTpa: diphtheria tetanus acellular pertussis (for individuals aged ≥10 years); dTpa-IPV: dTpa-inactivated polio vaccine (for individuals aged ≥10 years); HibMenC: *Haemophilus influenzae* type B meningococcal C conjugate vaccine; MenBV: meningococcal B vaccine

**Table 2. Adverse event rates for influenza vaccine, by age group and pregnancy status**

| Type of Adverse Event[a] | Group [n/N (%)] | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 months–4 years | 5–14 years | 15–39 years | 40–64 years | ≥65 years | Pregnant[c] | Total |
| *Any adverse event*[b] | 522/6,180 (8.4) | 295/4,415 (6.7) | 836/13,434 (6.2) | 1,533/21,709 (7.1) | 1,695/28,154 (6.0) | 118/2,018 (5.8) | 4,881/73,892 (6.6) |
| *Fever*[b] | 140/5,979 (2.3) | 54/4,266 (1.3) | 121/13,020 (0.9) | 190/20,953 (0.9) | 209/27,222 (0.8) | 20/1,963 (1.0) | 714/71,440 (1.0) |
| *Medical attendance*[b] | 59/6,180 (1.0) | 21/4,415 (0.5) | 75/13,434 (0.6) | 94/21,709 (0.4) | 77/28,154 (0.3) | 10/2,018 (0.5) | 326/73,892 (0.4) |

[a] Denominators differ between any adverse event/medical attendance and fever because reports of fever are solicited in an online survey following the initial SMS regarding an AEFI, and not all participants complete the survey.

[b] p<.001 for participants aged 6 months–4 years compared to all other age groups.

[c] Pregnant participants are also included in their respective age categories (age range: 15–49 years). They are not compared to another group in this table.

**Table 3. Adverse event rates and relative risks by age group, pregnancy, and concomitant vaccine status**

| Group | Type of Adverse Event[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Any adverse event [n/N (%)] | | | Fever [n/N (%)] | | | Medical attendance [n/N (%)] | | |
| | *Influenza vaccine + concomitant vaccine(s)* | *Influenza vaccine alone* | *Relative Risk (95% CI)[b]* | *Influenza vaccine + concomitant vaccine(s)* | *Influenza vaccine alone* | *Relative Risk (95% CI)[b]* | *Influenza vaccine + concomitant vaccine(s)* | *Influenza vaccine alone* | *Relative Risk (95% CI)[b]* |
| *6 months–4 years* | 189/1,295 (14.6) | 333/4,885 (6.8) | 2.1 (1.8–2.5) | 58/1,211 (4.8) | 82/4,768 (1.7) | 2. 8 (2.0–3.9) | 15/1,295 (1.2) | 44/4,885 (0.9) | 1.3 (0.7–2.3) |
| *5–14 years* | 33/295 (11.2) | 262/4,120 (6.4) | 1.8 (1.3–2.5) | 9/281 (3.2) | 45/3,985 (1.1) | 2.8 (1.4–5.7) | 2/295 (0.7) | 19/4,120 (0.5) | 1.5 (0.3–6.3) |
| *15–39 years* | 205/2,612 (7.8) | 631/10,822 (5.8) | 1.4 (1.2–1.6) | 27/2,491 (1.1) | 94/10,529 (0.9) | 1.2 (0.8–1.9) | 18/2,612 (0.7) | 57/10,822 (0.5) | 1.3 (0.8–2.2) |
| *40–64 years* | 138/1,516 (9.1) | 1,395/20,193 (6.9) | 1.3 (1.1–1.6) | 27/1,456 (1.9) | 163/19,497 (0.8) | 2.2 (1.5–3.3) | 19/1,516 (1.3) | 75/20,193 (0.4) | 3.4 (2.1–5.6) |
| *≥65 years* | 568/4,710 (12.1) | 1,127/23,444 (4.8) | 2.5 (2.3–2.8) | 89/4,439 (2.0) | 120/22,783 (0.5) | 3.8 (2.9–5.0) | 33/4,710 (0.7) | 44/23,444 (0.2) | 3.7 (2.4–5.9) |
| *Pregnant[c]* | 57/634 (9.0) | 61/1,384 (4.4) | 2.0 (1.4–2.9) | 7/602 (1.2) | 13/1,361 (1.0) | 1.2 (0.5–3.0) | 2/634 (0.3) | 8/1,384 (0.6) | 0.6 (0.1–2.6) |
| *Total* | 1,133/10,428 (10.9) | 3,748/63,464 (5.9) | 1.8 (1.7–2.0) | 210/9,878 (2.1) | 504/61,562 (0.8) | 2.6 (2.2–3.1) | 87/10,428 (0.8) | 239/63,464 (0.4) | 2.2 (1.7–2.8) |

[a] Denominators differ between any adverse event/medical attendance and fever because reports of fever are solicited in an online survey following the initial SMS regarding an AEFI, and not all participants complete the survey.

[b] Relative risk of any adverse event, fever, or medical attendance for influenza vaccine administered with any concomitant vaccine(s) as compared to influenza vaccine administered alone.

[c] Pregnant participants are also included in their respective age categories (age range: 15–49 years).

**Table 4. Adverse event rates and relative risks by age group, pregnancy status, and vaccine brand**

| Group | Type of Adverse Event[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Any adverse event [n/N (%)] | | | Fever [n/n (%)] | | | Medical attendance [n/N (%)] | | |
| | *FluQuadri* | *Fluarix Tetra* | *Relative Risk[b] (95% CI)* | *FluQuadri* | *Fluarix Tetra* | *Relative Risk[b] (95% CI)* | *FluQuadri* | *Fluarix Tetra* | *Relative Risk[b] (95% CI)* |
| *3–14 years[c]* | 317/4,076 (7.8) | 150/2,203 (6.8) | 1.1 (1.0–1.4) | 68/3,933 (1.7) | 29/2,133 (1.4) | 1.3 (0.8–2.0) | 14/4,076 (0.3) | 20/2,203 (0.9) | 0.4 (0.2–0.8) |
| *15–39 years* | 479/7,484 (6.4) | 295/5,059 (5.8) | 1.1 (1.0–1.3) | 65/7,254 (0.9) | 46/4,908 (0.9) | 1.0 (0.7–1.4) | 40/7,484 (0.5) | 33/5,059 (0.7) | 0.8 (0.5–1.3) |
| *40–64 years* | 805/10,620 (7.6) | 607/9,252 (6.6) | 1.16 (1.0–1.3) | 101/10,237 (1.0) | 76/8,938 (0.9) | 1.2 (0.9–1.6) | 45/10,620 (0.4) | 42/9,252 (0.5) | 0.9 (0.6–1.4) |
| *≥65 years* | 638/8,916 (7.2) | 912/16,938 (5.4) | 1.3 (1.2–1.5) | 81/8,587 (0.9) | 117/16,426 (0.7) | 1.3 (1.0–1.8) | 22/8,916 (0.2) | 43/16,938 (0.3) | 1.0 (0.6–1.6) |
| *Pregnant[d]* | 60/963 (6.2) | 43/901 (4.8) | 1.3 (0. 9–1.9) | 7/932 (0.8) | 10/885 (1.1) | 0.7 (0.3–1.7) | 4/963 (0.4) | 6/901 (0.7) | 0.6 (0.2–2.2) |
| *Total* | 2,239/31,096 (7.2) | 1,964/33,452 (5.9) | 1.2 (1.2–1.3) | 317/30,136 (1.1) | 268/32,420 (0.8) | 1.3 (1.1–1.5) | 121/31,096 (0.4) | 138/33,452 (0.4) | 0.9 (0.7–1.2) |

