



Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Vaxtracker: Active on-line surveillance for adverse events following inactivated influenza vaccine in children



Patrick Cashman^{a,*}, Sarah Moberley^a, Craig Dalton^a, Jody Stephenson^a, Elissa Elvidge^a, Michelle Butler^a, David N. Durrheim^{a,b}

^a Hunter New England Population Health, Newcastle, NSW 2287, Australia

^b Hunter Medical Research Institute, 1 Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia

ARTICLE INFO

Article history:

Received 30 March 2014
Received in revised form 21 June 2014
Accepted 15 July 2014
Available online 28 July 2014

Keywords:

Vaccine safety
Adverse Events Following Immunisation (AEFI)
Post marketing surveillance
Active surveillance
Online survey
Influenza vaccine

ABSTRACT

Vaxtracker is a web based survey for active post marketing surveillance of Adverse Events Following Immunisation. It is designed to efficiently monitor vaccine safety of new vaccines by early signal detection of serious adverse events. The Vaxtracker system automates contact with the parents or carers of immunised children by email and/or sms message to their smart phone. A hyperlink on the email and text messages links to a web based survey exploring adverse events following the immunisation. The Vaxtracker concept was developed during 2011 ($n=21$), and piloted during the 2012 ($n=200$) and 2013 ($n=477$) influenza seasons for children receiving inactivated influenza vaccine (IIV) in the Hunter New England Local Health District, New South Wales, Australia. Survey results were reviewed by surveillance staff to detect any safety signals and compare adverse event frequencies among the different influenza vaccines administered. In 2012, 57% ($n=113$) of the 200 participants responded to the online survey and 61% (290/477) in 2013. Vaxtracker appears to be an effective method for actively monitoring adverse events following influenza vaccination in children.

Crown Copyright © 2014 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-SA license (<http://creativecommons.org/licenses/by-nc-sa/3.0/>).

1. Introduction

Inactivated influenza vaccines (IIV) are prepared annually with limited safety and efficacy trials able to be performed before a new influenza strain is included in the formulation [1]. Active post marketing surveillance of IIV has not routinely been conducted in Australia. Local side effects, such as swelling, redness and pain at the injection site, are common, occurring in more than 10% of recipients. Fever, tiredness and myalgia also occur commonly (1–10%). In children less than five years of age, these adverse events may be more pronounced [2].

In Australia in 2010 the inactivated CSL IIV caused an excess of febrile reactions including febrile convulsions (up to 1 per 100) [3]. A joint working group of the Therapeutic Goods Administration (TGA) and the Australian Technical Advisory Group on

Immunisation (ATAGI) investigated data on the safety of different brands of 2010 and 2011 IIVs in children and adults. In its December 2011 report the working group recommended that: “options for enhanced surveillance, designed to detect clinically important differences in the safety profile of influenza vaccines, be explored to reinforce public and provider confidence in program safety” [4]. A separate independent investigation recommended that Adverse Events Following Immunisation (AEFI) reporting by consumers themselves be incorporated into the notification system [5]. A subsequent review undertaken by former Australian Chief Medical Officer, Professor John Horvarth AO, recommended more timely AEFI reporting and electronic collection of vaccine usage and safety data [6].

A novel active online surveillance system (Vaxtracker) was trialled for Adverse Events Following Immunisation during the 2012 and 2013 influenza seasons. Vaxtracker is based on the success of the ‘Flutracking’ influenza-like-illness surveillance platform, which has been used in Australia nationally since 2006 and successfully engages over 15,000 community members in regular weekly reporting during each influenza season [7]. In 2011, 21 children were enrolled using email surveys alone to refine the surveillance concept. In 2012, 200 children were enrolled from 16 general medical practices in Newcastle and the Children’s Hospital Westmead, Sydney. This testing resulted in: a new platform that was more

* Corresponding author. Tel.: +61 2 49246477; fax: +61 2 49246490.

