Post-vaccination healthcare attendance rate as a proxy measure for syndromic surveillance of adverse events following immunisation

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Abstract

Objective: This study explored whether all-cause healthcare attendance rate post-vaccination could detect the two historical influenza safety episodes occurring in 2010 and 2015 using a large de-identified general practitioner (GP) consultations dataset.

Methods: A retrospective observational cohort study was conducted using GP consultation data routinely collected from 2008 to 2017 in Victoria, Australia. Post-vaccination GP consultation rates were monitored, over a 22-week surveillance period each year that aligned with each year's influenza vaccination season, using the Observed minus Expected (O-E) and the Log-Likelihood Ratio (LLR) CUSUM charts. Days 1–7 post-vaccination were considered as the risk period. The LLR CUSUM was designed to detect both a 50% and two-fold rise in the odds of the baseline post-vaccination GP consultation rates.

Results: Over the 10-year study period, more than 1.5 million seasonal influenza vaccines doses were administered to 295,091 persons. Overall, 1.29% had a GP consultation within one week of vaccination, but 98.53% of the consultations occurred in days 1–3 post-vaccination. The LLR CUSUM chart detected significant increases in the weekly rates of post-vaccination GP consultation in 2010 in children aged under ten years and in 2015 in adults aged 19–64 years. These increases were aligned by week, but one week earlier and by age category, with the historical adverse events following immunisation (AEFI) signals occurring in 2010 and 2015. However, in the absence of historical AEFI signals, increased rates of post-vaccination GP consultations were identified in three of the eight influenza vaccination years.

Conclusion: The crude post-vaccination healthcare attendance rate has the potential to offer a sensitive proxy to monitor vaccine safety signal.

Implications for public health: Vaccine safety monitoring using syndromic indicator has the potential to augment the existing surveillance systems as part of an integrated vaccine safety monitoring approach.

Key words: vaccine safety signal detection, post-vaccination healthcare attendance, syndromic surveillance, vaccine safety

Public and healthcare worker perceptions of vaccine safety are crucial drivers of vaccine hesitancy, which is defined as a reluctance or refusal to vaccinate despite the availability of vaccines.[1] Vaccine hesitancy has been identified by the World Health Organization (WHO) as one of the 10 threats to global health.[2,3] Post-licensure vaccine safety surveillance remains the cornerstone for the detection of adverse events following immunisation (AEFI).[4] While most AEFI are mild and self-limiting, early detection of increased rates of known AEFI or AEFI not detected during clinical trials are critical to maintain trust in immunisation programs and minimise vaccine hesitancy.[5,6]

While spontaneous (passive) surveillance systems are the mainstay of post-licensure safety monitoring, these systems rely on voluntary reporting of AEFI by the community, mainly healthcare workers and vaccine recipients or their caregivers. Notably, because of the wider population coverage, surveillance systems can detect rare or long-term AE signals. A vaccine safety signal, as defined by the WHO, is "reported information on a possible causal relationship between an adverse event and a vaccine, the relationship being unknown or incompletely documented previously. The information can arise from one or multiple sources".[7] However, while recent innovations in data visualisation and automated disproportionality analyses show promise,[8] passive surveillance systems are limited by underreporting and a lack of timely vaccine administration denominator data for early vaccine safety signal detection.[9,10]

Near real-time active surveillance systems have been established in the US and Australia to facilitate early detection and verification of vaccine safety signals.[11,12] In the US, since 2005, all newly licensed vaccines have been monitored in near real-time using the VSD, a distributed network of clinical information databases from 10 healthcare organisations. In this approach, a set of pre-selected AEFI is monitored by analysing data weekly using the rapid cycle analysis method.[13] However, any medical condition that is a potential vaccine safety concern, but is not included in the pre-selected conditions, may go undetected. An alternative approach used in Australia is the participant-centred near real-time active

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AEFI surveillance system 'AusVaxSafety', which has operated since 2014. Information is actively solicited from vaccine recipients (or their caregivers) via an SMS or email in the days following vaccination. Essentially, selected immunisation clinics across Australia (at the time of writing, >300 sentinel sites, predominantly GPs) send an automated SMS or email to individuals who have been vaccinated at their clinic asking whether they experienced any adverse event within three days of vaccination (a 'Yes' or 'No' question). If an individual's answer is 'Yes', the vaccine recipient or their caregiver receives a link to a web-based survey asking for more information regarding the adverse events.[11,14] Until 2020, the scope of AusVaxSafety had been limited to specific vaccines (i.e. influenza vaccine, pertussis vaccine and zoster vaccine), and it had relied on an active response from each person.