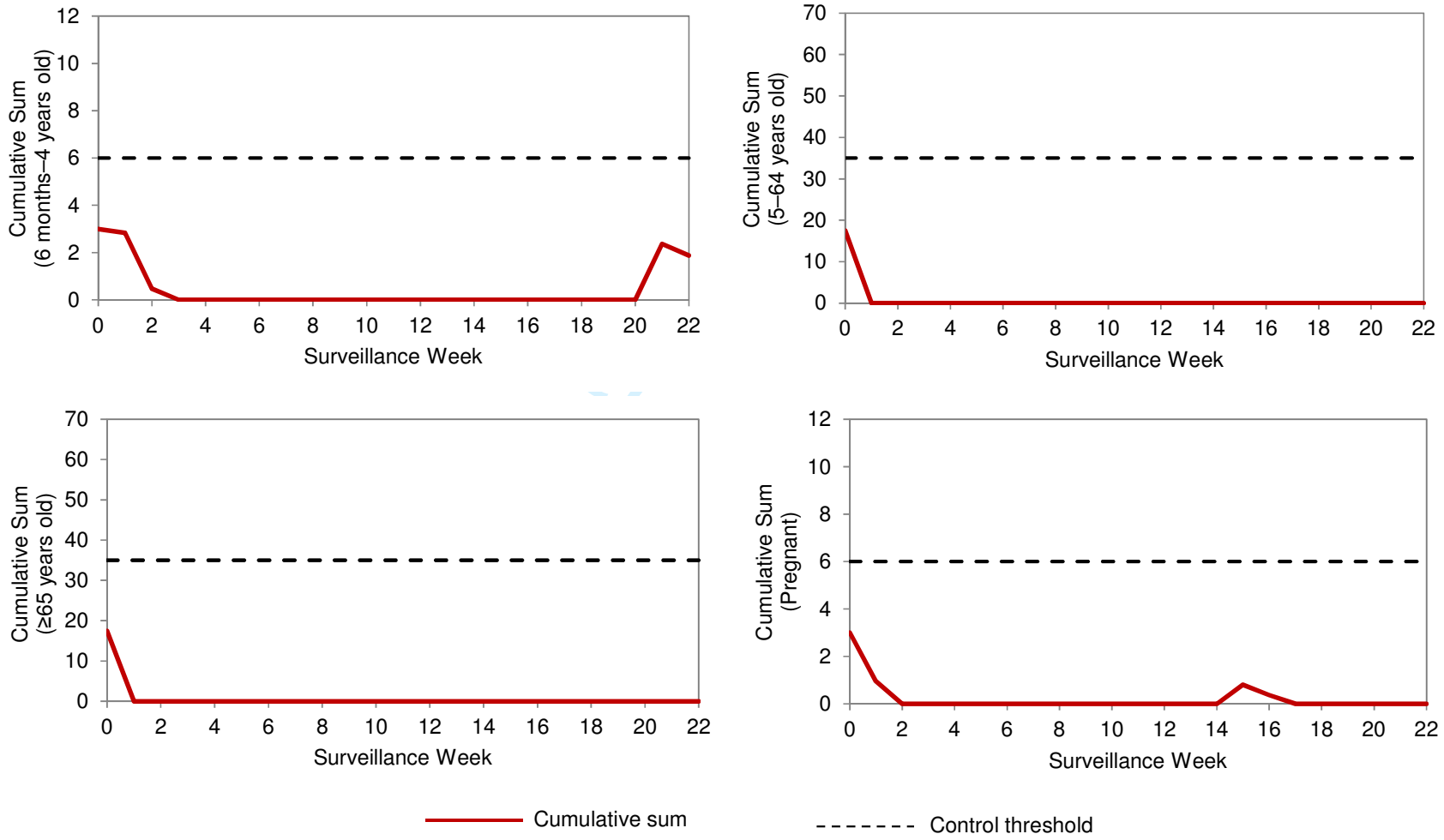
[a] Denominators differ between any adverse event/medical attendance and fever because reports of fever are solicited in an online survey following the initial SMS regarding an AEFI, and not all participants complete the survey.

[b] Relative risk of any adverse event or medical attendance for FluQuadri compared to Fluarix Tetra.

[c] Fluarix Tetra (GlaxoSmithKline) and FluQuadri (Sanofi-Aventis) are each licensed for use in individuals aged ≥3 years. We excluded n = 15 individuals aged 6 months–2 years who were reported to have received Fluarix Tetra, and n = 129 individuals aged 6 months–2 years who were reported to have received FluQuadri, from this analysis.

[d] Pregnant participants are also included in their respective age categories (age range: 15–49 years).

**eFigure1. Fast initial response cumulative sum (FIR CUSUM) safety signal detection charts for medical attendance during the surveillance period, by age group and pregnancy status**




Note: Surveillance week 1 started on 1 April and ended on 9 April, for a total of 9 days. Surveillance week 22 started on 28 August and ended on 31 August, for a total of 4 days.

**eTable 1. Secondary outcome adverse event rates, by age group and pregnancy status**

| Adverse Event[a] | 6 months–4 years | 5–14 years | 15–39 years | 40–64 years | ≥65 years | Pregnant[b] | Total |
|---|---|---|---|---|---|---|---|
| *Pain at the injection site* | 113/5,979 (1.9) | 86/4,266 (2.0) | 255/13,020 (2.0) | 419/20,953 (2.0) | 354/27,222 (1.3) | 36/1,963 (1.8) | 1,227/71,440 (1.7) |
| *Tired/fatigued*[c] | 83/5,571 (1.5) | 52/4,249 (1.2) | 183/12,862 (1.4) | 368/20,661 (1.8) | 331/27,069 (1.2) | 22/1,961 (1.1) | 1,017/70,412 (1.4) |
| *Swelling and/or redness at the injection site*[d] | 95/5,968 (1.6) | 71/4,255 (1.7) | 172/12,875 (1.3) | 306/20,692 (1.5) | 289/27,127 (1.1) | 24/1,963 (1.2) | 933/70,917 (1.3) |
| *Headache*[c] | 7/5,567 (0.1) | 42/4,247 (1.0) | 155/12,859 (1.2) | 286/20,659 (1.4) | 231/27,060 (0.9) | 26/1,960 (1.3) | 721/70,392 (1.0) |
| *Sleep pattern change*[c] | 55/5,570 (1.0) | 28/4,248 (0.7) | 53/12,851 (0.4) | 111/20,648 (0.5) | 101/27,029 (0.4) | 5/1,960 (0.3) | 348/70,346 (0.5) |
| *Irritable*[c] | 94/5,571 (1.7) | 21/4,245 (0.5) | 56/12,855 (0.4) | 77/20,641 (0.4) | 56/27,016 (0.2) | 5/1,961 (0.3) | 304/70,328 (0.4) |
| *Rash*[e] | 31/5,979 (0.5) | 10/4,266 (0.2) | 26/13,020 (0.2) | 40/20,953 (0.2) | 70/27,222 (0.3) | 1/1,963 (0.1) | 177/71,440 (0.2) |
| *Vomiting*[c] | 29/5,568 (0.5) | 8/4,246 (0.2) | 33/12,849 (0.3) | 27/20,643 (0.1) | 12/27,011 (0.04) | 9/1,960 (0.5) | 109/70,317 (0.2) |
| *Diarrhea*[c] | 15/5,567 (0.3) | 4/4,246 (0.1) | 26/12,851 (0.2) | 41/20,644 (0.2) | 33/27,018 (0.1) | 3/1,960 (0.2) | 119/70,326 (0.2) |
| *Rigors*[f] | 7/5,579 (0.1) | 3/4,257 (0.1) | 15/12,997 (0.1) | 34/20,903 (0.2) | 34/27,113 (0.1) | 2/1,960 (0.1) | 93/70,849 (0.1) |
| *Non-responsiveness/loss of consciousness*[c] | 0/5,567 (0.0) | 0/4,245 (0.0) | 0/12,848 (0.0) | 1/20,637 (0.005) | 2/27,010 (0.007) | 0/1,960 (0.0) | 3/70,307 (0.004) |
| *Convulsions/seizures*[g] | 0/5,979 (0.0) | 0/4,266 (0.0) | 0/13,020 (0.0) | 0/20,953 (0.0) | 2/27,222 (0.007) | 0/1,963 (0) | 2/71,440 (0.003) |
| *Other*[h] | 86/5,979 (1.4) | 28/4,266 (0.7) | 88/13,020 (0.7) | 196/20,953 (0.9) | 247/27,222 (0.9) | 13/1,963 (0.7) | 645/71,440 (0.9) |

[a] Denominators differ between adverse events because symptoms are solicited in an online survey following the initial SMS regarding an AEFI, and not all participants complete the survey.
[b] Pregnant participants are also included in their respective age categories (age range: 15–49 years).
[c] Collected by SmartVax only.
[d] SmartVax and STARSS collect data on injection site swelling and/or redness in one question, while Vaxtracker has separate questions for injection site redness and injection site swelling. The Vaxtracker data for injection site redness and injection site swelling have been combined for this table.
[e] STARSS specifies that the rash is over a large area of the body.
[f] SmartVax includes a description ("shaking or shivering with high temperature"), while STARSS and Vaxtracker do not refer to rigors and instead collect data on "chills and shakes".
[g] SmartVax collects data on "convulsions/seizures", while Vaxtracker collects information on "seizures", and STARSS collects information on "seizures or fits".
[h] A free-text response box is provided for participants responding that they had an "Other" reaction to describe the event(s).

**eTable 2. Primary and secondary outcome adverse event rates, by vaccine brand [a]**

| Adverse event[b] | Afluria Quad | Fluarix Tetra | FluQuadri | FluQuadri Junior |
|---|---|---|---|---|
| *Any event* | 316/4,857 (6.5) | 1,965/33,467 (5.9) | 2,250/31,225 (7.2) | 336/4,147 (8.1) |
| *Fever* | 32/4,679 (0.7) | 268/32,420 (0.8) | 317/30,136 (1.1) | 96/4,016 (2.4) |
| *Medical attention* | 20/4,857 (0.4) | 138/33,467 (0.4) | 121/31,225 (0.4) | 46/4,147 (1.1) |
| *Pain at the injection site* | 70/4,679 (1.5) | 460/32,420 (1.4) | 646/30,136 (2.1) | 48/4,016 (1.2) |
| *Tired/fatigued*[c] | 55/4,618 (1.2) | 422/31,974 (1.3) | 488/29,875 (1.6) | 50/3,757 (1.3) |
| *Swelling and/or redness at the injection site*[d] | 59/4,624 (1.3) | 350/32,062 (1.1) | 474/30,030 (1.6) | 47/4,012 (1.2) |
| *Headache*[c] | 50/4,614 (1.1) | 298/31,967 (0.9) | 371/29,868 (1.2) | 2/3,755 (0.1) |
| *Sleep pattern change*[c] | 15/4,614 (0.3) | 121/31,938 (0.4) | 171/29,850 (0.6) | 41/3,756 (1.1) |
| *Irritable*[c] | 17/4,613 (0.4) | 91/31,928 (0.3) | 128/29,842 (0.4) | 68/3,757 (1.8) |
| *Rash*[e] | 8/4,679 (0.2) | 58/32,420 (0.2) | 91/30,136 (0.3) | 20/4,016 (0.5) |
| *Vomiting*[c] | 3/4,611 (0.1) | 39/31,924 (0.1) | 48/29,838 (0.2) | 19/3,756 (0.5) |
| *Diarrhea*[c] | 7/4,613 (0.2) | 42/31,931 (0.1) | 57/29,839 (0.2) | 13/3,755 (0.3) |
| *Rigors*[f] | 5/4,667 (0.1) | 39/32,287 (0.1) | 45/29,947 (0.2) | 4/3,760 (0.1) |
| *Non-responsiveness/loss of consciousness*[c] | 0/4,611 (0.0) | 1/31,920 (0.003) | 2/29,833 (0.007) | 0/3,755 (0.0) |
| *Convulsions/seizures*[g] | 0/4,679 (0.0) | 1/32,420 (0.003) | 1/30,136 (0.003) | 0/4,016 (0.0) |
| *Other*[h] | 40/4,679 (0.9) | 255/32,420 (0.8) | 286/30,136 (0.9) | 61/4,016 (1.5) |

Median age for each brand (interquartile range): Afluria Quad: 63 years (47–71 years), Fluarix Tetra: 65 years (45–71 years), FluQuadri: 51 years (29–66 years), FluQuadri Junior: 1 year (1–2 years)

[a] Vaccine brand could not be determined for 196 participants (0.3%), who were excluded from this analysis.