E-mail addresses: Patrick.Cashman@hnehealth.nsw.gov.au (P. Cashman), sarah.moberley@gmail.com (S. Moberley), Craig.Dalton@hnehealth.nsw.gov.au (C. Dalton), Jody.Stephenson@hnehealth.nsw.gov.au (J. Stephenson), Elissa.Elvidge@hnehealth.nsw.gov.au (E. Elvidge), Michelle.Butler@hnehealth.nsw.gov.au (M. Butler), David.Durrheim@hnehealth.nsw.gov.au, David.Durrheim@newcastle.edu.au (D.N. Durrheim).

mobile phone browser compatible to enhance readability and interaction on a mobile phone and an automated email to Vaxtracker team members alerting them that a serious symptom had been reported (hospitalisation and seizure). We report on the evaluation of the systems performance in the 2013 influenza seasons.

2. Methods

In 2013, 15 large general medical practices in the Newcastle metropolitan and Tamworth rural population centres in northern NSW participated (Fig. 1). The general practice clinics were visited by a Vaxtracker staff member to demonstrate the system and answer questions. Prior to influenza vaccination, participating clinics provided parents and carers with an information sheet (Fig. 2) on the Vaxtracker programme and they were asked if they would like to participate. Following parental consent, clinic staff enrolled participants by entering the child's name and their parent or carer's contact details (email, mobile phone number or both) and brand of IIV administered into a simple secure web-based form.

The Vaxtracker system automated contact with the parents or carers of immunised children by email and/or sms message to their smart phone after the child has received an influenza immunisation. Each participant was automatically contacted to complete two online surveys, the first to explore for initial reactions and a final survey to capture any late reactions. The first survey reminder was sent three days after the immunisation to facilitate timely signal detection and the final survey 42 day post-vaccination, which was considered adequate to detect rare late adverse events such as Guillain-Barré syndrome. Participants who did not respond to the first survey did not progress to be sent the final survey on day 42.

Children who receive IIV for the first time are recommended to have two doses of IIV at a one month interval [2]. These children received an automated reminder when the second IIV dose was due (one month later) and a link to the Vaxtracker survey was sent three days after the second dose due date. Participants received a link to a Vaxtracker online survey after both dose one and dose two of IIV.

The online survey sent on day 3 after the first and second IIV doses was structured to collect information on 11 symptoms, while the day 42 survey for late adverse events only enquired about visits to hospital. Delayed participant survey responses were accepted until the end of the influenza season.

The online survey took less than a minute for parents and carers to complete if there were no symptoms to report and a few minutes if symptoms were reported. To decrease data entry for the clinic staff date of birth and gender were entered on-line by survey respondents. The survey provided simple check-boxes and free text boxes as required.

The 2013 Vaxtracker online survey was simplified by adding a screening question so that the 11 symptom questions only appeared if the parent or carer clicked "yes" to the question: "Did (child's first name) experience and kind of reaction, illness or discomfort after the vaccination?" An answer of "yes" to any of the symptom questions in the first online survey activated a drop down box with additional questions regarding severity, whether medical advice was sought and duration of the event. The 11 symptoms explored in the 2012 and 2013 pilot studies were: reaction at injection site, fatigue, influenza-like illness, muscle aches, headaches, joint pain, fever, lymph node swelling, weakness, seizures and "other" symptoms.

Recruitment and adverse events were reviewed by surveillance staff to detect any signal of adverse events. Data on recruitment and adverse events were available through the dedicated secure website and was downloaded twice weekly to monitor adverse events, recruitment by each clinic and prepare weekly reports. An automated email alert to the Vaxtracker team was generated when a seizure or hospitalisation was reported so that review could occur

rapidly. Survey completion rates were calculated as the number of participants who completed the survey divided by the total participants due to have completed the survey. Weekly reports were shared with health departments at State and National level and a final report with the Therapeutic Goods Administration (TGA).

All serious adverse events including high fever, seizures, unresolved systemic symptoms or hospitalisation were followed up by telephone by a registered nurse and reviewed with a public health physician and if required notified to NSW Health through usual AEFI notification channels. Adverse events were described according to demographic characteristics of the participants, previous vaccine history and the brand of IIV administered. Factors associated with adverse events were investigated by comparing participants who experienced an adverse event with those who did not experience an adverse event by the following factors; age (*t* test of mean age), gender and first year of IIV administration (comparison of proportions using Pearsons Chi-squared test). The analysis controlled for gender, age by year and whether first time influenza vaccine was received in the current season. There is a Vaxtracker Standing Operating Procedure for validating reports that are questionable with attending clinicians.

