



Active SMS-based influenza vaccine safety surveillance in Australian children



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ARTICLE INFO

Article history:

Received 12 July 2017

Received in revised form 27 October 2017

Accepted 30 October 2017

Available online 8 November 2017

Keywords:

Vaccine safety

Active surveillance

Influenza vaccine

Adverse event following immunisation

ABSTRACT

Introduction: Australia's novel, active surveillance system, AusVaxSafety, monitors the post-market safety of vaccines in near real time. We analysed cumulative surveillance data for children aged 6 months to 4 years who received seasonal influenza vaccine in 2015 and/or 2016 to determine: adverse event following immunisation (AEFI) rates by vaccine brand, age and concomitant vaccine administration.

Methods: Parent/carer reports of AEFI occurring within 3 days of their child receiving an influenza vaccine in sentinel immunisation clinics were solicited by Short Message Service (SMS) and/or email-based survey. Retrospective data from 2 years were combined to examine specific AEFI rates, particularly fever and medical attendance as a proxy for serious adverse events (SAE), with and without concomitant vaccine administration. As trivalent influenza vaccines (TIV) were funded in Australia's National Immunisation Program (NIP) in 2015 and quadrivalent (QIV) in 2016, respectively, we compared their safety profiles.

Results: 7402 children were included. Data were reported weekly through each vaccination season; no safety signals or excess of adverse events were detected. More children who received a concomitant vaccine had fever (7.5% versus 2.8%; $p < .001$). Meningococcal B vaccine was associated with the highest increase in AEFI rates among children receiving a specified concomitant vaccine: 30.3% reported an AEFI compared with 7.3% who received an influenza vaccine alone ($p < .001$). Reported fever was strongly associated with medical attendance (OR: 42.6; 95% Confidence Interval (CI): 25.6–71.0). TIV and QIV safety profiles included low and expected AEFI rates (fever: 4.3% for TIV compared with 3.2% for QIV ($p = .015$); injection site reaction: 1.9% for TIV compared with 3.0% for QIV ($p < .001$)). There was no difference in safety profile between brands.

Discussion: Active participant-reported data provided timely vaccine brand-specific safety information. Our surveillance system has particular utility in monitoring the safety of influenza vaccines, given that they may vary in composition annually.

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1. Introduction

The composition of northern and southern hemisphere seasonal influenza vaccines may vary every 6 months depending upon

anticipated virus circulation and the effectiveness of recent vaccine strains. The availability of quadrivalent influenza vaccines (QIVs) which incorporate a second B strain in addition to the one B and two A strains already included in the trivalent influenza vaccine (TIV), has added to the variety of vaccines utilised. These variations in composition, the short time required to prepare each new seasonal vaccine, and the paucity of head-to-head comparison data on safety derived from clinical studies, underpin the need to have timely post-marketing surveillance of vaccine safety profiles. Although the European Medicines Agency (EMA) recently suggested that annual vaccine brand-specific safety data be provided by manufacturers [1], few studies appear to have provided those data using population-based denominators [2].

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In Australia, recommendations were made to strengthen vaccine adverse event reporting following an unexpected increase in fever and febrile seizures in young children following administration of one brand of influenza vaccine (Fluvax; BioCSL (now Seqirus)) in 2010 [3]. This major safety incident led to a 3 month suspension of paediatric influenza immunisation, withdrawal of the vaccine [4,5] and a subsequent decrease in public confidence and uptake of paediatric influenza vaccination [6,7]. Two subsequent reviews highlighted that vaccine safety surveillance needed improved transparency with more timely release of information to the public [8,9].

We developed a novel, active, participant-based, national sentinel vaccine safety surveillance system, AusVaxSafety, following the 2010 incident. Initially, AusVaxSafety has focused on reporting brand-specific safety data on influenza vaccines administered to Australian children [10]. Data are collated, analysed and reported to public health authorities on a weekly basis. In addition to these near real-time results, at the end of each season detailed analyses are performed. The aim of this study was to: (a) provide a brief overview of the real-time reporting of influenza vaccine safety data in Australian children in 2015 and 2016, and; (b) analyse cumulative data for the same period, comparing available vaccine brands, QIV and TIV vaccines, and the effect of concomitant vaccine administration.