[b] Denominators differ between adverse events because symptoms are solicited in an online survey following the initial SMS regarding an AEFI, and not all participants complete the survey.

[c] Collected by SmartVax only.

[d] SmartVax and STARSS collect data on injection site swelling and/or redness in one question, while Vaxtracker has separate questions for injection site redness and injection site swelling. The Vaxtracker data for injection site redness and injection site swelling have been combined for this table.

[e] STARSS specifies that the rash is over a large area of the body.

[f] SmartVax includes a description ("shaking or shivering with high temperature"), while STARSS and Vaxtracker do not refer to rigors and instead collect data on "chills and shakes".

[g] SmartVax collects data on "convulsions/seizures", while Vaxtracker collects information on "seizures", and STARSS collects information on "seizures or fits".

[h] A free-text response box is provided for participants responding that they had an "Other" reaction to describe the event(s).

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 4-5 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 6-7 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 7 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 7-11 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7-8 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 7-8 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-10 |
| Bias | 9 | Describe any efforts to address potential sources of bias | None |
| Study size | 10 | Explain how the study size was arrived at | N/A |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-11 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 10-11 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 10-11 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | N/A |
| | | (*e*) Describe any sensitivity analyses | N/A |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 11-12 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | - |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 11-12; 21-22 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 21-22 |
| | | (c) Summarise follow-up time (eg, average and total amount) | - |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 11-12; 23-25 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 21-25 |
| | | (*b*) Report category boundaries when continuous variables were categorized | - |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | - |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 11-12; 23-25 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 12-15 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 12-15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 13-15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 5 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# Active surveillance of 2017 seasonal influenza vaccine safety: an observational cohort study of individuals aged 6 months and older in Australia



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| Keywords: | Epidemiology < INFECTIOUS DISEASES, vaccine safety, active surveillance |
| | |

**TITLE**

# Active surveillance of 2017 seasonal influenza vaccine safety: an observational cohort study of individuals aged 6 months and older in Australia

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**ABSTRACT**

**Objective:** To actively solicit adverse events experienced in the days following immunisation with quadrivalent inactivated influenza vaccine using Australia's near real-time, participant-based vaccine safety surveillance system, AusVaxSafety.

**Design and setting:** Observational cohort study conducted in 194 sentinel surveillance immunisation sites (primary care, hospital, and community-based clinics) across Australia.

**Participants:** Individuals aged ≥6 months who received a routine seasonal influenza vaccine at a participating site (N=102,911) and responded to a survey (via Short Message Service or email) sent 3 days post-vaccination about adverse events experienced (N =73,892; 71.8%).

**Main Outcome Measure:** Near real-time and cumulative participant-reported rates of any adverse event, fever or medical attendance experienced within 3 days post-vaccination overall, by brand, age, pregnancy status, and concomitant vaccine receipt.

**Results:** Participant median age was 57 years (range: 6 months–102 years); 58.1% (N=42,869) were female and 2.7% (N=2,018) were pregnant. Near real-time fast initial response cumulative summation and Bayesian analyses of weekly event rates did not demonstrate a safety signal. Children aged 6 months–4 years had higher event rates (522/6,180; 8.4%) compared to older ages; participants aged ≥65 years reported fewer events (1,695/28,154; 6.0%). There were no clinically significant differences in safety between brands, by age group or overall. Cumulative data analysis demonstrated that concomitant vaccination was associated with increased rates of fever (2.1% versus 0.8%) and medical attendance (0.8% versus 0.4%), although all rates were low and did not exceed expected levels.

**Conclusions:** Novel, post-marketing AusVaxSafety surveillance demonstrated comparable and expected safety outcomes for the 2017 quadrivalent inactivated influenza vaccines brands used in

Australia. These near real-time, participant-reported data are expected to encourage confidence in vaccine safety and promote uptake.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- A large number of vaccinated individuals of all ages across Australia participated, leading to a greater ability to detect serious adverse events.
- Comprehensive data enabled analysis of adverse events with respect to age, pregnancy, vaccine brand, and concomitant vaccination with a wide variety of vaccines.
- Safety signal detection was conducted in near real time using multiple statistical methods, with results reported to the public each week.
- Individuals participating in active surveillance may be less inclined to report common and expected reactions, limiting the ability to compare reported adverse event rates with those from clinical trials.
- Some outcomes of vaccine safety, such as participant-reported fever, are subjective and have not been verified.



## FUNDING

AusVaxSafety surveillance was funded under a contract with the Australian Government Department of Health.

## COMPETING INTERESTS

All authors are either located at organisations that hold the AusVaxSafety contract from the Australian Government Department of Health or are subcontract holders. None of the authors has any other conflicts of interest to declare.

## INTRODUCTION

Influenza vaccines are given to hundreds of millions of people within short, fixed periods of time worldwide each year.[1] This widespread use, coupled with the high degree of influenza vaccine variability, including multiple vaccine types (live, inactivated, subunit, or adjuvanted), manufacturing processes (in eggs, cell lines, or with recombinant techniques), and strain compositions (trivalent or quadrivalent, with the potential for vaccine viruses to change twice yearly across the Southern and Northern Hemisphere seasons), underscores the need for timely post-marketing vaccine safety surveillance. The European Medicines Agency (EMA) now requires manufacturers to address the paucity of clinical trial safety data available for vaccine changes by conducting enhanced post-marketing safety surveillance for seasonal influenza vaccines.[2]

AusVaxSafety, an automated, active vaccine safety surveillance system, reports near real-time, brand-specific data independently of manufacturers using participant-reported outcomes. AusVaxSafety was established to improve vaccine safety monitoring following recommendations of an independent inquiry into the unprecedented increase in febrile seizures observed in young Australian children in 2010, ultimately determined to be associated with one influenza vaccine brand (Fluvax/Afluria; bioCSL).[3] This incident, which led to temporary nationwide suspension of paediatric influenza immunisation, resulted in a loss of confidence in influenza vaccines among consumers and immunisation providers and decreased influenza vaccine uptake.[4 5]

From 2014–2016 AusVaxSafety conducted influenza vaccine safety surveillance in 8,184 children aged 6 months–4 years.[6 7] A retrospective analysis comparing safety profiles of trivalent inactivated influenza vaccine (TIIV) and quadrivalent inactivated influenza vaccine (QIIV) brands in 2015 and 2016 demonstrated that concomitant vaccine administration in young children was associated with increased fever and medical attendance (MA) rates post-vaccination, although rates were low and within expected ranges.[7] Importantly, detailed follow-up data on the small number of children who

sought medical attention showed no serious or unexpected vaccine-associated adverse events following immunisation (AEFI).

In 2017, AusVaxSafety surveillance expanded to include influenza vaccine recipients of all ages. Here we provide an overview of AusVaxSafety's weekly surveillance and a detailed analysis of cumulative (end of vaccine season) safety data by QIIV brand, age, pregnancy status and concomitant vaccine receipt.

## METHODS

### AusVaxSafety active vaccine safety surveillance

Surveillance included individuals aged ≥6 months who received a 2017 seasonal influenza vaccine between 1 April–31 August 2017 at one of 194 participating immunisation providers across Australia, including general practices, hospitals, community-based clinics and Aboriginal Medical Services. . Annual influenza vaccination is recommended for all individuals aged 6 months and older who wish to protect themselves from influenza, but it is funded (available for free) under the Australian National Immunisation Program (NIP) for groups at increased risk of complications from influenza. These include individuals aged 65 years and older; Aboriginal and Torres Strait Islander people aged six months to four years and 15 years and older; pregnant women; and anyone six months and older who has a medical condition (including heart or lung disease, asthma, chronic neurological conditions, immune compromising conditions or other chronic illnesses such as diabetes).[8] In 2017, one state (Western Australia) also funded influenza vaccine for all children aged six months to four years.

Most individuals were enrolled using the opt-out, computer-based monitoring platform SmartVax, which integrates with immunisation provider management software to issue automated surveys to vaccine recipients or their caregivers via SMS, as previously described.[9] A minority of AusVaxSafety sites (n=30) utilised one of two alternative computer-based monitoring platforms—Vaxtracker[10]

(recipients aged 6 months–4 years only) or STARSS (Stimulated Telephone-Assisted Rapid Safety Surveillance)[11]—to solicit influenza vaccine adverse events following opt-in enrolment.