Surveillance of AEFIs is conducted in NSW under the NSW Public Health Act, therefore ethical review was not required for this enhancement to existing surveillance.

3. Results

Between 21 March and 30 June 2013, a total of 477 participants who received IIV were recruited to Vaxtracker. Of these 290 (61%) parents or carers completed the Vaxtracker online survey at day 3 following the first dose of IIV with 134 (47%) of those went on to complete the final survey at day 43 (Fig. 3). Most respondents to the online survey were aged between 5 years and 9 years 11 months (55%), 32% were aged between 2 and 5 years and 12% aged less than 2 years. 53% of respondents were males ($n = 154$).

The mean number of days from sending the web survey link to completion of the survey dispatched on day 3 was 3.33 days ($n = 290$). The mean number of days from sending web survey link to completion of the final 42 day survey was 2.01 days ($n = 120$).

Survey completion rates were highest when both email and mobile phone contact details were provided ($n = 35$, 74%) compared to email ($n = 135$, 58%) or mobile phone ($n = 120$, 60%) alone. Among the 477 participants, Vaxigrip (Sanofi) ($n = 334$) was the most commonly administered IIV, followed by Fluarix (GlaxoSmithKline) ($n = 78$), Influvac (Abbott) ($n = 59$), Vaxigrip Junior (Sanofi) ($n = 4$) and Agrippal (Novartis) ($n = 2$).

Eighteen percent of respondents in the day three survey (52/290) reported any reaction following dose 1 across all IIV brands, three of whom reported receipt of another vaccine within one week of IIV administration. Over-all 8% of respondents (23/290) experienced a local reaction and 3% (8/290) reported fever.

When considering specific IIV brands, Vaxtracker found a higher rate of all reported reactions following Vaxigrip/Vaxigrip jnr (21.5% (95% CI: 16.0–27.0%); $n = 46/214$) compared to all the other inactivated vaccine brands administered to participants (7.9% (95% CI: 1.8–14.0%); $n = 6/76$, $p = 0.0079$) (Table 1). However for fever there was no significant difference between Vaxigrip/Vaxigrip jnr (2.8% (95% CI: 0.6–5.0%); $n = 6/214$) and the other brands of IIV (2.6% (95% CI: 0.0–6.2%); $n = 2/76$, $p = 0.9270$).

Participants who had received an IIV in the previous year also appeared to have a higher rate of reactions than participants who did not (25.8% versus 13.2% respectively). The odds of having a reaction for those who had IIV last year compared to those who did not is 1.95 ($p = 0.036$) when controlling for vaccine type, gender and age.