Some studies have shown that vaccine safety signals could be tracked using proxy measures, such as post-vaccination medical attendance rates.[15,16] The 2010 vaccine safety episode in Australia involving increased rates of post-vaccination fever and febrile convulsions in children was found to be due to one widely used brand of seasonal influenza vaccine (CSL products Fluvax™ and Fluvax Junior™).[17] An analysis of the Medicare Benefits Schedule claims data in Australia demonstrated that the number of people who visited a general practitioner (GP) after receiving the seasonal influenza vaccination in 2010 had increased.[15] Emergency department (ED) analyses conducted in Canada[18] and the UK[16] also reported considerably high numbers of ED presentations in the days following vaccination. Further, the AusVaxSafety system uses the self-reported 'medical attendance rate within three days after vaccination' as a surrogate measure of severe AEFI.[11,19] Notably, in communicable disease surveillance, syndromic surveillance using proxy measures has become widely used as an essential tool to provide an early warning of increased disease activity, such as influenza-like illnesses and gastroenteritis.[20,21]

Objective

The objective of this study was to examine whether a large de-identified GP dataset, available in near real-time, could detect in a timely manner an increase in the all-cause GP consultation rate after vaccination using historical Australian historical influenza vaccine safety signals. These were the 2010 febrile seizures and the 2015 allergy-related reactions following influenza vaccination.[17,22]

Methods

Study design and data source

A retrospective observational cohort study was conducted using GP consultation data extracted from the Outcome Health's GP dataset, Population Level Analysis and Reporting (POLAR GP) Data Space (Aurora). The Aurora dataset, a subset of POLAR GP, comprises de-identified electronic medical records (including patient information such as demographics, clinical, immunisation history and prescriptions) extracted from Australian general practices who have consented for de-identified data to be used for approved research studies.[23,24] In 2020, more than 1,000 general practices in New South Wales and Victoria contribute data to the Aurora, serving a population of approximately three million people.[24,25] At the time this study was conducted, 300 general practices located within Victoria contributed data to Aurora.

Study participants

All people (aged 6 months and older) who had received seasonal influenza vaccination and been registered in the Aurora dataset between 2008 and 2017 were included in the analysis. Of note, practices and individuals who opted out of sharing their data for research activities were not included in the analysis. Approval was obtained from the Monash Health Human Research Ethics Committee (HREC/18/MonH/345) and data access approval was obtained from the Outcome Health POLAR research council.

Outcomes

The primary outcome measure was the post-vaccination GP consultation rate, a proxy measure of AEFI instances. Days 1–7 following vaccination were considered the risk period. Day 0 (the day of vaccination) was excluded from the risk period because of the difficulty of differentiating between individuals' GP consultations to receive a vaccination and consultations for other reasons on the same day. The post-vaccination risk period was constructed using the recorded date of vaccination and the GP consultation date after vaccination. The post-vaccination GP consultation rate was calculated using the number of individuals who had received the influenza vaccine from all participating practices as the denominator and the number of individuals who had received the influenza vaccine and revisited the practice during days 1–7 post-vaccination for any reason as the numerator.

Each calendar year was categorised by epidemiological weeks. The surveillance period was the first 22 weeks from each year's influenza vaccination period, aligned with each year's vaccination commencement date. Specifically, the surveillance period was between 5 March and 5 August for the vaccination years between 2008 and 2014, inclusive, and between 2 April and 2 September for the vaccination years between 2015 and 2017, inclusive.

Exposure

Influenza vaccines can change from year to year as new strains of influenza virus appear. The seasonal influenza vaccines available with respect to age group for each of the study years under observation has been provided in Supplementary Table 1.

Data analysis

The validity of the syndrome 'post-vaccination GP consultation rate' was evaluated based on its ability to detect the two historical AEFI signals: febrile convulsions in 2010[17] and allergy-related reactions in 2015.[22] Cumulative rates of all-cause post-vaccination GP consultations per week per 100 vaccine doses, by age group and vaccination year, were calculated. The temporal pattern of the post-vaccination GP consultation rates was examined on a weekly basis using two Cumulative SUM (CUSUM) charts, the Observed minus Expected (O–E) and one-sided log-likelihood ratio (LLR) CUSUM.