Vaccinated individuals/caregivers received an SMS from their medical provider 3 days post-vaccination inquiring about AEFI ("We would like to know if there were any reactions to the vax. Please reply with JUST a Y or N."). Those who responded "Y" or "N" were classified as participants, and those who responded "Y" were then asked whether or not the event was medically attended. "Yes" responders were asked to detail the adverse event(s) and/or medical attention in a short online survey, which listed a range of symptoms and asked participants to tick all symptoms experienced. As children aged 6 months–8 years and immunocompromised individuals of any age are recommended to receive two vaccine doses at least four weeks apart when first immunised, some may have been represented by more than one record.

Primary outcomes surveyed were reports of any event (yes or no), fever (solicited in the online survey), and MA (yes or no). Secondary outcomes (solicited in the online survey) were injection site (IS) pain, swelling and/or redness; tiredness/fatigue; headache; sleep pattern change; irritability; rash; vomiting; diarrhoea; rigors; non-responsiveness/loss-of-consciousness; and convulsions/seizures. Unsolicited symptoms were detailed by participants in free text.

Detailed clinical data from MAs were sought using additional information from participants' immunisation providers and/or by a public health authority, who attempted to contact participants/caregivers to ascertain whether or not MAs were serious (as defined by the Australian Therapeutic Goods Administration (TGA)).[12]

**Ethics**

The AusVaxSafety surveillance system and its data monitoring platforms operate nationally under human research ethical approval obtained from the Sydney Children's Hospital Network

(HREC/16/SCHN/19) and the Royal Australian College of General Practitioners National Research and Evaluation Ethics Committee (NREEC15-007).

**Patient involvement**

The AusVaxSafety surveillance system does not specifically recruit patients but does rely on community participation. The majority of participants are included in the surveillance system because their primary care provider or immunisation clinic has installed the SmartVax data monitoring platform, which functions in conjunction with the clinic software. Where installed, SmartVax automatically sends text messages to all patients who receive any vaccine to seek information regarding any AEFI as a routine part of patient management and after-care. In this study, we report only on patient responses regarding influenza vaccine. A small proportion of participant data are provided to AusVaxSafety via the Vaxtracker or STARSS data monitoring platforms which similarly survey individuals who have received an influenza vaccination from a participating provider or clinic. The data monitoring platforms were piloted and developed with feedback from users. The AusVaxSafety surveillance system Advisory Committee includes a consumer/patient representative. Surveillance results are uploaded to the AusVaxSafety website (www.ausvaxsafety.org.au) weekly and available to the public.

**Near real-time reporting and analysis**

De-identified records (including demographic, immunisation visit, and SMS/survey response data) were uploaded to the computer-based monitoring systems and exported weekly to the AusVaxSafety coordinating centre for aggregation and analysis. MA reports triggered clinical follow-up by designated public health authorities each weekday. Weekly analysis of cumulative data (received up to 5 days prior) for age- and pregnancy-specific AEFI rates and participant demographic characteristics were reported in detail to the Australian Department of Health and summary results published online each Friday (www.ausvaxsafety.org.au) from week three of surveillance for the duration of the surveillance period.

**Weekly signal detection**

Participant-reported rates of fever (for those aged 6 months–4 years) and MA (for all participants, grouped by age: 6 months–4 years, 5–64 years, and ≥65 years; and pregnant participants) as a surrogate for serious adverse events (SAE)[7] were considered the most objective outcome measures of vaccine safety and were monitored weekly using signal detection methods.

Fast initial response cumulative summation (FIR CUSUM) control charts monitored log-likelihood ratios of each event rate being at a maximum acceptable level versus expected level.[13] Expected and maximum acceptable rates were set based on syntheses of clinical trial data and previous surveillance results.[6 7 10 14-16] The expected MA rate was set at 1%, and the expected fever rate at 3%. Maximum acceptable rates were set at 3% and 10% for MA and fever, respectively. A safety signal is generated if the log-likelihood ratio (a measure of the degree to which the data are more consistent with an event rate equal to the maximum acceptable rate versus the expected rate) rises above a predetermined threshold. The threshold log-likelihood ratio was selected such that across 10,000 simulated vaccination seasons there would be ≥80% probability of signal generation within 3 weeks of commencement if the event rate is at the maximum acceptable level, and ≤2% probability of (false) signal generation over the entire season when the event rate is at the expected level.

Bayesian analysis was also performed weekly for robust, optimal estimation of the 95% credibility interval (CI) for true cumulative event rates. Beta distributions with means derived from 2016 surveillance data and literature review (MA: 1% for participants aged 6 months–4 years; 0.3% for participants aged 5–64 years and ≥65 years; 1% for pregnant participants; and fever: 3% for participants aged 6 months–4 years)[7] were used as priors at the start of the 2017 season. Priors were updated with each week's observed data and credibility intervals from the posterior beta distribution were reported weekly.

**End-of-surveillance cumulative analysis**

Cumulative data were reported by epidemiological week and demographic information including age (6 months–4 years, 5–14 years, 15–39 years, 40–64 years, and ≥65 years), sex, pregnancy status (available for SmartVax participants only), Aboriginal and/or Torres Strait Islander (hereafter referred to as Indigenous) status, and concomitant vaccine administration (defined as any additional vaccine(s) received at the same visit as influenza vaccine).

For any adverse event, fever, and MA, rates were calculated for each age group and pairwise proportion tests with Holm adjustment for multiple comparisons were performed to compare AEFI rates between pairs of age groups using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). AEFI rates in pregnant women were compared to those of non-pregnant female SmartVax participants of the same age range (15–49 years) using Pearson's chi-square test in Stata version 14.2 (Statacorp LLC, College Station, TX, USA). Rates of primary and secondary outcomes were calculated by brand, and secondary outcomes were calculated for each age group and pregnant women.

Primary outcome AEFI rates were also calculated for age groups and pregnant women by vaccine brand and concomitant vaccine receipt (yes or no). The relative risk of each adverse event was compared for those receiving influenza vaccine plus any concomitant vaccine(s) versus influenza vaccine alone, and for those receiving FluQuadri verus Fluarix Tetra, using a generalised linear model with a log link and binomial distribution in Stata version 14.2.

## RESULTS

### Weekly signal detection throughout 2017

No safety signals were detected by the FIR CUSUM method (eFigure 1). Weekly and cumulative Bayesian rates of fever and MA remained well below their respective maximum acceptable rates over the surveillance period: the cumulative (end-of-season) fever rate in children aged 6 months–4 years was 2.3% (95% posterior CI: 2.0, 2.7), while cumulative MA rates were 1.0% (95% CI: 0.73,

1.21) in children aged 6 months–4 years, 0.5% (95% CI: 0.41, 0.55) in participants aged 5–64 years, 0.3% (95% CI: 0.22, 0.34) in participants aged ≥65 years and 0.5% (95% CI: 0.26, 0.87) in pregnant women. For those MAs that were followed up, none of these events was categorised as serious.

**End-of-surveillance analysis**

Over the surveillance period, 73,892 of 102,911 enrollees (71.8%) responded to the post-vaccination SMS; over 95% of participants with response time available (N=71,093) responded on the same day of SMS receipt. Participants received one of four available QIIVs: Fluarix Tetra (GlaxoSmithKline; 45.3%), FluQuadri (Sanofi-Aventis; 42.3%), FluQuadri Junior (Sanofi-Aventis; 5.6%), or Afluria Quad (Seqirus; 6.8%); less than 1.0% received a vaccine whose brand could not be determined. Half of all vaccines were administered within 5 weeks of starting surveillance, with older participants (≥65 years) receiving vaccines earlier compared to young children (6 months–4 years old) and pregnant women (Figure 1).

Among all participants, 58.1% were female and the median age was 57 years (range: 6 months–102 years). Two percent (1,156/58,145 with data available) were Indigenous, which is representative of the Australian national Aboriginal and/or Torres Strait Islander population (2.8%) (Table 1). Among female participants aged 15–49 years for whom pregnancy status was available (98.6%), 15.2% (2,018/13,242) were pregnant. Individuals aged ≥65 years represented the largest proportion of participants (38.1%; 33.6% aged 65–79 years and 4.5% aged ≥80 years). Approximately 14% of participants (10,428/73,892) received a concomitant vaccine, of which 86.6% received only one. The most commonly received concomitant vaccines are listed in Table 1.

Compared to other age groups, children aged 6 months–4 years were reported as having significantly higher rates of any adverse event, while participants aged ≥65 years reported events less often (Table 2). Pregnant women reported significantly lower rates of any adverse event compared to non-pregnant women of the same age range (15–49 years; p=.019, data not shown).

Rates of more subjective secondary outcomes surveyed showed similar trends across age groups and by pregnancy status (eTable 1).

Participants who received concomitant vaccine(s) had an elevated risk of reporting any adverse event and fever compared to participants who received influenza vaccine alone (Table 3). This pattern was seen for all age groups, with the exception of fever in participants aged 15–39 years and pregnant women. Participants aged ≥40 years who received concomitant vaccine(s) reported MA at a significantly higher rate than those who received only an influenza vaccine.

Brand-specific AEFI rates were similar, particularly for FluQuadri and Fluarix Tetra, the brands administered to the majority of participants (Table 4, eTable 2).