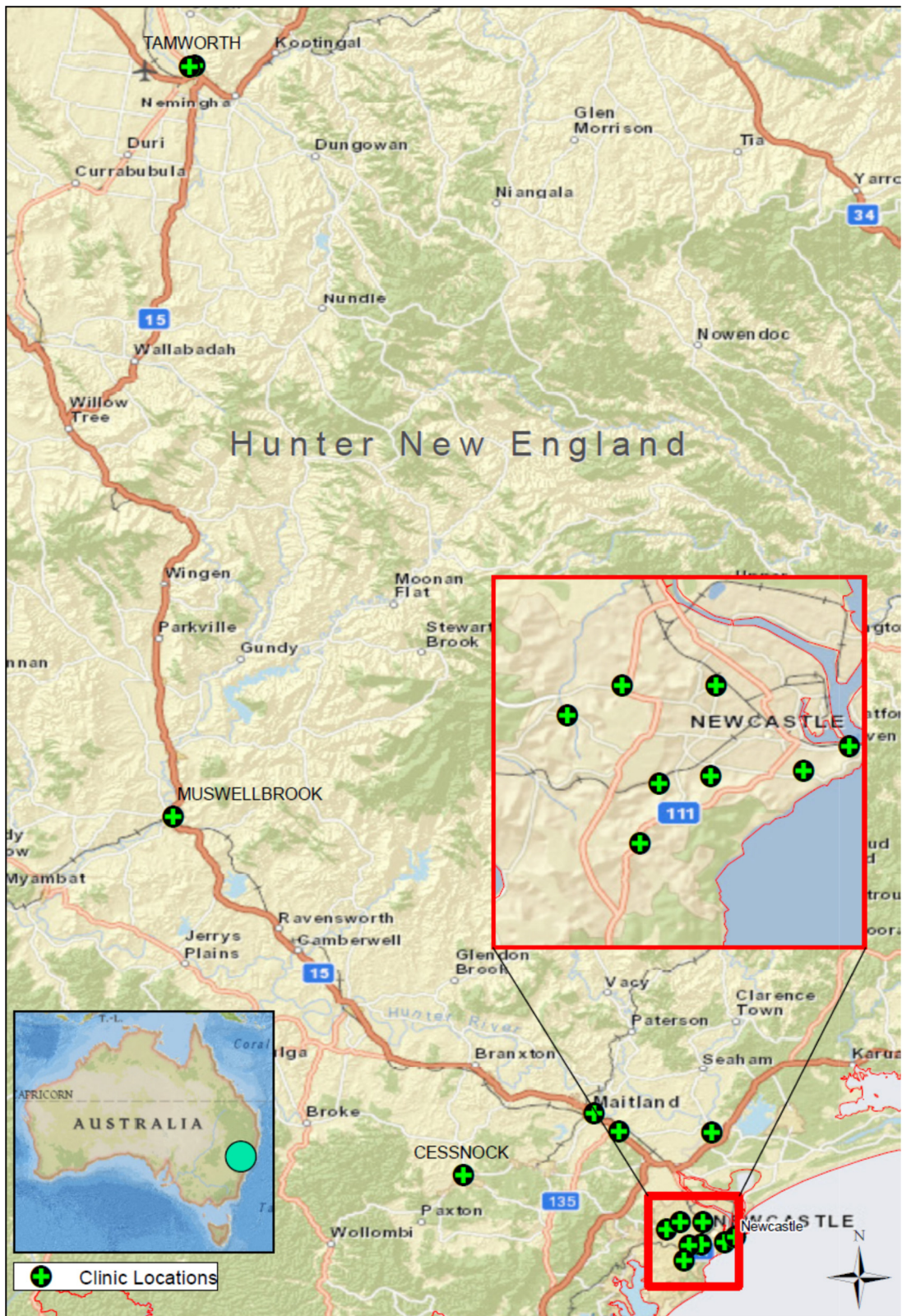


Fig. 1. Vaxtracker clinic locations 2013, Hunter New England Local Health District, NSW, Australia.

Vaxtracker – monitoring children for adverse reactions to vaccines

Vaxtracker is an online survey that checks in with parents after their children are vaccinated to monitor for adverse reactions to vaccination.

What happens when you join?

- You will complete this form providing your email address or mobile phone number (if you have a smart phone with internet access) and your child's name.
- The clinic will enter this information into a confidential online database plus the date of vaccination and the brand of influenza vaccine your child received.
- 3 days after the vaccination, you will receive an email or SMS link to an online survey with questions about any reactions.
- You will receive a final online survey 42 days after the first influenza vaccination.
- The survey takes about 30 seconds to complete if your child has not had a reaction but could take several minutes if there was a reaction to report.
- If your child has a reaction and you have agreed to a follow up phone call, a nurse may contact you to ask for further information.

How to join

Please complete this form and return it to the clinic administrative staff.

Yes, I would like Vaxtracker to email me and monitor my child for adverse reactions to influenza immunisation.

Childs name and surname: _____

Parents email address & or mobile number (smart phones only) : _____

Fig. 2. Vaxtracker 2013 parent information sheet.

Of the 134 respondents who completed the final survey, three (2.2%) reported a hospitalisation in the 42 day period following vaccination which triggered an email alert and clinical review on all three occasions. However, on clinical review each hospitalisation episode was determined to be unrelated to vaccination (two asthmatic children had experienced asthma attacks and one child had suffered a fracture following an accident).

4. Discussion

The Vaxtracker surveillance system found an intriguing difference in adverse event reaction rates between influenza vaccine brands in this cohort of children. Most focus is on fever following the febrile convulsion experience in Australia in 2010 and importantly Vaxtracker found no difference in rates of parent reported fever across the brands of IIV.

Table 1

Adverse events following the first dose of inactivated influenza vaccine by brand in 2013 Vaxtracker survey participants. Participants could report multiple adverse events.

