Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Investigating adverse events following immunisation with pneumococcal polysaccharide vaccine using electronic General Practice data

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ARTICLE INFO

Article history:
Received 15 February 2016
Received in revised form 24 January 2017
Accepted 30 January 2017
Available online xxxx

Keywords:
Adverse events following immunisation
Pneumococcal polysaccharide vaccine
Public health surveillance
Primary health care
Electronic medical records

ABSTRACT

Background: In early 2011, following an increased number of reports of severe vaccine-related injection site reactions, Australian authorities recommended against administering repeat doses of the 23-valent pneumococcal polysaccharide vaccine (23vPPV) in otherwise healthy adults. The aim of this study was to assess a source of electronic medical record data from primary care providers (General Practitioners, GPs), for validity and ability to retrospectively detect this adverse event signal.

Methods: The General Practice Research Network (GPRN) holds data routinely collected from a representative sample of Australian GPs. Data were extracted on persons 18 years or older who had received at least one dose of 23vPPV or influenza vaccine (as comparator) between January 2002 and June 2012. Increases above background levels were assessed using 95% confidence intervals of reaction rates, calculated from the Poisson distribution of counts.

Results: There was an average of 253 practices and 532 GPs contributing data per year. Over the study period there were 95,760 recorded 23vPPV administrations and 823 reactions, of which 233 were local. For influenza vaccine the numbers were 683,829 doses, 3001 and 387 respectively. Patterns of vaccinations and reactions were consistent with known safety profiles. There were 3 local reactions following 23vPPV in early 2011 (235/100,000 doses, 95% CI 49–717), which was not significantly different to the historical average (260, 225–298). We estimate that this system could have detected a 3-fold increase over background levels.

Conclusions: Using GP consultation data, we were unable to confirm an increase in local reactions detected by passive surveillance, suggesting that this apparent signal was artefactual. GP consultation data captures large numbers of vaccine recipients and medically attended adverse reactions at low cost. If available in a timely manner and expanded, this system has significant potential for use in validation of apparent signals from passive surveillance.

1. Introduction

In 2005 the 23-valent pneumococcal polysaccharide vaccine (23vPPV) was funded under the Australian National Immunisation Program (NIP) for all persons aged ⩾65 years (population 3.3 million), and recommended or funded for some high risk groups aged <65 years [1]. At least one revaccination was recommended 5 years after the first dose for all persons, while a third dose was recommended for those with medical risk conditions first vaccinated at age <65 years, and Indigenous people at <50 years [1]. Rates of moderate to severe injection site reactions of up to 5% have been reported following 23vPPV, more commonly after revaccination than following the first dose [2,3], and if the dose was given <5 years after the previous dose [2]. Therefore, a peak of second doses, and perhaps local reactions to 23vPPV, may have been anticipated in 2010.

The primary surveillance mechanism for adverse events following immunisation (AEFI) in Australia is passive reporting to the

Abbreviations: 23vPPV, 23-valent pneumococcal polysaccharide vaccine; AEFI, adverse events following immunisation; GPRN, General Practice Research Network; GP, General Practitioner; TGA, Therapeutic Goods Administration.

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http://dx.doi.org/10.1016/j.vaccine.2017.01.063
0264-410X/

Therapeutic Goods Administration (TGA), from immunisation service providers, states and territories and members of the public. In March 2011 a cluster of seven severe local injection site reactions was reported to the TGA. As a result, a batch of the vaccine was recalled and the TGA issued an interim advice to health professionals in April 2011 advising against administering repeat vaccinations of 23vPPV [4]. On further investigation it was determined that the cluster was not caused by a particular batch of vaccine. In December 2011 a review pointed to the larger number of people receiving a second dose compared to other years as a likely contributor, and the Australian Technical Advisory Group on Immunisation recommended that revaccination be restricted to people at highest risk of serious pneumococcal disease [5].

During this safety signal investigation, limitations were identified in the quality of available data, and consequently the evidence underpinning a change in recommendation. Of particular importance were the lack of denominator data (doses administered), and numbers of repeat vs first doses. As vaccination of the elderly in Australia is almost exclusively conducted by General Practitioners (GPs), this study aimed to retrospectively evaluate data from GP clinic databases for the potential to provide an initial adverse event signal, and/or to provide useful information during or after the adverse event investigation.