**DISCUSSION**

AusVaxSafety surveillance utilised almost 74,000 actively solicited participant-reported outcomes to demonstrate that the four brands of QIIV used in Australia in 2017 were safe and had low and comparable adverse event rates within expected ranges for all age groups and pregnant women.[10 14-16] This novel system provided reassuring, locally-derived feedback on vaccine safety in near real time to the public and immunisation providers as influenza vaccination was rolled out across Australia.[17]

Consistent with data published from vaccine clinical trials, the most common participant-reported event following influenza immunisation was IS pain (1.7% overall). IS pain was also commonly reported in clinical trials, but at higher rates than those demonstrated in this post-marketing surveillance. Clinical trials in children reported IS pain in approximately two-thirds of those aged 3–17 years[18] with similarly high rates (up to 72.4%) in adults aged 18–60 years.[19 20] This difference is likely due to more active solicitation of AEFI in clinical trials via daily diary cards, resulting in more complete reporting. Also, as AusVaxSafety participants may be informed of expected common vaccine reactions by their clinicians, these symptoms may be less likely to be reported. By comparison, data from both this post-marketing surveillance and clinical trials confirmed low rates

of SAEs (0.4% for AusVaxSafety compared with 0.0–2.3% for the clinical trials), despite differences in SAE definitions. Equally reassuring, both IS pain rates and SAEs among pregnant women in our surveillance were low and consistent with rates reported among participants of all ages.

Adverse event rates were similar for Fluarix Tetra (GlaxoSmithKline) and FluQuadri (Sanofi-Aventis), the two most utilised QIIVs in Australia in 2017. Though small and variable differences in AEFI rates between brands were reported, this is likely attributable to factors such as age and uncontrolled confounding, and is not of clinical significance. Ongoing brand-specific surveillance will provide valuable safety data in future years, especially as two new, more immunogenic vaccine types—the high dose TIIV (Fluzone High Dose, Sanofi-Aventis) and the MF-59 adjuvanted influenza vaccine (Fluad, Seqirus)—are being included on the Australian NIPfor adults aged ≥65 years from 2018.[21]

We previously observed that AusVaxSafety participants aged 6 months–4 years who received influenza vaccine and another vaccine concomitantly (in particular diphtheria-tetanus-acellular pertussis-inactivated poliovirus (DTPa-IPV) or meningococcal B vaccines) had significantly increased AEFI rates (especially fever) compared to those receiving influenza vaccine alone.[6 7] The present analysis showed that AEFI were more common with concomitant vaccination among participants of all ages, including increased fever rates in both children and older adults and an increased risk of MA among those aged ≥40 years. The most commonly received concomitant vaccines were 23-valent pneumococcal vaccine, reduced antigen pertussis-containing vaccine (dTpa) and live attenuated zoster vaccine, which are reactogenic when administered individually.[22-28] It has been shown that concomitant receipt of influenza and 13-valent pneumococcal vaccines results in increased local and systemic events, including fever among children[29-31], while such differences in AEFI rates were not observed with concomitant receipt of influenza and pertussis or zoster vaccines.[32-35] Importantly, the increased risks of AEFI occurring with concomitant vaccination reported by AusVaxSafety—including those requiring MA—were low and likely not of clinical importance. This information may help providers to reassure patients who are receiving more than one vaccine at the same time that

although they may have a slightly higher rate of side effects, the absolute rate is low overall. As more vaccines become available, assessment of adverse events associated with concomitant vaccination using surveillance like AusVaxSafety has the potential to contribute valuable detail to post-marketing pharmacovigilance.

To the best of our knowledge, AusVaxSafety is a unique post-marketing vaccine safety surveillance system in its high level of automation, patient and provider engagement and ability to provide data on vaccine brand-specific AEFI rates in near real time. However, since the EMA recommendation to provide annual brand-specific safety data, there has been an increase in pilot and feasibility studies of influenza vaccine safety surveillance methods and systems. [36-40] Several are enhanced passive surveillance systems relying on patients returning adverse events reports via cards or telephone.[36 38] Such systems are limited by potential under-reporting of events and are likely slower and more resource-intensive as staff must enter AEFI details or conduct interviews. The Canadian National Vaccine Safety (CANVAS) Network has conducted a small pilot of a mobile phone app for reporting adverse events.[40] Eighty-six percent of those replying to questions about the usability of an app for reporting AEFI said they would prefer an app to visiting a website. Nevertheless, investigators acknowledged that the app was limited by download requirements and low survey completion rates. The US Centers for Disease Control and Prevention's Vaccine Safety Datalink (VSD), which utilises large linked databases from health care organisations, conducts Rapid Cycle Analysis (RCA) to report AEFI rates in near real time but may be limited by delays between AEFI occurrence and electronic reporting to administrative datasets. VSD's surveillance compares outcomes of interest in those who received the vaccine against the same outcomes experienced by a group of individuals who did not receive the vaccine (or in a control period for the vaccine recipient for self-controlled case series). [41] [42] While AusVaxSafety does not currently monitor some of the more severe adverse events that the VSD's RCA may detect (particularly those occurring more than 3 days following vaccination), AusVaxSafety's strength comes from its ability to quickly estimate the number of vaccine recipients who have (or have not) experienced an AEFI without relying on complex analytical methods.

There are several limitations of AusVaxSafety surveillance and the analysis in this report. Firstly, self- or parent/carer-reports of outcomes gathered through participant-based feedback may be less accurate for common and expected reactions than those solicited from clinical trial participants or those detected by systems like the VSD. Secondly, though we have attempted to adjust for potential biases by reporting the more objective outcomes of MA and fever, it should be noted that participant-reported fever is subjective and has not been confirmed. Also, should a very serious event, such as death, occur post-immunisation, an individual may not be capable of participating in AusVaxSafety surveillance; the system may therefore not identify the most serious adverse events. Thirdly, not all adverse events are vaccine-attributable, and AEFI rates may be affected by other illnesses with similar outcomes, e.g. fever from intercurrent viral illness. Finally, in this report, data did not allow for comparisons of the reactogenicity of each non-influenza vaccine administered alone, and therefore conclusions made about increased adverse event rates associated with concomitant vaccination must be tempered. As AusVaxSafety expands to include safety surveillance for more vaccines, the system's capacity to make such comparisons and provide data on the reactogenicity of more and varied vaccines will be enhanced.

In its requirement that annual enhanced post-authorisation influenza vaccine safety monitoring occur for all seasonal influenza vaccines, the EMA stated a preference for active surveillance.[2] Data in this report and for other vaccines in the AusVaxSafety system (including pertussis, human papillomavirus (HPV) and herpes zoster vaccines[17]) from hundreds of thousands of vaccinated participants since 2014 demonstrate the value of active vaccine safety surveillance systems. Age- and brand-specific AEFI rates are available within weeks of the commencement of each year's seasonal influenza immunisation program, which ensure early detection of potential safety signals. This includes 2018 southern hemisphere seasonal influenza vaccines, for which data from more than 140,000 influenza vaccine recipients vaccinated between April and June 2018 demonstrate no safety concerns (data not shown, but available in summary form at www.ausvaxsafety.org.au).

Australia also has a comprehensive national passive vaccine safety surveillance system.[43] However, all passive or spontaneous reporting systems have inherent limitations, including incomplete and under-reporting, stimulated reporting, and limited data on vaccine brands. Importantly, with passive systems, it is often difficult to determine AEFI rates due to lack of denominator data on vaccines administered. In Australia, these limitations have especially affected passive influenza vaccine safety surveillance, , and have led to previous difficulty in interpreting early or potential vaccine safety signals.[44]In this context, AusVaxSafety provides important data to ensure confidence in the safety of vaccines in use in large populations in near-real time.

## CONCLUSIONS

Approximately 74,000 influenza vaccine recipients reported low adverse event rates following immunisation with the four brands of QIIV used in Australia in 2017. Concomitant vaccination was associated with an increased AEFI risk, but rates were still low and within expected ranges. Our novel participant-based post-marketing vaccine safety surveillance system is a valuable tool for monitoring immunisation, especially for annually changing influenza vaccines.

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**Contributors:**

AP, CG, HQ and KM made substantial contributions to the conception or design of the manuscript. AP and CG were responsible for drafting the manuscript and conducting all data analyses, with the exception of signal detection analyses, which were performed by PF. TS, PJ and PF were responsible for the conceptualisation and execution of the weekly safety signal detection analyses. AL, as co-developer of the SmartVax system, served as the system operator and advisor regarding SmartVax data. PC served as the system operator and advisor regarding Vaxtracker data. PC, AL, CB, MG, TS and KM were integral to the design and development of the AusVaxSafety vaccine safety surveillance system and served as key vaccine safety experts. All authors made substantial contributions to the analysis and interpretation of data for the work and revised the manuscript critically for important intellectual content. All authors had final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

This manuscript was written on behalf of the AusVaxSafety Expert Leadership Group: Jim Buttery, Nigel Crawford, David Durrheim, Paul Effler and Nicholas Wood.

**Data sharing statement:**

AusVaxSafety compiles ongoing, de-identified surveillance data of patient-reported adverse events for specific vaccines as contracted by the Australian Government Department of Health. Summarised results are publicly available on the AusVaxSafety website (www.ausvaxsafety.org.au) but AusVaxSafety datasets are not publicly available.

**Figure legends:**

**Figure 1**: Counts of enrollees and participants by epidemiological week and age group or pregnancy status (A: 6 months-4 years; B: 5-64 years; ≥65 years; D: Pregnant). Each bar displays the number of participants (dark grey) out of the total number of enrolees (light grey) for each week.

**eFigure 1**: Fast initial response cumulative sum (FIR CUSUM) safety signal detection charts for medical attendance during the surveillance period, by age group (A: 6 months-4 years; B: 5-64 years; C: ≥65 years) and pregnancy status (D). X axes demonstrate surveillance week. Surveillance week 1 started on 1 April 2017 and ended on 9 April 2017, for a total of 9 days. Surveillance week 22 started on 28 August 2017 and ended on 31 August 2017, for a total of 4 days. Red, solid lines plot the CUSUM for medical attendances reported by participants of each group over the surveillance period, with the control thresholds appearing as dotted lines. A safety signal is generated if the red, solid lines cross the dotted threshold line.