2. Methods

2.1. AusVaxSafety surveillance

Under the Australian National Immunisation Program (NIP), influenza vaccine is funded and free at point of care for children aged 6 months to 4 years who have high risk medical conditions (including heart or lung disease; asthma; chronic neurological conditions; immune compromising conditions or other chronic illnesses such as diabetes [11]) and/or who identify as Aboriginal and/or Torres Strait Islander. One state, Western Australia, has funded influenza vaccination for all children in this age group since 2008.

All children aged 6 months to 4 years at the time of vaccination during the 2015 and 2016 influenza vaccination seasons (defined by vaccine availability as 1 April–31 August 2015 and 1 April–4 September 2016) at participating national sentinel General Practice (GP) clinics, hospitals, community clinics or other primary healthcare providers including Aboriginal Medical Services (AMSs) were eligible to be included (enrolled) in AusVaxSafety surveillance following routine receipt of any registered seasonal influenza vaccine. In 2016, QIV replaced TIV as the NIP-funded vaccine, and there were changes to the strains included in the vaccines (Table 1).

All parents/carers of enrolled children received a Short Message Service (SMS) and/or email via one of several AusVaxSafety-contributing computer-based data monitoring platforms (Vaxtracker [12], SmartVax [13] or STARSS (Stimulated Telephone-Assisted Rapid Safety Surveillance [14]) at approximately 3 days after vaccination. Participation at clinics using SmartVax was on an opt-out basis, as this platform routinely sends SMSs to all vaccine recipients; those recruited via Vaxtracker or STARSS opted into enrolment (Table 2). The national AusVaxSafety surveillance system and its monitoring platforms operate under human research ethical approval obtained at 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).

The SMS/email asked whether or not the child had experienced an adverse event, and if so, requested completion of a short survey. Children whose parents/carers replied either 'yes' or 'no' to the SMS/email regarding the occurrence of an adverse event following immunisation (AEFI) were defined as participants. If a child

received 2 doses of influenza vaccine in the same season they were counted twice as a participant, once for each vaccination encounter. As described previously, demographic details available on participants included age, sex and Indigenous status [10]. Vaccine brand was available for both years, and for 2016 data details about which concomitant vaccines were received were available. The survey seeks details on specific adverse events experienced, such as fever, injection site reaction, and rash, and allows parents to report on any 'other' events experienced. It also asks parents/carers whether their child required medical advice or sought medical attention for their adverse event. Serious adverse events (SAEs) were defined as one or more of the following: a seizure requiring emergency department (ED) attendance and/or hospitalisation; an event that resulted in death; was life-threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; was a medically important event or reaction [15]. For all medically attended events, designated public health authorities sought additional clinical details from parent/carers within days of notification, and provided clinical advice and follow up, as necessary.

During the active surveillance periods, de-identified, aggregated AEFI data were summarised in weekly reports made available to Government, immunisation providers and the public. For rapid signal detection, fast initial response cumulative summation (FIR CUSUM) and Bayesian methods were employed. These methods, previously described [10], rely on assessing reported adverse event rates against pre-specified threshold rates to determine whether or not a safety signal, or excess of adverse events, has occurred and requires further investigation. These results are not reported specifically in this analysis but no safety signals occurred.

2.2. Cumulative analysis of 2015 and 2016 influenza surveillance data

For this cumulative analysis of 2015 and 2016 data, descriptive details of participants including gender, age and Indigenous status were provided. Participation rates, the proportion of those who received TIV or QIV, and detail of concomitant vaccination receipt were also analysed. Denominators were based on the total number of respondents.

Adverse event analysis focussed on the most objective parent/carer-reported outcomes of fever and medical attendance. As parent-reported data may be less precise than those derived from prospective clinical trials, under AusVaxSafety medical attendance is viewed as a proxy for a SAE [6] and is considered to be a potentially 'medically important event'.

Fever and medical attendance rates were each compared according to Indigenous status, gender, age (6–<12 months; 12–<24 months; 24–<60 months), vaccine formulation (TIV or QIV), brand and concomitant vaccination. Comparisons were conducted using Pearson's chi-squared and Fisher's exact test, with a p-value of <.05 considered statistically significant. Logistic regression was conducted to examine the association between fever and medical attendance adjusting for variables (Indigenous status, gender, age, vaccine formulation, brand and concomitant vaccination) that may have been potential confounders based on univariate analysis as described above. All data analysis was conducted using Stata 14.

Finally, details regarding the adverse events which were classified as serious were outlined.

3. Results

3.1. Participant demographics and vaccines used

The total number of children enrolled over the two influenza vaccination seasons was 9504: 4394 in 2015 and 5110 in 2016.

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