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Continuous active surveillance of adverse events following immunisation using SMS technology

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ABSTRACT

Introduction: On-going post-licensure surveillance of adverse events following immunisation (AEFI) is critical to detecting and responding to potentially serious adverse events in a timely manner. SmartVax is a vaccine safety monitoring tool that uses automated data extraction from existing practice management software and short message service (SMS) technology to follow-up vaccinees in real-time. We report on childhood vaccine safety surveillance using SmartVax at a medical practice in Perth, Western Australia.
Methods: Parents of all children under age five years who were vaccinated according to the Australian National Immunisation Schedule between November 2011 and June 2015 were sent an SMS three days post administration to enquire whether the child had experienced a suspected vaccine reaction. Affirmative replies triggered a follow-up SMS requesting details of the reaction(s) via a link to a survey that could be completed using a smartphone or the web. Rates of reported AEFI including fever, headache, fatigue, rash, vomiting, diarrhoea, rigours, seizures, and local reactions were calculated by vaccination time point.
Results: Overall, 239 (8.2%; 95% CI 7.2–9.2%) possible vaccine reactions were reported for 2897 vaccination visits over the 44 month time period. The proportion of children experiencing a possible AEFI, mostly local reactions, was significantly greater following administration of diphtheria–tetanus–pertussis–poliomyelitis vaccine at 4 years of age (77/441; 17.5%; 95% CI 13.9–21.0%) compared to the vaccinations given at 2–18 months ($p < 0.001$). Across all time points, local reactions and fatigue were the most frequently reported AEFI.
Conclusion: Automated SMS-based reporting can facilitate sustainable, real-time, monitoring of adverse reactions and contribute to early identification of potential vaccine safety issues.

1. Introduction

Post-marketing surveillance of vaccines is critical to identify potential safety issues [1,2] as quickly as possible, so that changes in practice can occur in a timely manner. Important policy responses to safety signals identified through post-marketing surveillance include the withdrawal of the first rotavirus vaccine because of increased rates of intussusception [3,4] and a contraindication for administering one brand of influenza vaccine to children less than 5 years of age due to the increased risk of severe febrile reactions [5].

Ongoing monitoring is also important for maintaining public confidence in the safety of vaccines. While pre-licensure safety studies are critical, they can be limited by relatively small sample sizes, may not reflect use of the vaccine outside the clinical trial setting (e.g. use with other vaccines or in alternate patient cohorts), and do not capture changes to the vaccine that may occur after licensure (e.g. annual strain changes in the influenza vaccine) [1,2,6]. Post-marketing vaccine safety surveillance is therefore important, however current mechanisms are mostly passive and may be unfavourably affected by underreporting, reporting biases, and the lack of accurate denominators for determining rates [7,8]. To help address the limitations of passive surveillance, routine, active vaccine safety monitoring has recently been established in the United States [9,10]. Here we describe ongoing efforts to

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develop a system for active post-marketing vaccine safety surveillance in Australia. SmartVax is a vaccine safety monitoring tool that uses automated data extraction from provider-based electronic patient records and short message service (SMS) technology to follow-up vaccinees in real-time. This report describes how SmartVax was used to establish reactogenicity profiles for paediatric vaccine combinations and assess the impact of changes to the childhood immunisation schedule.

2. Methods

2.1. Setting

In Australia, more than 70% of vaccinations are given by general practitioners (GPs) [9]. SmartVax has been used at a single GP medical practice in metropolitan Perth, the capital of Western Australia (WA), since 2011. The practice has approximately ten full-time practitioners, 21,000 active patients, and administers approximately 2000 paediatric vaccinations each year. Details on operational aspects of the SmartVax system have been previously described [11]. In brief, parents or guardians of vaccinated children (hereafter patients) were explained the risks and benefits of vaccination prior to consenting, as per routine clinic practice. Patients were informed that they would be contacted by SMS in three days. Those who preferred not to be contacted by SMS could opt-out of SMS communication by advising their provider; no patients declined participation. Each weekday the SmartVax tool extracted vaccination data from the practice's commercially available management software. SMS text messages were sent to patients three days post-vaccination to query whether they had experienced any perceived reactions following their vaccination. The SMS read, "*Thank you for caring to have a vaccination. We would like to know if there were any reactions. Kindly reply Y or N only*." Affirmative replies to this query were followed up by two additional SMSs, the first to ascertain whether the reported adverse event was medically attended and the second with a link to a survey that could be completed on a smartphone to obtain details of the nature, duration and severity of the possible AEFI (Supplementary material). All SMS replies received from patients were automatically written back into the tool database. Medically attended reactions were automatically sent to the correspondence inbox of the practice software where they were entered into the electronic patient record.