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**Table 1. Descriptive variables of 73,892 participants in AusVaxSafety's 2017 influenza vaccine safety surveillance**

| Variable | Description | n (%) |
|---|---|---|
| *Sex*[a] | Male | 30,968 (41.9) |
| | Female | 42,869 (58.1) |
| *Indigenous status*[b] | Aboriginal | 1,000 (1.7) |
| | Torres Strait Islander | 32 (0.1) |
| | Both | 124 (0.2) |
| | Total | 1,156 (2.0) |
| *Pregnant*[c] | 2,018 (2.8) | |
| *Age* median (IQR; range) | 57 years (31–69 years; 6 months–102 years) | |
| *Age group* | 6 months–4 years | 6,180 (8.4) |
| | 5–14 years | 4,415 (6.0) |
| | 15–39 years | 13,434 (18.2) |
| | 40–64 years | 21,709 (29.4) |
| | ≥65 years | 28,154 (38.1) |
| Number of participants receiving concomitant vaccine(s) | 10,428 (14.1) | |
| *Most common concomitant vaccines by group*[d,e] | | |
| Overall (N = 10,428) | 23vPPV | 2,756 (26.4%) |
| | dTpa /dTpa-IPV | 2,504 (24.0%) |
| | Zoster | 1,708 (16.4%) |
| 6 months–4 years (N = 1,295) | DTPa-IPV | 268 (20.7%) |
| | HibMenCCV + MMR | 235 (18.1%) |
| | MenBV | 206 (15.9%) |
| | DTPa + MMRV | 205 (15.8%) |
| 5–14 years (N = 295) | HPV | 46 (15.6%) |
| | Typhoid + Hepatitis A | 43 (14.6%) |
| | Hepatitis A | 39 (13.2%) |
| | MenBV | 34 (11.5%) |
| 15–39 years (N = 2,612) | dTpa /dTpa-IPV | 1,743 (66.7%) |
| | Typhoid-Hepatitis A | 94 (3.6%) |
| | Hepatitis A | 85 (3.3%) |
| 40–64 years (N = 1,516) | dTpa /dTpa-IPV | 534 (35.2%) |
| | 23vPPV | 311 (20.5%) |
| | Typhoid | 87 (5.7%) |
| ≥65 years (N = 4,710) | 23vPPV | 2,403 (51.0%) |
| | Zoster | 1,699 (36.1%) |
| | dTpa /dTpa-IPV | 220 (4.7%) |
| Pregnant[f] (N = 634) | dTpa /dTpa-IPV | 633 (99.8%) |
| | dTpa /dTpa-IPV + Hepatitis B | 1 (0.2%) |

[a] Sex available for N = 73,837 participants.
[b] Indigenous status available for N = 58,145 participants.
[c] Pregnancy status available for N = 72,951 participants (SmartVax only).
[d] The percentages listed under "concomitant vaccines" are the percentage of all concomitant vaccine(s) administered per group.

[e] + indicates two separate vaccines administered concomitantly.

[f] Pregnant participants are also included in their respective age categories (age range: 15–49 years).

Abbreviations: IQR: interquartile range; MMR: measles mumps rubella; 23vPPV: 23-valent pneumococcal polysaccharide vaccine. DTPa: Diphtheria tetanus acellular pertussis (for children aged <10 years); DTPa-IPV: DTPa-inactivated polio vaccine (for children aged <10 years); dTpa: diphtheria tetanus acellular pertussis (for individuals aged ≥10 years); dTpa-IPV: dTpa-inactivated polio vaccine (for individuals aged ≥10 years); HibMenC: *Haemophilus influenzae* type B meningococcal C conjugate vaccine; MenBV: meningococcal B vaccine

**Table 2. Adverse event rates for influenza vaccine, by age group and pregnancy status**

| Type of Adverse Event[a] | Group [n/N (%)] | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 months–4 years | 5–14 years | 15–39 years | 40–64 years | ≥65 years | Pregnant[c] | Total |
| *Any adverse event*[b] | 522/6,180 (8.4) | 295/4,415 (6.7) | 836/13,434 (6.2) | 1,533/21,709 (7.1) | 1,695/28,154 (6.0) | 118/2,018 (5.8) | 4,881/73,892 (6.6) |
| *Fever*[b] | 140/5,979 (2.3) | 54/4,266 (1.3) | 121/13,020 (0.9) | 190/20,953 (0.9) | 209/27,222 (0.8) | 20/1,963 (1.0) | 714/71,440 (1.0) |
| *Medical attendance*[b] | 59/6,180 (1.0) | 21/4,415 (0.5) | 75/13,434 (0.6) | 94/21,709 (0.4) | 77/28,154 (0.3) | 10/2,018 (0.5) | 326/73,892 (0.4) |

[a] Denominators differ between any adverse event/medical attendance and fever because reports of fever are solicited in an online survey following the initial SMS regarding an AEFI, and not all participants complete the survey.

[b] p<.001 for participants aged 6 months–4 years compared to all other age groups.

[c] Pregnant participants are also included in their respective age categories (age range: 15–49 years). They are not compared to another group in this table.

**Table 3. Adverse event rates and relative risks by age group, pregnancy, and concomitant vaccine status**

| Group | Type of Adverse Event[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Any adverse event [n/N (%)] | | | Fever [n/N (%)] | | | Medical attendance [n/N (%)] | | |
| | *Influenza vaccine + concomitant vaccine(s)* | *Influenza vaccine alone* | *Relative Risk (95% CI)[b]* | *Influenza vaccine + concomitant vaccine(s)* | *Influenza vaccine alone* | *Relative Risk (95% CI)[b]* | *Influenza vaccine + concomitant vaccine(s)* | *Influenza vaccine alone* | *Relative Risk (95% CI)[b]* |
| *6 months–4 years* | 189/1,295 (14.6) | 333/4,885 (6.8) | 2.1 (1.8–2.5) | 58/1,211 (4.8) | 82/4,768 (1.7) | 2. 8 (2.0–3.9) | 15/1,295 (1.2) | 44/4,885 (0.9) | 1.3 (0.7–2.3) |
| *5–14 years* | 33/295 (11.2) | 262/4,120 (6.4) | 1.8 (1.3–2.5) | 9/281 (3.2) | 45/3,985 (1.1) | 2.8 (1.4–5.7) | 2/295 (0.7) | 19/4,120 (0.5) | 1.5 (0.3–6.3) |
| *15–39 years* | 205/2,612 (7.8) | 631/10,822 (5.8) | 1.4 (1.2–1.6) | 27/2,491 (1.1) | 94/10,529 (0.9) | 1.2 (0.8–1.9) | 18/2,612 (0.7) | 57/10,822 (0.5) | 1.3 (0.8–2.2) |
| *40–64 years* | 138/1,516 (9.1) | 1,395/20,193 (6.9) | 1.3 (1.1–1.6) | 27/1,456 (1.9) | 163/19,497 (0.8) | 2.2 (1.5–3.3) | 19/1,516 (1.3) | 75/20,193 (0.4) | 3.4 (2.1–5.6) |
| *≥65 years* | 568/4,710 (12.1) | 1,127/23,444 (4.8) | 2.5 (2.3–2.8) | 89/4,439 (2.0) | 120/22,783 (0.5) | 3.8 (2.9–5.0) | 33/4,710 (0.7) | 44/23,444 (0.2) | 3.7 (2.4–5.9) |
| *Pregnant[c]* | 57/634 (9.0) | 61/1,384 (4.4) | 2.0 (1.4–2.9) | 7/602 (1.2) | 13/1,361 (1.0) | 1.2 (0.5–3.0) | 2/634 (0.3) | 8/1,384 (0.6) | 0.6 (0.1–2.6) |
| *Total* | 1,133/10,428 (10.9) | 3,748/63,464 (5.9) | 1.8 (1.7–2.0) | 210/9,878 (2.1) | 504/61,562 (0.8) | 2.6 (2.2–3.1) | 87/10,428 (0.8) | 239/63,464 (0.4) | 2.2 (1.7–2.8) |

[a] Denominators differ between any adverse event/medical attendance and fever because reports of fever are solicited in an online survey following the initial SMS regarding an AEFI, and not all participants complete the survey.

[b] Relative risk of any adverse event, fever, or medical attendance for influenza vaccine administered with any concomitant vaccine(s) as compared to influenza vaccine administered alone.

[c] Pregnant participants are also included in their respective age categories (age range: 15–49 years).