The CUSUM chart is a sequential data monitoring method that allows the detection of sustained shifts of cumulative event rates over time.[26,27] The O–E CUSUM chart was used in this study to plot the difference between the observed and expected post-vaccination GP consultation rate at each week across the surveillance period, and to visualise the general pattern of the post-vaccination GP consultation rate. Essentially, the chart is expected to oscillate around the horizontal line at zero if the weekly-observed post-vaccination GP consultation rate is consistent with the expected (baseline) rate. Conversely, the LLR CUSUM chart was used to

determine if the observed post-vaccination GP consultation rates had significantly changed from the expected rates, to identify statistical signals. Essentially, the LLR CUSUM compared two likelihood models: the baseline model, which claimed that the observed post-vaccination GP consultation rate was consistent with the expected rate, and the alternative model, which claimed that the observed rate was different from the expected rate, being either greater than or equal to a predetermined maximum acceptable rate (stated as an alternative odds ratio [OR_A]). The expected post-vaccination GP consultation rate for each studied vaccination year was estimated based on the average of the two preceding vaccination years, using data from years 2008–2016. Of note, post-vaccination GP consultation rates from 2010 and 2015 were excluded while calculating the expected rates, as there were confirmed vaccine safety episodes in those years.

In this study, the LLR CUSUM chart was designed to detect a 50% increase (OR_A=1.5) or a two-fold increase (OR_A=2) of the odds of the baseline post-vaccination GP consultation rate. Suppose that after 't' weeks there was a total of 'k1' patients who had visited the GP post-vaccination and a total of 'k2' patients who had not visited the GP post-vaccination. Then the LLR of this data (which adds over time) is:

$$LLR(t)=k1(t)\log(OR)/(1-po+ORpo))+k2(t)\log(1/(1-po+ORPo))$$

where *Po* is the baseline post-vaccination GP consultation rate, and is the odds ratio that corresponds to the minimum unacceptable post-vaccination GP consultation rate (threshold) that the chart should detect. The LLR CUSUM chart limit was placed at '+1' to declare a weekly signal that corresponded to the likelihood of the data being approximately twice as likely under the alternative model compared to the baseline model.

All analyses were categorised by age group (6 months – 9 years, 10–18 years, 19–64 years and ≥65 years) and vaccination year. Data analyses were undertaken using Stata 15 (Statacorp, Texas) and Microsoft Excel 2016 (Redmond, CA).

Result

Influenza vaccination

During the study period, there were 1,576,545 records of seasonal influenza vaccinations in the Aurora dataset that were administered to 295,091 persons. Of these records, 916,335 (58.12%) influenza vaccine doses were given to females and 932,159 (59.13%) doses were given to individuals aged ≥65 years. The median age of vaccinated individuals was 68 years (range: 6 months – 109 years, and interquartile range=24 years). Generally, the number of administered influenza vaccine doses increased over the study period, except for a slight decrease in 2011 and 2012 (Supplementary Table 2).

General practice consultations following vaccination

During the 10-year study period, there were 20,272 (1.29%) GP consultations in the one-week post-vaccination period. Of these consultations, 98.53% occurred on days 1–3 post-vaccination. Post-vaccination GP consultation rates ranged from 1.10% in 2008 to 1.64% in 2017 and were comparable between females and males. However, the post-vaccination GP consultation rates were significantly higher in individuals aged 19–64 and ≥65 years ($p< 0.001$); see Supplementary Figure 1. Additionally, the post-vaccination GP consultation rate was increased significantly over the 10-year study period (*p*-value for trend <0.001).