	Agrippal	Fluarix	Influvac	Vaxigrip	Vaxigrip Jnr	Total
All participants	2	78	59	334	4	477
Participants 1st survey	1	43	32	212	2	290
Any adverse event 1st dose	0	5 (11%)	1 (3%)	46 (22%)	0	52 (18%)
Serious adverse event	–	0	0	0	–	0
Sought medical attention	–	0	0	4	–	4
Reaction at injection site	–	1	1	21	–	23 (8%)
Fever	–	1	1	6	–	8 (3%)
Headaches	–	2	0	7	–	9
Fatigue	–	1	0	14	–	15
Joint pain	–	0	0	6	–	6
Influenza-like illness	–	2	1	9	–	12
Lymph node swelling	–	1	0	2	–	3
Seizures	–	0	0	0	–	0
Muscle aches	–	2	0	12	–	14
Weakness	–	1	0	1	–	2
Other symptoms	–	1	0	8	–	9

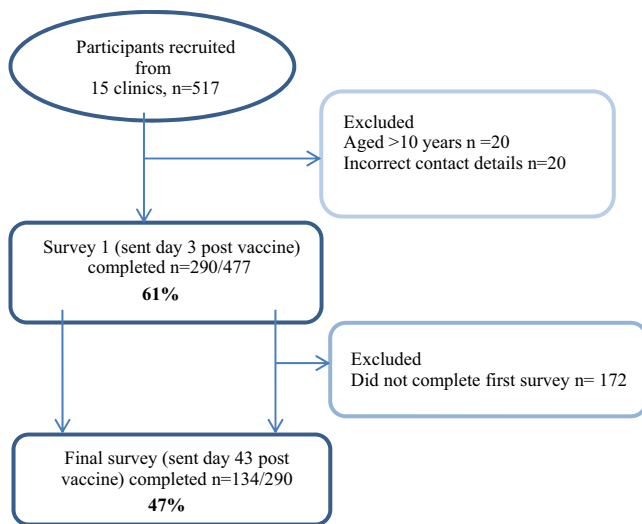


Fig. 3. Vaxtracker recruitment and retention, 2013.

Passive surveillance systems are able to identify safety signals, but are subject to known limitations, due to underreporting, delayed reporting and a lack of denominator data. Active surveillance in a defined cohort of vaccines can complement passive surveillance by overcoming problems of delayed and underreporting and enabling calculation of adverse event rates. Recent studies internationally have emphasised the importance of active surveillance to detect important signals early so that appropriate investigations can be launched and necessary actions taken [8,9].

Internationally the usefulness of Patient Reported Outcomes (PROs) utilising available internet tools has been increasingly recognised. There is evidence that in relation to adverse events PROs can identify real-world signals earlier and in higher volume, accurately characterise the signals, allow a focus on specific events or populations of interest, and permit ongoing efficient safety monitoring [10].

The finding that there was a significantly higher rate of reactions in participants who received IIV in the previous year deserves further investigation as it has not been a consistent finding in previous studies [3].

The initial practice visit by Vaxtracker staff of this pilot phase could be replaced by a brief diagrammatic user guide or online web demonstration to further improve efficiency and reduce the cost of the roll out phase. We estimate that once established the ongoing human resources to operate the system are not great as survey results provide sufficient information for assessment and very few respondents require subsequent telephone clarification of clinical details or support. After the Vaxtracker survey was completed by respondents, case review and data analysis for signal detection quickly take place. The automatic management of survey dispatch and return of completed surveys and email alerts has allowed for the efficient and prompt review of AEFIs and rapid data analysis and rate calculation.

It is essential to reassure the community of vaccine safety and to prompt early investigation should severe reactions occur or if there is an unexpected increase in the frequency of clinical events [11]. The Vaxtracker active surveillance system achieved encouraging completion rates. These were found to be higher where parents received both mobile phone and email reminders.

Feedback and a certificate of appreciation were provided to all General Practice clinics that enrolled participants. Respondents who reported serious AEFI were contacted by telephone to discuss their report, ensure that appropriate clinical management had occurred if required and enquire whether symptoms had resolved.