2. Methods

2.1. The General Practice Research Network

In 2010/11 there were approximately 24,000 practicing GPs in Australia. An estimated 94% recorded at least some, and 65% recorded all, of their clinical records electronically [6]. In 2010/11 MedicalDirector® was the clinic software package used by 55% of computerised GPs [6], down from 73% in 2005 [7]. The General Practice Research Network (GPRN) was established in 1999, as a nationally representative cohort of GPs using MedicalDirector®. Participating GPs allow extraction of most fields from their electronic medical records, with the exception of names and addresses, and free-text clinical notes which may contain identifying information. In this database, individual patients are issued a unique identification number (ID) at each participating practice they attend, and attendances of the same patient at different clinics cannot be linked. GPs and clinics may join, leave or re-join the network at any time. The data have been used for studies on heart disease, diabetes and prescribing patterns, with results published in peer-reviewed journals and for industry market research [8–11].

2.2. Data processing and quality assessment

Data on all patient IDs that were recorded to have received one or more pneumococcal or influenza vaccinations between January 2002 and June 2012, or had an attendance related to receiving a pneumococcal or influenza vaccination, were provided by the GPRN to study investigators. Reactions to trivalent inactivated influenza vaccines were used as a comparator to pneumococcal polysaccharide vaccine. The information used for analysis was patient's age and gender, date of encounter, reason(s) for visiting GP, diagnoses, records of immunisation and description of reaction(s). Free-text clinical notes were not available. Vaccinations given before the age of 18 years were excluded from further analysis, as the area of interest was AEFI with pneumococcal vaccination of adults.

Duplicate records with the same patient IDs at the same practice were deleted. Apparent duplicates - with different IDs at the same practice, but with the same date of birth, gender, dates of encounters, diagnoses, vaccines and other medications for at least three encounters, were also deleted. Data were recoded to correct typographical and other data entry errors.

Data were assessed for internal consistency by comparing the number of vaccine doses, seasonality, vaccination intervals and age at vaccination, with the recommendations for the relevant vaccine, and for factors known to be associated with reactions such as revaccination, gender and age.

2.3. Vaccination records

23vPPV doses recorded within 6 months of a previous dose recorded for a patient ID were assumed to be double entries and ignored, as were influenza vaccinations within 2 months of a previous dose.

The majority of vaccinations had no recorded dose number (84% for 23vPPV and 96% for flu vaccine). Therefore for the same individual, the dose with the earliest vaccination date was regarded as the "first vaccination" and later doses as "repeat" vaccinations.

2.4. Determination of reactions

Recorded reactions to either vaccine were included for analysis if less than 35 days after receipt of either vaccine, or less than 7 days for severe reactions. Reactions including redness, swelling, tenderness, soreness, rash, limitation of arm movement, cellulitis/abscess of the upper limb, and shoulder region diseases, were grouped as 'local reactions'. Severe local reactions (cellulitis/abscess and severe reactions) were included in 'local reactions' and also analysed separately. Reactions including nausea, headache, dermatitis, myalgia, joint pain, fatigue and fever were grouped as 'non-local reactions'. When there was insufficient detail to determine if a reaction was local or non-local (e.g. only "rash" without location) the reaction was included only in the "any reaction" category. Recorded reactions considered unlikely to be related to 23vPPV (eg. "face swelling") were excluded.

Logistic regression was used to test factors for association with local reactions. Data were analysed in Stata 12.

2.5. AEFI signal detection sensitivity

Given the limited number of participating GPs and reactions recorded, the dataset was also assessed for its sensitivity in detecting an increase in AEFI in the one-month period in which the batch recall and increase in reports to TGA occurred (March 2011), compared to the historical average for this dataset. A one month period was selected as a period which would have been of use to the safety investigation at the time, and statistical significance determined from the 95% confidence intervals of reaction rates per 100,000 vaccine doses, using Poisson distributions of the reaction numbers.

3. Results

3.1. Data cleaning and internal validity

The dataset included 1,060,008 records from 332,149 patient IDs which contained one or more pneumococcal and/or influenza vaccinations. A total of 64,450 (6.1%) duplicates were removed. After exclusions, 95,760 records of 23vPPV and 683,829 records of influenza vaccine administration were included in the analyses. The average number of practices contributing data was 253 per year and the average number of participating GPs was 532.

Among adults aged $\geqslant$18 years, 82% of all recorded doses of 23vPPV and 65% of influenza doses were given to people aged 65 years or older. The receipt and timing of vaccine doses were

Please cite this article in press as: Trinh L et al. Investigating adverse events following immunisation with pneumococcal polysaccharide vaccine using electronic General Practice data. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.01.063