Weekly cumulative post-vaccination general practice consultation rate

A: 2010 influenza vaccine safety episodes

The end of surveillance period post-vaccination GP consultation rate in children aged 6 months – 9 years for 2010 was 0.84%, higher than the same periods in 2008 and 2009 combined (0.56%), although not statistically significant (IRR=1.50, 95%CI [0.95–2.37]); see Supplementary Table 3. The O–E CUSUM chart (Figure 1a) illustrates that the weekly post-vaccination GP consultation rate for children aged 6 months – 9 years across the surveillance period (weeks 10–32, inclusive) was higher than the baseline rate (i.e. the rates of 2008 and 2009 combined); see Figure 1a. Furthermore, the LLR CUSUM chart detected a 50% increase (ORA = 1.5) of post-vaccination GP representation rate from the baseline rate in all weeks of the surveillance period except weeks 10, 11 and 12, with the observed weekly rates leading to signals ranging from 0.80% to 1.06%. Alternatively, considering an OR_A of 2, the LLR CUSUM also indicated statistical signals for six consecutive weeks (weeks 13–18, inclusive). The weekly post-vaccination GP consultation rates leading to signals were 0.99%, 1.06%, 0.94%, 0.96%, 0.89% and 0.89%, respectively (see Figure 1b). The end of surveillance period rate was also higher for individuals 19–64 years (IRR=1.13, 95%CI [1.02–1.25]); however, the LLR CUSUM chart did not show a statistical signal in either scenario.

B. 2015 influenza vaccine safety episode

Generally, the 2015 end of surveillance period post-vaccination GP consultation rates were higher across all age groups – except in the 10–18 years group – compared to the baseline rates that were estimated from the 2013 and 2014 seasons combined. The observed post-vaccination GP consultation rates for the age categories of 6 months – 9 years, 10–18 years, 19–64 years and ≥65 years were 0.61%, 0.61%, 1.53% and 1.39%, respectively, and the baseline rates for the respective age categories were 0.58%, 0.64%, 1.23% and 1.27%. The unadjusted IRR showed that rates were significantly higher for the age categories of 19–64 years (IRR=1.29, 95%CI [1.21–1.38]) and ≥65 years (IRR=1.11, 95%CI [1.05–1.17]); see Supplementary Table 2.

The O–E CUSUM chart also showed that the weekly rates of period post-vaccination GP consultation were higher across all age groups – except in the 10–18 years group (Figure 2a). However, the LLR CUSUM chart demonstrated a 50% increase of post-vaccination GP consultation rates only for individuals aged 19–64 years, with rates ranging from 1.53% to 1.74%, from week 16 to 35 of the surveillance period. Conversely, unlike the 2010 rates, the LLR CUSUM chart did not show a signal across all age categories considering an OR_A of 2 (Figure 2b).

For vaccination years 2011–14, inclusive, and 2016, the weekly cumulative LLR CUSUM chart did not show any statistical signal except in 2012 for the age group of 6 months – 9 years. In 2012, signals were detected from week 18 to 31 considering an OR_A of 1.5. Compared to 2014 and 2016 combined, signals were also detected in 2017 in children aged 6 months – 9 years and 10–18 years considering both OR_A of 1.5 and 2 (Table 1).

Discussion

Using aggregated GP consultation data and post-vaccination GP consultation rate as a proxy measure for AEFI surveillance, the two historical AEFI signals in Australia following seasonal influenza vaccination were detected.

These were the fever and febrile seizure signal in 2010 and allergy-related AEFIs signal in 2015. Hence, the post-vaccination medical attendance rate could be a timely and sensitive proxy measure to monitor AEFI signals, particularly in the context of multimodal signal detection systems. As 98.53% of the representations occurred on days 1–3 post-vaccination, such a system would be timely and suitable to detect early-onset AEFI. However, in the absence of historical AEFI signals, statistically significant increases in post-vaccination GP consultation rates were also detected in three of the eight signal-free vaccination years.

Post-vaccination GP consultation rates varied considerably across age groups and surveillance years. Generally, the rate was lower in children <19 years than it was in adults. The AusVaxSafety active SMS-based AEFI surveillance system reported comparable findings for children aged <5, where between 0.7% and 1.1% of children sought medical attendance within three days of receiving the influenza vaccine in 2015, 2017 and 2019.[11,19,28] In contrast to this study's findings, these studies also reported low medical attendance rates (<0.5%) in individuals aged 19 years and older. The observed higher post-vaccination GP consultation rates in this study may be due to a number of potential reasons. Solicited response rates regarding medical attendance may be age dependant, and potentially occurring at a higher rate regarding children. This study also considered a longer post-vaccination risk period (days 1–7 rather than the first three days for AusVaxSafety). Additionally, adults and the elderly are more likely to visit GPs often due to healthcare issues other than AEFI, such as appointments for management of multiple medical problems, and these may also require multiple visits clustered over a short time period.