There was no formal feedback to respondents in this pilot but plans are underway to make Vaxtracker safety data available to the public on a website as the programme is expanded. Previous studies have found differences in adverse event rates between influenza vaccine brands in children [12]. Our findings support the need to confirm this differential rate in a larger cohort of children.

Vaxtracker has been adopted for active surveillance of IIV in the community by the AusVaxSafety consortium and expanded for use in two Australian states, New South Wales and Victoria. Sites selected include paediatric hospitals and general practice settings. To maintain the simplicity of Vaxtracker data for clinicians the collection of additional data to provide a richer analysis, such as medical conditions, will be collected from respondents when completing the online survey.

5. Conclusions

The need to ensure high quality active surveillance for safety signals when introducing new vaccines at population level has been increasingly recognised. Early experience with the Vaxtracker on-line surveillance system suggests that it provides effective post-marketing surveillance, which is ideally suited to the introduction of vaccines for children. It allowed rapid analysis of reported adverse events by public health authorities.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We thank Stephen Clarke for his assistance with the online software and database development. We would like to acknowledge the general practice clinics and Vaxtracker participants for their contribution to vaccine safety surveillance. We would also like to acknowledge Dr. Bronwen Harvey at TGA for generous advice and proof reading.

Whilst the Australian Department of Health provided financial assistance to Hunter New England Population Health, the material contained in the reports produced by the Centre should not be taken to represent the views of the Australian Department of Health. The content of the reports is the sole responsibility of the Hunter New England Population Health.

References

- [1] European Medicines Agency. Explanatory note on the withdrawal of the note for guidance on harmonisation of requirements for influenza vaccines (CPMP/BWP/214/96) and of the core SmPC/PL for inactivated seasonal influenza vaccines; 2013. EMA/CHMP/VWP/232674/2013.
- [2] Australian Technical Advisory Group on Immunisation. The Australian immunisation handbook. 10th ed. Canberra: National Health and Medical Research Council; 2013.
- [3] Armstrong PK, Dowse GK, Effler PV, Carcione D, Blyth CC, Richmond PC, et al. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. *BMJ Open* 2011;1:e000016. <http://dx.doi.org/10.1136/bmjopen-2010-000016>.
- [4] Joint Australian Technical Advisory Group on Immunisation (ATAGI) and Therapeutic Goods Administration (TGA) Seasonal Influenza Vaccine Safety Ad Hoc Working Group. Review of data on the safety of seasonal influenza vaccines, particularly Fluvax (CSL Biotherapies) in adults and children >10 years; 2012.
- [5] Stokes B. Ministerial review into the public health response into the adverse events to the seasonal influenza vaccine. Department of Health, Government of Western Australia; 2010.
- [6] Horvath J. Review of the management of adverse events associated with Panvax and Fluvax. Commonwealth of Australia; 2011.
- [7] Dalton CB, Carlson SJ, Butler MT, Elvidge E, Durrheim DN. Building influenza surveillance pyramids in near real time, Australia. *Emerg Infect Dis* [Internet] 2013;(November (11)). <http://dx.doi.org/10.3201/eid1911.121878>.

- [8] Patel MM, Haber P, Baggs J, Zuber P, Bines JE, Parashar UD. Intussusception and rotavirus vaccination: a review of the available evidence. *Expert Rev Vaccines* 2009;8(November (11)):1555–64.
- [9] Global Advisory Committee on Vaccine Safety (GACVS), WHO secretariat. Global safety of vaccines: strengthening systems for monitoring, management and the role of GACVS. *Expert Rev Vaccines* 2009;8(June (6)): 705–16.
- [10] Banerjee AK, Okun S, Edwards IR, Wicks P, Smith M, Mayall S, et al. Patient-Reported Outcome Measures in Safety Event Reporting – PROSPER Consortium Guidance. *Drug Saf* 2013;36:1129–49.
- [11] Mehta U, Milstien JB, Duclos P, Folb PI. Developing a national system for dealing with adverse events following immunization. *Bull World Health Organ* 2000;78(2):170–7.
- [12] Petousis-Harris H, Poole T, Turner N, Reynolds GI. Febrile events including convulsions following the administration of four brands of 2010 and 2011 inactivated seasonal influenza vaccine in NZ infants and children: the importance of routine active safety surveillance. *Vaccine* 2012;30(33): 4945–52.