PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Active surveillance of 2017 seasonal influenza vaccine safety: an observational cohort study of individuals aged 6 months and older in Australia
AUTHORS	Pillsbury, Alexis; Glover, Catherine; Jacoby, Peter; Quinn, Helen; Fathima, Parveen; Cashman, PM; Leeb, Alan; Blyth, Christopher C.; Gold, Michael; Snelling, Tom; Macartney, Kristine

VERSION 1 – REVIEW

REVIEWER	Andreia Leite London School of Hygiene and Tropical Medicine, UK
REVIEW RETURNED	19-Apr-2018

GENERAL COMMENTS	This is a well-written paper on near real-time influenza, participant-based vaccine safety surveillance. However, I have a few questions to improve the paper: 1 - It would be useful to mention (possibly in the introduction) what are the Australian recommendations regarding influenza vaccine administration. 2 - This is a near real-time surveillance study based on SMS sent 3 days post-immunisation. However there is no indication of the participant's time till response (for those who replied). I suggest you include this information. 3 - In the Discussion you provide examples of existing near real time systems (page 14/15, lines 38-onwards). You mention US rapid cycle analysis and its limitations regarding timeliness. However this system differs from ours in terms of the events captured. I suggest you elaborate on the discussion regarding difference between existing system in this regard (i.e. events captured) 4 - You do provide a paragraph on the limitations and future developments of the system. However there is no indication regarding the place/importance of this system in the wider picture of post-licensure vaccine pharmacovigilance systems/methods. I suggest you include such reference. This will help understanding the importance and usefulness of existing systems in this area.

REVIEWER	Caterina Rizzo Istituto Superiore di Sanità, Rome, Italy
REVIEW RETURNED	01-Jun-2018

GENERAL COMMENTS	The article describes the active surveillance of 2017 seasonal influenza vaccine safety in individuals aged >6 months in Australia. The methodology proposed also included a specific methods to identify safety signals of influenza vaccines administered in Australia, is very interesting especially because

	seems to permits nearly real-time evaluations of different influenza vaccines by age and brand. The manuscript is well written and clear however, it needs some minor improvement before considering it publishable: - Introduction: please include the influenza vaccine recommendations in Australia for the 2016/2017 season in order to give an idea of the target population included in the study. - Patient involvement section: the patient's involvement strategy should be clarified and better defined. Is it a cohort of resident population? Do they report other heath info such as chronic conditions? please give more details - Results (page 12): in the text it is stated that among female participants aged 15-49 years from whom pregnancy status was available 15.2% were pregnant, but this number is not consistent with that reported in Table 1 - Table 1 please clarify the denominator of the percentage reported - It is not clear form the manuscript if in the medically attended AEFI there were any severe reaction reported that needs to be specified. Form the AUS Vax Safety surveillance do not seems to be any severe reaction. It would be useful to specify if such information were recorded and in case yes if they were classified according to the WHO causality assessment.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Andreia Leite
Institution and Country: London School of Hygiene and Tropical Medicine, UK
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This is a well-written paper on near real-time influenza, participant-based vaccine safety surveillance. However, I have a few questions to improve the paper:

1 - It would be useful to mention (possibly in the introduction) what are the Australian recommendations regarding influenza vaccine administration.

Thank you for the helpful advice. We have added this information to the end of the first paragraph of the Methods section. That paragraph now reads:

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.

2 - This is a near real-time surveillance study based on SMS sent 3 days post-immunisation. However there is no indication of the participant's time till response (for those who replied). I suggest you include this information.

This is a great suggestion. We have added this information to the beginning of the second paragraph of the Results section. That paragraph now reads:

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).

3 - In the Discussion you provide examples of existing near real time systems (page 14/15, lines 38-onwards). You mention US rapid cycle analysis and its limitations regarding timeliness. However this system differs from ours in terms of the events captured. I suggest you elaborate on the discussion regarding difference between existing system in this regard (i.e. events captured)

To address the above suggestion, we have amended the end of the fifth paragraph in the Discussion (see track changes in the revised manuscript) as detailed below:

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 can monitor (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 unspecified AEFI without relying on complex analytical methods.

4 - You do provide a paragraph on the limitations and future developments of the system. However there is no indication regarding the place/importance of this system in the wider picture of post-licensure vaccine pharmacovigilance systems/methods. I suggest you include such reference. This will help understanding the importance and usefulness of existing systems in this area.

Thank you and we agree. In response, we have added the following paragraphs to the end of the Discussion:

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 ensures 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 has 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.