The weekly LLR CUSUM chart detected the 2010 event one week earlier than it had been detected at the time. Western Australian authorities notified the TGA on 13 April 2010 following an apparent increase in children with fever, vomiting and febrile convulsions visiting EDs soon after receiving the trivalent influenza vaccine.[29] Other studies, using different data sources and data analysis

Figure 1a: Age-specific O–E CUSUM chart of weekly cumulative all-cause post-vaccination GP consultation rate: The 2010 vaccination season compared to the 2008 and 2009 seasons combined.

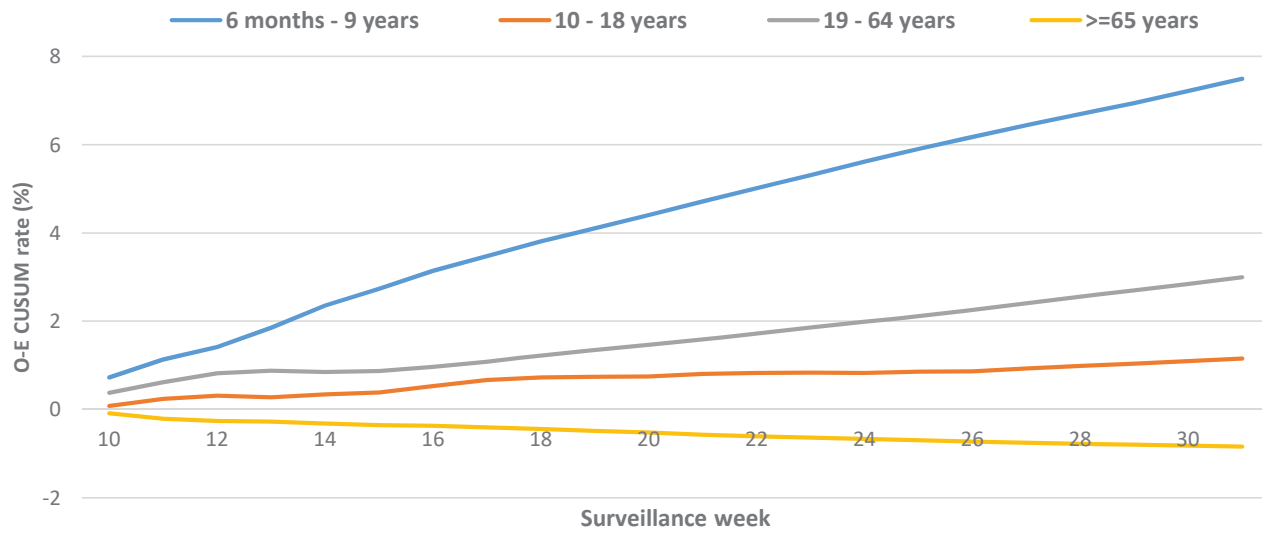
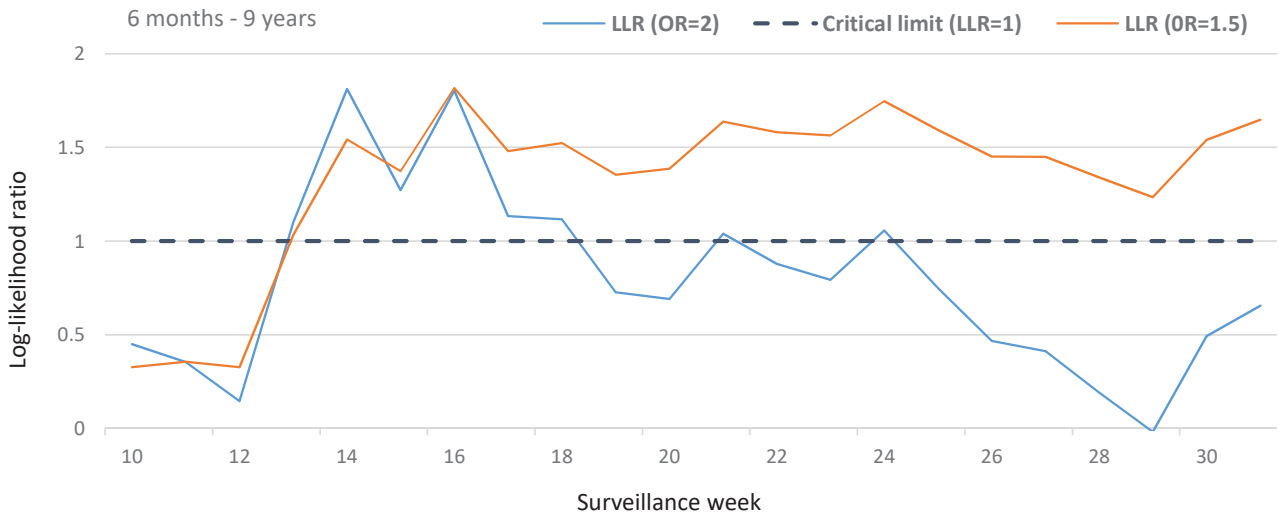