Patients who indicated they had experienced a reaction but did not reply to the survey request, as well as those who did not respond to the first SMS, were telephoned by a practice nurse or doctor.

Ethics approval for analysis of AEFI data from SmartVax was received by the WA Department of Health Human Research Ethics Committee.

2.2. Participants

All children under five years of age who received one or more vaccines recommended in the Australian Childhood Immunisation Schedule [12] at 2, 4, 6, 12, 18 and/or 48 months between 9 November 2011 and 9 June 2015 were included in this analysis. Since SmartVax is intended to be an SMS/Smartphone-based system, the responses of those who did not reply by SMS but were subsequently reached by telephone were not included in the primary analysis. However, a secondary analysis compared the age, sex and reactions reported using SMS/Smartphones and those who required follow-up by voice telephone call.

2.3. Outcome measures

Possible AEFI were defined as a patient's affirmative reply to the first SMS. Patients reporting a possible AEFI were then asked if they sought medical attention and whether they experienced any of the following symptoms: fever, headache, fatigue, rash, vomiting, diarrhoea, rigours, seizures, and local reactions (pain or swelling at the injection site). A serious adverse event (SAE) was defined using the US Vaccine Adverse Events Reporting System criteria; an event where the patient experienced a health-risk, a life-threatening illness, was hospitalised, had a permanent disability, or died [7].

2.4. Statistical analysis

The response rate was defined as the proportion of patients who responded to the clinic's SMS with a reply SMS. Patients who provided an incorrect or disconnected mobile number or did not answer after three attempted phone calls were classified as uncontactable. Duplicate observations and SMS replies that were unrelated to the vaccination event (e.g. "wrong number" or "stop and get milk on your way home") were removed prior to analysis.

The proportion of patients reporting each clinical symptom, or possible AEFI, at each time point on the vaccination schedule was defined as the number of patients reporting the symptom divided by the total number of vaccinations given for that age time point $\times 100$.

We compared proportions of possible AEFI by year for each time point to determine if there were differences in reports by year. On 1 July 2013, measles–mumps–rubella–varicella (MMRV) vaccine replaced the varicella-only vaccine dose at 18 months and the dose of MMR vaccine at four years of age was removed on the national immunisation schedule. We report the proportion of reported reactions at 18 months of age prior to and after this change using a two-sample test of proportions assuming equal variances.

We also looked at individual patients to calculate SMS response times; this sub-analysis was restricted to the first vaccination visit only so each patient would contribute equally. In addition we determined whether individuals who had more than one visit, and who reported a possible AEFI after their first visit, were more likely to report a possible AEFI at a subsequent visit.

Finally, we compared demographic characteristics of those who did not reply by SMS to determine whether they were different to all those who did reply by SMS (i.e. voice telephone only respondents and those who were uncontactable).

Data were analysed using Stata 14 (Stata Corp., College Station, TX). Descriptive data are presented as proportions with 95% confidence intervals (CI). Logistic regression was used with reaction (Y/N) as the dependent variable, sex and scheduled time point as independent variables. Subsequent logistic regression was used with each reaction type (fever, local reaction, fatigue, etc.) as the dependent variable. Results were considered significant at $\alpha < 0.05$.

3. Results

Between November 2011 and June 2015, 1667 patients who were aged five years or under had a total of 3922 vaccination visits. Post-visit SMSs were sent to 3906/3922 (99.6%) of these patients and 2897/3906 (74.2%) SMS replies were received. Of the 1009/3906 (25.8%) patients sent an SMS who did not reply to the initial SMS, 284/1009 (28.1%) were reached through follow-up telephone calls. Post-vaccination information on possible reactions was unavailable for the remaining 725/3906 (18.6%) vaccination visits.

There was no significant difference in age, sex or reporting of possible AEFI between those patients who replied to the initial SMS and those who provided information only after being telephoned (Table 1); there was also no significant difference in terms of age, sex and number of vaccination visits between patients who were uncontactable and those who replied by SMS (Table 2). The final dataset for primary analysis included a total of 2897 SMS replies

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