**Table 4. Adverse event rates and relative risks by age group, pregnancy status, and vaccine brand**

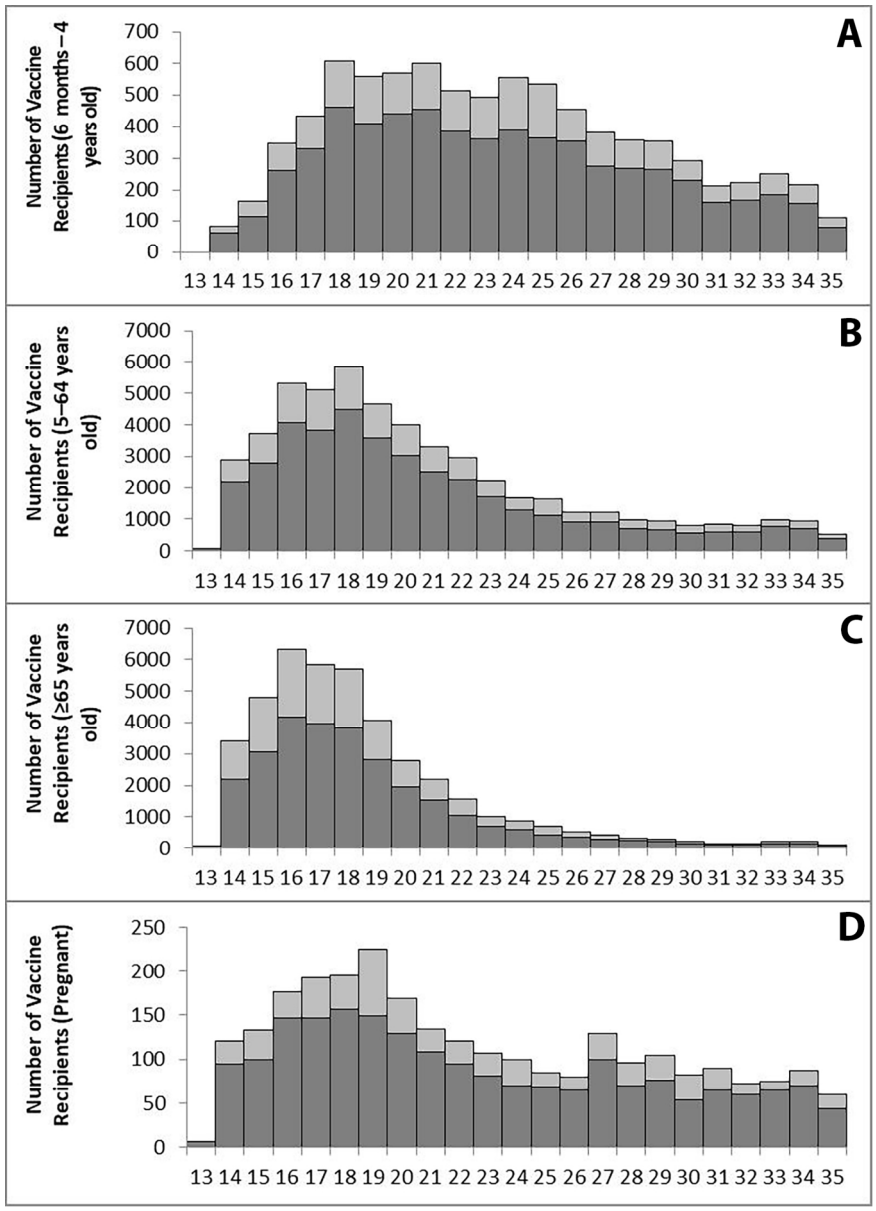
| Group | Type of Adverse Event[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Any adverse event [n/N (%)] | | | Fever [n/n (%)] | | | Medical attendance [n/N (%)] | | |
| | *FluQuadri* | *Fluarix Tetra* | *Relative Risk[b] (95% CI)* | *FluQuadri* | *Fluarix Tetra* | *Relative Risk[b] (95% CI)* | *FluQuadri* | *Fluarix Tetra* | *Relative Risk[b] (95% CI)* |
| *3–14 years[c]* | 317/4,076 (7.8) | 150/2,203 (6.8) | 1.1 (1.0–1.4) | 68/3,933 (1.7) | 29/2,133 (1.4) | 1.3 (0.8–2.0) | 14/4,076 (0.3) | 20/2,203 (0.9) | 0.4 (0.2–0.8) |
| *15–39 years* | 479/7,484 (6.4) | 295/5,059 (5.8) | 1.1 (1.0–1.3) | 65/7,254 (0.9) | 46/4,908 (0.9) | 1.0 (0.7–1.4) | 40/7,484 (0.5) | 33/5,059 (0.7) | 0.8 (0.5–1.3) |
| *40–64 years* | 805/10,620 (7.6) | 607/9,252 (6.6) | 1.16 (1.0–1.3) | 101/10,237 (1.0) | 76/8,938 (0.9) | 1.2 (0.9–1.6) | 45/10,620 (0.4) | 42/9,252 (0.5) | 0.9 (0.6–1.4) |
| *≥65 years* | 638/8,916 (7.2) | 912/16,938 (5.4) | 1.3 (1.2–1.5) | 81/8,587 (0.9) | 117/16,426 (0.7) | 1.3 (1.0–1.8) | 22/8,916 (0.2) | 43/16,938 (0.3) | 1.0 (0.6–1.6) |
| *Pregnant[d]* | 60/963 (6.2) | 43/901 (4.8) | 1.3 (0. 9–1.9) | 7/932 (0.8) | 10/885 (1.1) | 0.7 (0.3–1.7) | 4/963 (0.4) | 6/901 (0.7) | 0.6 (0.2–2.2) |
| *Total* | 2,239/31,096 (7.2) | 1,964/33,452 (5.9) | 1.2 (1.2–1.3) | 317/30,136 (1.1) | 268/32,420 (0.8) | 1.3 (1.1–1.5) | 121/31,096 (0.4) | 138/33,452 (0.4) | 0.9 (0.7–1.2) |

[a] Denominators differ between any adverse event/medical attendance and fever because reports of fever are solicited in an online survey following the initial SMS regarding an AEFI, and not all participants complete the survey.

[b] Relative risk of any adverse event or medical attendance for FluQuadri compared to Fluarix Tetra.

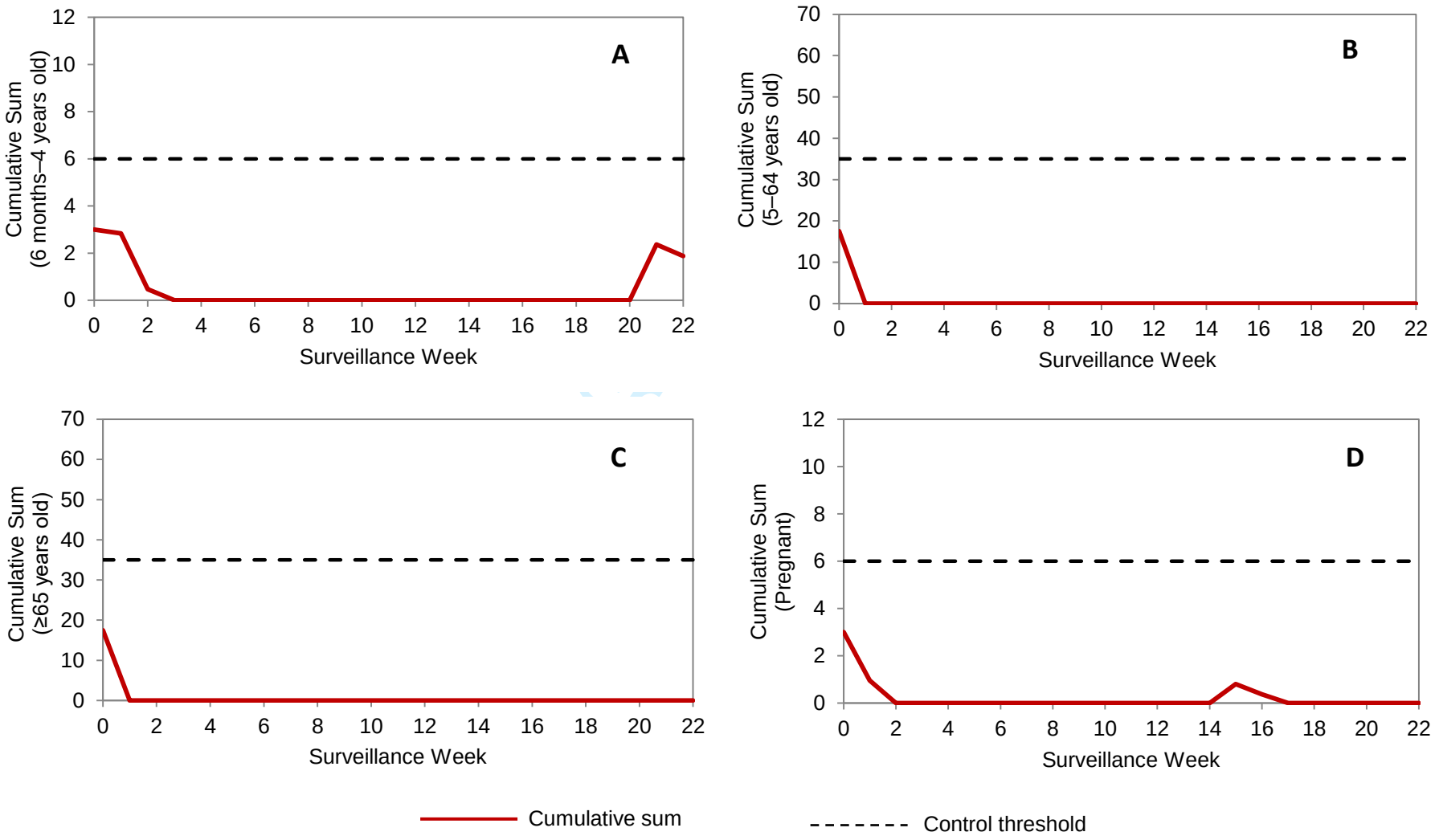
[c] Fluarix Tetra (GlaxoSmithKline) and FluQuadri (Sanofi-Aventis) are each licensed for use in individuals aged ≥3 years. We excluded n = 15 individuals aged 6 months–2 years who were reported to have received Fluarix Tetra, and n = 129 individuals aged 6 months–2 years who were reported to have received FluQuadri, from this analysis.

[d] Pregnant participants are also included in their respective age categories (age range: 15–49 years).