Figure 1b: Cumulative LLR CUSUM chart of all-cause post-vaccination GP consultation rate for children aged 6 months – 9 years: The 2010 influenza vaccination season.



approaches, also demonstrated that the event could have been detected earlier. Specifically, a recent study demonstrated that a signal could have been identified on 28 March by re-analysing the SAEFVIC data using a disproportionality analysis algorithm (proportional reporting ratio).[8] In addition, our previous study that used a weekly analysis of AEFI-related telephone helpline calls in Victoria, Australia, detected the event within two weeks of the influenza vaccination season commencing (Figure 3).[30]

Regarding the 2015 signal, SAEFVIC detected increased allergy-related AEFI following the seasonal influenza vaccination – predominantly in adults – two weeks after the program had started. This signal was confirmed using proportional reporting rate analyses at the time and re-confirmed at the end of the season. This signal was reported to the TGA, which conducted similar analyses and did not detect signals in jurisdictions other than Victoria. As the clinical severity of the allergic events was low, with no increase in severe events such as anaphylaxis, no regulatory action was needed, unlike the 2010 event.[22] The weekly LLR CUSUM did not show a two-fold increase in the odds of the baseline post-vaccination GP consultation rate over the 22-week surveillance period in 2015; however, there was at least a 50% increase in the 19–64 years group starting from week 11. The SAEFVIC proportional reporting rate[8] and telephone helpline call data analyses[30] indicated the signal 11 and 7 days before 3 May 2015, respectively.

Syndromic surveillance systems face a tension between detecting signals corresponding to significant events in the context of 'background noise'.[31] In this study, in the absence of historical AEFI clusters having occurred, the weekly LLR CUSUM chart demonstrated additional signals in 2012 (6 months – 9 years) and 2017 (6 months – 9 years and 10–18 years). Similar to other statistical tests, the LLR CUSUM chart can lead to false-positive signals, particularly due to an incorrect choice of a maximum acceptable 'baseline threshold' event rate. To help differentiate real signals from 'noise' in the post-vaccination GP consultation data, considering the following may be of value: duration of signal in weeks (whether signal occurring successively or not); data analysis

Figure 2a. Age-specific O–E CUSUM chart of weekly cumulative all-cause post-vaccination GP consultation rate: The 2015 vaccination season compared to the 2013 and 2014 seasons combined.