Reviewer: 2
Reviewer Name: Caterina Rizzo
Institution and Country: Istituto Superiore di Sanità, Rome, Italy
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The article describes the active surveillance of 2017 seasonal influenza vaccine safety in individuals aged >6 months in Australia. The methodology proposed also included a specific methods to identify safety signals of influenza vaccines administered in Australia, is very interesting especially because seems to permits nearly real-time evaluations of different influenza vaccines by age and brand.
The manuscript is well written and clear however, it needs some minor improvement before considering it publishable:

- Introduction: please include the influenza vaccine recommendations in Australia for the 2016/2017 season in order to give an idea of the target population included in the study.

As detailed in response to the first reviewer above who made the same suggestion, we have added the following information to the end of the first paragraph of the Methods section:

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.

- Patient involvement section: the patient's involvement strategy should be clarified and better defined. Is it a cohort of resident population? Do they report other heath info such as chronic conditions? please give more details

Thank you for your feedback. Below we endeavour to provide additional details as requested by the reviewer. The highlighted section has been included in the revised manuscript.

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 vaccine from a participating provider or clinic. More details are included in the Methods section regarding each of these three platforms. In summary, eligible participants are those who have received an influenza vaccine from an immunisation provider/clinic that has chosen to employ a technological platform that feeds data into AusVaxSafety surveillance. The response to the reviewer comment above details who is eligible for Australian government-funded influenza vaccines. The patient details that AusVaxSafety obtains are de-identified, as explained in the Methods section, and include basic demographic details, details on which vaccines were given, adverse events reported, and any medical attention sought. We do not currently obtain information regarding participants' underlying medical conditions.

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.

- Results (page 12): in the text it is stated that among female participants aged 15-49 years from whom pregnancy status was available 15.2% were pregnant, but this number is not consistent with that reported in Table 1

The text on page 12 refers to female participants aged 15-49 years for whom pregnancy status was available. There were 13,242 women aged 15-49 years who provided data. Thus, 15.2%, or 2,018/13,242, of these women were pregnant. Table 1 uses all participants with pregnancy status available as the denominator. Hence, only 2.8%, or 2,018/72,951, of all participants (of any age or sex) were pregnant.

- Table 1 please clarify the denominator of the percentage reported

The denominator for Table 1 is all participants (73,892 as stated in the table caption) unless detailed in the table footnotes.

- It is not clear form the manuscript if in the medically attended AEFI there were any severe reaction reported that needs to be specified. Form the AUS Vax Safety surveillance do not seems to be any severe reaction. It would be useful to specify if such information were recorded and in case yes if they were classified according to the WHO causality assessment.

If a participant reported that they experienced an adverse event following immunisation, the participant has the opportunity to provide further details regarding specific events experienced in an online survey. The adverse events solicited by AusVaxSafety in this survey are listed in eTable2, and include the more serious adverse events of convulsions/seizures and non-responsiveness/loss of consciousness. Additionally, participants have the opportunity to report any adverse event, including serious adverse events, in the "Other" category, which enables a detailed free text response.

Rates of medical attendance were 0.4% among all participants and 1.0% for those aged 6 months – 4 years.

Systems are in place for GPs and/or local health department representatives to follow up medically attended events. Unfortunately, this does not happen uniformly, and such events are not classified using the WHO's causality guidelines. However, in the instance of a safety signal being generated, AusVaxSafety will ensure that individuals reporting the event of interest are followed up, and investigation of the safety signal would be undertaken at the direction of the Australian Government Department of Health.

In 2017, for those who reported seeking medical attendance who were followed up, none of these events was categorised as serious according to the definition of serious adverse event endorsed by Australia's Therapeutic Goods Administration (TGA). Medically attended events reported included symptoms like influenza-like illness, irritability, and injection site reactions. Most who reported seeking medical attention attended a GP and not an emergency department.

To assist in explaining elements of the above response more clearly, the manuscript has been revised as follows.

The fifth paragraph in the Methods section has been amended to read:

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]

The following sentence was added to the end of the first paragraph in the Results section:

For those MAs that were followed up, none of these events was categorised as serious.

VERSION 2 – REVIEW

REVIEWER	Andreia Leite London School of Hygiene and Tropical Medicine, UK
REVIEW RETURNED	31-Jul-2018

GENERAL COMMENTS	Many thanks for addressing the comments and suggestions. The manuscript has improved and it now seems suitable for publication.