134x185mm (300 x 300 DPI)

**eFigure1. Fast initial response cumulative sum (FIR CUSUM) safety signal detection charts for medical attendance during the surveillance period, by age group and pregnancy status**




Note: Surveillance week 1 started on 1 April and ended on 9 April, for a total of 9 days. Surveillance week 22 started on 28 August and ended on 31 August, for a total of 4 days.

**eTable 1. Secondary outcome adverse event rates, by age group and pregnancy status**

| Adverse Event[a] | 6 months–4 years | 5–14 years | 15–39 years | 40–64 years | ≥65 years | Pregnant[b] | Total |
|---|---|---|---|---|---|---|---|
| *Pain at the injection site* | 113/5,979 (1.9) | 86/4,266 (2.0) | 255/13,020 (2.0) | 419/20,953 (2.0) | 354/27,222 (1.3) | 36/1,963 (1.8) | 1,227/71,440 (1.7) |
| *Tired/fatigued*[c] | 83/5,571 (1.5) | 52/4,249 (1.2) | 183/12,862 (1.4) | 368/20,661 (1.8) | 331/27,069 (1.2) | 22/1,961 (1.1) | 1,017/70,412 (1.4) |
| *Swelling and/or redness at the injection site*[d] | 95/5,968 (1.6) | 71/4,255 (1.7) | 172/12,875 (1.3) | 306/20,692 (1.5) | 289/27,127 (1.1) | 24/1,963 (1.2) | 933/70,917 (1.3) |
| *Headache*[c] | 7/5,567 (0.1) | 42/4,247 (1.0) | 155/12,859 (1.2) | 286/20,659 (1.4) | 231/27,060 (0.9) | 26/1,960 (1.3) | 721/70,392 (1.0) |
| *Sleep pattern change*[c] | 55/5,570 (1.0) | 28/4,248 (0.7) | 53/12,851 (0.4) | 111/20,648 (0.5) | 101/27,029 (0.4) | 5/1,960 (0.3) | 348/70,346 (0.5) |
| *Irritable*[c] | 94/5,571 (1.7) | 21/4,245 (0.5) | 56/12,855 (0.4) | 77/20,641 (0.4) | 56/27,016 (0.2) | 5/1,961 (0.3) | 304/70,328 (0.4) |
| *Rash*[e] | 31/5,979 (0.5) | 10/4,266 (0.2) | 26/13,020 (0.2) | 40/20,953 (0.2) | 70/27,222 (0.3) | 1/1,963 (0.1) | 177/71,440 (0.2) |
| *Vomiting*[c] | 29/5,568 (0.5) | 8/4,246 (0.2) | 33/12,849 (0.3) | 27/20,643 (0.1) | 12/27,011 (0.04) | 9/1,960 (0.5) | 109/70,317 (0.2) |
| *Diarrhea*[c] | 15/5,567 (0.3) | 4/4,246 (0.1) | 26/12,851 (0.2) | 41/20,644 (0.2) | 33/27,018 (0.1) | 3/1,960 (0.2) | 119/70,326 (0.2) |
| *Rigors*[f] | 7/5,579 (0.1) | 3/4,257 (0.1) | 15/12,997 (0.1) | 34/20,903 (0.2) | 34/27,113 (0.1) | 2/1,960 (0.1) | 93/70,849 (0.1) |
| *Non-responsiveness/loss of consciousness*[c] | 0/5,567 (0.0) | 0/4,245 (0.0) | 0/12,848 (0.0) | 1/20,637 (0.005) | 2/27,010 (0.007) | 0/1,960 (0.0) | 3/70,307 (0.004) |
| *Convulsions/seizures*[g] | 0/5,979 (0.0) | 0/4,266 (0.0) | 0/13,020 (0.0) | 0/20,953 (0.0) | 2/27,222 (0.007) | 0/1,963 (0) | 2/71,440 (0.003) |
| *Other*[h] | 86/5,979 (1.4) | 28/4,266 (0.7) | 88/13,020 (0.7) | 196/20,953 (0.9) | 247/27,222 (0.9) | 13/1,963 (0.7) | 645/71,440 (0.9) |

[a] Denominators differ between adverse events because symptoms are solicited in an online survey following the initial SMS regarding an AEFI, and not all participants complete the survey.
[b] Pregnant participants are also included in their respective age categories (age range: 15–49 years).
[c] Collected by SmartVax only.
[d] SmartVax and STARSS collect data on injection site swelling and/or redness in one question, while Vaxtracker has separate questions for injection site redness and injection site swelling. The Vaxtracker data for injection site redness and injection site swelling have been combined for this table.
[e] STARSS specifies that the rash is over a large area of the body.
[f] SmartVax includes a description ("shaking or shivering with high temperature"), while STARSS and Vaxtracker do not refer to rigors and instead collect data on "chills and shakes".
[g] SmartVax collects data on "convulsions/seizures", while Vaxtracker collects information on "seizures", and STARSS collects information on "seizures or fits".
[h] A free-text response box is provided for participants responding that they had an "Other" reaction to describe the event(s).

## eTable 2. Primary and secondary outcome adverse event rates, by vaccine brand [a]

| Adverse event[b] | Afluria Quad | Fluarix Tetra | FluQuadri | FluQuadri Junior |
|---|---|---|---|---|
| *Any event* | 316/4,857 (6.5) | 1,965/33,467 (5.9) | 2,250/31,225 (7.2) | 336/4,147 (8.1) |
| *Fever* | 32/4,679 (0.7) | 268/32,420 (0.8) | 317/30,136 (1.1) | 96/4,016 (2.4) |
| *Medical attention* | 20/4,857 (0.4) | 138/33,467 (0.4) | 121/31,225 (0.4) | 46/4,147 (1.1) |
| *Pain at the injection site* | 70/4,679 (1.5) | 460/32,420 (1.4) | 646/30,136 (2.1) | 48/4,016 (1.2) |
| *Tired/fatigued*[c] | 55/4,618 (1.2) | 422/31,974 (1.3) | 488/29,875 (1.6) | 50/3,757 (1.3) |
| *Swelling and/or redness at the injection site*[d] | 59/4,624 (1.3) | 350/32,062 (1.1) | 474/30,030 (1.6) | 47/4,012 (1.2) |
| *Headache*[c] | 50/4,614 (1.1) | 298/31,967 (0.9) | 371/29,868 (1.2) | 2/3,755 (0.1) |
| *Sleep pattern change*[c] | 15/4,614 (0.3) | 121/31,938 (0.4) | 171/29,850 (0.6) | 41/3,756 (1.1) |
| *Irritable*[c] | 17/4,613 (0.4) | 91/31,928 (0.3) | 128/29,842 (0.4) | 68/3,757 (1.8) |
| *Rash*[e] | 8/4,679 (0.2) | 58/32,420 (0.2) | 91/30,136 (0.3) | 20/4,016 (0.5) |
| *Vomiting*[c] | 3/4,611 (0.1) | 39/31,924 (0.1) | 48/29,838 (0.2) | 19/3,756 (0.5) |
| *Diarrhea*[c] | 7/4,613 (0.2) | 42/31,931 (0.1) | 57/29,839 (0.2) | 13/3,755 (0.3) |
| *Rigors*[f] | 5/4,667 (0.1) | 39/32,287 (0.1) | 45/29,947 (0.2) | 4/3,760 (0.1) |
| *Non-responsiveness/loss of consciousness*[c] | 0/4,611 (0.0) | 1/31,920 (0.003) | 2/29,833 (0.007) | 0/3,755 (0.0) |
| *Convulsions/seizures*[g] | 0/4,679 (0.0) | 1/32,420 (0.003) | 1/30,136 (0.003) | 0/4,016 (0.0) |
| *Other*[h] | 40/4,679 (0.9) | 255/32,420 (0.8) | 286/30,136 (0.9) | 61/4,016 (1.5) |

Median age for each brand (interquartile range): Afluria Quad: 63 years (47–71 years), Fluarix Tetra: 65 years (45–71 years), FluQuadri: 51 years (29–66 years), FluQuadri Junior: 1 year (1–2 years)

[a] Vaccine brand could not be determined for 196 participants (0.3%), who were excluded from this analysis.

[b] Denominators differ between adverse events because symptoms are solicited in an online survey following the initial SMS regarding an AEFI, and not all participants complete the survey.

[c] Collected by SmartVax only.

[d] SmartVax and STARSS collect data on injection site swelling and/or redness in one question, while Vaxtracker has separate questions for injection site redness and injection site swelling. The Vaxtracker data for injection site redness and injection site swelling have been combined for this table.

[e] STARSS specifies that the rash is over a large area of the body.

[f] SmartVax includes a description ("shaking or shivering with high temperature"), while STARSS and Vaxtracker do not refer to rigors and instead collect data on "chills and shakes".

[g] SmartVax collects data on "convulsions/seizures", while Vaxtracker collects information on "seizures", and STARSS collects information on "seizures or fits".

[h] A free-text response box is provided for participants responding that they had an "Other" reaction to describe the event(s).

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 4-5 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 6-7 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 7 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 7-11 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7-8 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 7-8 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-10 |
| Bias | 9 | Describe any efforts to address potential sources of bias | None |
| Study size | 10 | Explain how the study size was arrived at | N/A |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-11 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 10-11 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 10-11 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | N/A |
| | | (*e*) Describe any sensitivity analyses | N/A |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 11-12 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | - |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 11-12; 21-22 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 21-22 |
| | | (c) Summarise follow-up time (eg, average and total amount) | - |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 11-12; 23-25 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 21-25 |
| | | (*b*) Report category boundaries when continuous variables were categorized | - |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | - |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 11-12; 23-25 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 12-15 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 12-15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 13-15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 5 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.