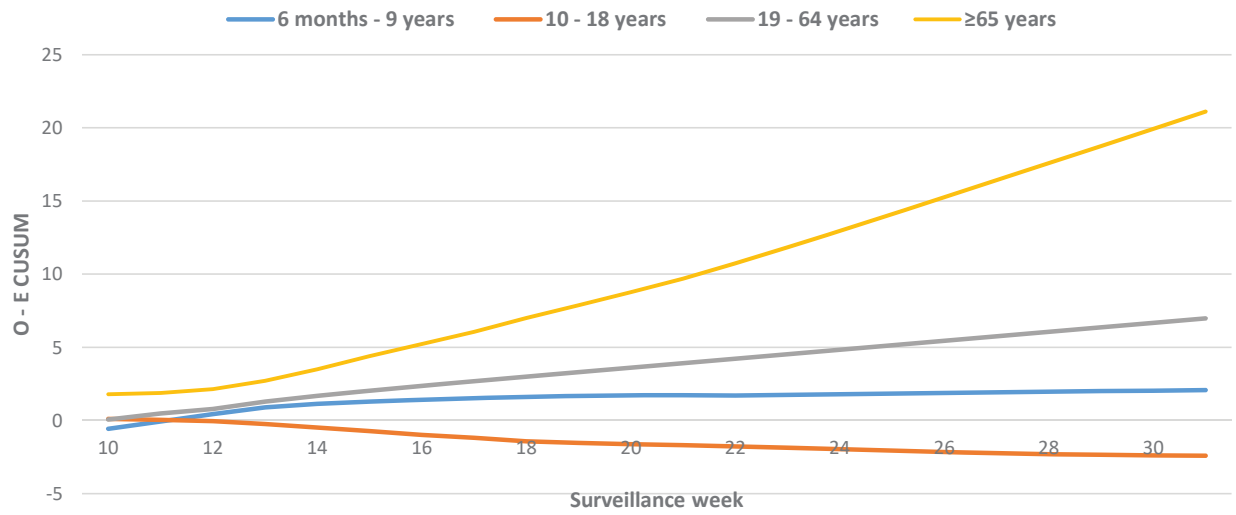
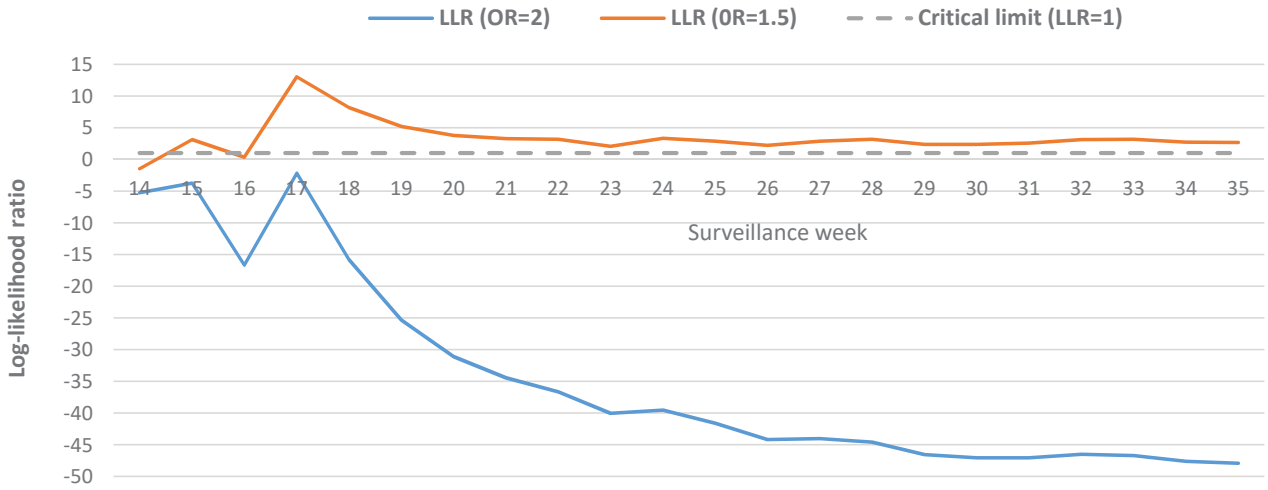


Figure 2b. Cumulative weekly LLR CUSUM chart of all-cause post-vaccination GP consultation rate for adults aged 19–64 years, 2015 (influenza vaccination commenced in April, week 14).



by vaccine brand; and whether other existing AEFI surveillance systems have indicated similar safety concerns.

Strengths and limitations

This study is one of the few that has attempted to examine the utility of syndromic AEFI surveillance using post-vaccination healthcare attendance as a proxy measure of AEFIs with the aim of augmenting existing AEFI signal detection systems. However, this study only examined routine GP consultations after the influenza vaccination. In Australia, healthcare advice can also be accessed from funded telephone helpline services, after-hours GP services and hospital EDs, all of which may have a potential to augment AEFI monitoring. Additionally, this study employed an LLR CUSUM signal detection algorithm based on an observed vs. expected analysis. This algorithm works best when the time series of the outcome measures (post-vaccination GP consultation rate) is stationary over time. However, in this study, the post-vaccination GP consultation rate increased over the study period, specifically in adults and the elderly (Supplementary Figure 1). This may be due to the increasing prevalence of complex chronic diseases, which may necessitate repeat attendances, as noted previously. A similar trend has been observed in analyses of post-vaccination GP consultation rate in adolescents following the HPV vaccine in the UK (Andrews N, Public Health England March 2020, personal communication). Last, to evaluate the applicability of these findings, further research in a prospective setting is required using multi-jurisdiction GP consultation data and alternate analysis methods, such as temporal–spatial analysis. Since this study was performed, near real-time available GP datasets have increased more than four times in size and are more nationally representative,[24] offering increased sensitivity and generalisability.

Table 1: Summary of post-vaccination GP consultation rate signals detected based on the LLR CUSUM chart.

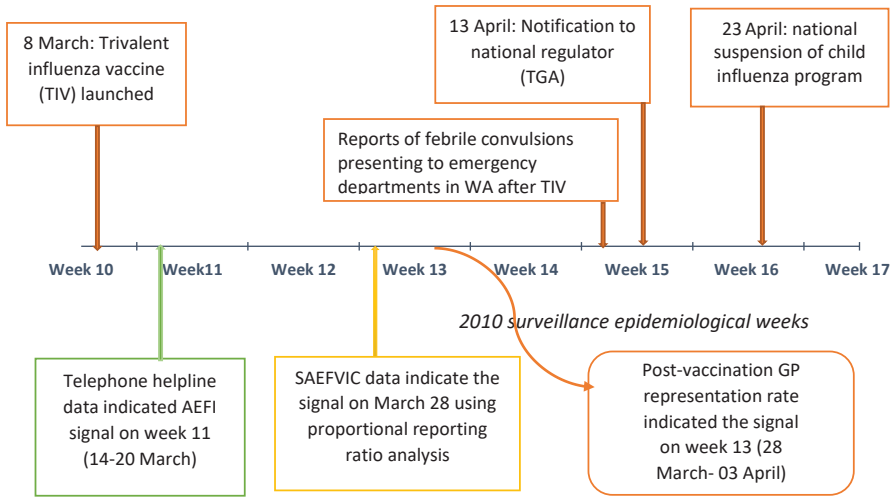
Examined vs Baseline influenza vaccination year	Age category	Acceptable post-vaccination GP consultation rate	Post-vaccination GP consultation rate signal duration in weeks	Historical AEFI signal (yes/no)
2010 vs 2008 and 2009 combined	6 months–9 years	ORA of 2	weeks 13–18	Yes, on week 15
		ORA of 1.5	weeks 14–31	
2012 vs 2009 and 2011 combined	6 months–9 years	ORA of 2	weeks 14–31	No
		ORA of 1.5	weeks 18–31	
2015 vs 2013 and 2014 combined	19–64 years	ORA of 1.5	weeks 16–35	Yes, on week 18
2016 vs 2013 and 2014 combined	10–18 years	ORA of 1.5	weeks 15–19	No
2017 vs 2014 and 2016 combined	6 months–9 years	ORA of 2	Weeks 18–31	No
		ORA of 1.5	Weeks 18–31	
	10–18 years	ORA of 2	Weeks 22–31	No
		ORA of 1.5	Weeks 18–31	

Notes:

For the GP data examined annually between 2008 and 2017 (over ten years), this method using either the ORA=1.5 or 2 criteria, was able to identify all the two historical AEFI signals occurred in Australia in 2010 and 2015. This method however also indicated additional signals in three of eight vaccination years without a historical AEFI signal.

ORA –alternative odds ratio; ORA=2 refers a two-fold increase in the odds of baseline rate; ORA=1.5 refers a 50% increase in the odds of baseline rate; signal was declared if the LLR≥1 (corresponding

Figure 3: Timeline of 2010 AEFI signal detection using different data sources (week 10 began on 7 March and week 17 ended on 1 May), adapted from previous publication.[30]



Conclusion

Healthcare attendance rate after vaccination can be a sensitive proxy measure of AEFI signal monitoring, but use should be in the context of multiple and integrated AEFI surveillance systems, as it is less specific. Crucially, the de-identified dataset used for the retrospective analysis is potentially available in near real-time, updating daily.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary Figure 1: End of surveillance period all cause post-vaccination GP consultation rate on day 1-7 after vaccination by year and age groups.

Supplementary Table 1: Seasonal influenza vaccines available for use in Australia from 2010–2017.

Supplementary Table 2: Seasonal influenza vaccines doses administered and demographic characteristics of vaccinated individuals, 2008–2017.

Supplementary Table 3: End of season incidence rate ratios (IRR) of GP representation by age group on days 1–7 following influenza vaccination, 2008–2017.