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Active surveillance of adverse events following childhood immunization in Singapore

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ABSTRACT

Introduction: In Singapore, reporting of adverse events following immunization (AEFI) was historically passive. In 2009, Health Sciences Authority collaborated with KK Women's and Children's Hospital to perform active surveillance for AEFI. We report the methodology and initial findings of this surveillance following childhood vaccines.
Methods: From April 2010 to March 2012, we screened all paediatric admissions for possible relationships to vaccination, excluding elective admissions, and performed causality assessment for each case using standardized definitions for certain, probable, possible and unlikely. Baseline demographics, data on implicated vaccines and clinical details including severity and outcomes were collected. Total hospital admissions were used to calculate rates of AEFI.
Results: We screened 45,571 (80%) of 56,526 admissions, and evaluated 1988 (4.4%) children. Median age at presentation was 3.1 months, while median interval from vaccination to symptom onset was 6 days. There were 311 (15.6%) children with AEFI that were considered possibly, probably or certainly associated with vaccines. However, 98.8% recovered without any long-term sequelae. The hospital-based active surveillance of AEFI enabled the detection of a 5-fold increase (95% CI 1.2–33.1) in BCG-associated regional lymphadenitis in April 2010, which triggered follow-up safety analysis to guide public health advice.
Conclusions: Hospital-based active surveillance can enhance signal detection and follow-up investigations of AEFI. Subsequently, public health bodies are better equipped to maintain public confidence in vaccination programmes and physicians are able to provide relevant advice to parents. It also allows for a better understanding of risk-benefit ratios of specific vaccines and aids the generation of public health vaccination policy.

1. Introduction

Immunization has been described to be one of the most cost-effective of all healthcare interventions in history, and, with the possible exception of clean drinking water and modern sanitation, has been estimated to have saved more lives and life-years than all other medical intervention combined [1]. However, because vaccines would usually be given to healthy individuals (as opposed to therapeutic drugs used for the alleviation or cure of disease), there would be an expectation that immunizations were safe and would not lead to harm. As vaccination programmes improve and achieve high coverage, disease burden is expected to fall rapidly. In such scenarios, adverse events following immunization (AEFIs) would

Abbreviations: AEFI, adverse event following immunization; BCG, bacillus Calmette–Guérin; DTP, diphtheria–tetanus–pertussis; MMR, measles–mumps–rubella; PCV, pneumococcal conjugate vaccines.

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be increasingly scrutinized even if they are rare, and requires monitoring since the benefits of vaccination are quickly forgotten in an environment where exposure to disease is minimal. Any vaccine safety issue, whether real or perceived, could lead to false rumours if not rapidly and effectively managed, with severe consequences on public confidence, immunization coverage and disease incidence [2]. The recent resurgence of measles in the UK and Western Europe, resulting from the now discredited link between MMR and autism, demonstrates the severe public health consequences of such a false association, and could threaten Europe's commitment to eliminate measles in the region by 2015 [3].

AEFI surveillance is wrought with clinical, epidemiologic and statistical challenges, primarily due to the rarity of most adverse events. It would be unlikely that these rare events could be detected during pre-licensure trials, and therefore there would be a need to establish systems to detect AEFI post-licensure. Singapore, similar to most countries in the South-East Asian region, historically employed a passive surveillance system for reporting of adverse events for drugs (including vaccines), which is managed by the Health Science Authority (HSA, the country's national regulatory authority on medical products) [4]. However, a key limitation of such passive surveillance systems was its dependence on clinical vigilance, which varies between clinicians as well as within clinicians at different time points. As a result, the frequency of reported events could be low and vulnerable to chance fluctuations. Furthermore, such systems would be less sensitive in identifying signals from novel adverse events which have not been documented previously. Finally, it would be difficult to verify signals generated from passive surveillance systems to confirm or deny a correlation since the frequency of reports were usually low and had limited statistical power.

In 2009, the Vigilance Branch of HSA (which oversaw passive AEFI surveillance) partnered with KK Women's and Children's Hospital (KKH) to conduct active surveillance for AEFI after influenza vaccination, as part of vaccine safety monitoring following pandemic influenza A (H1N1) public vaccination campaign. [5] When the pandemic subsided, the programme was extended in March 2010 to include active surveillance for all vaccines given in childhood. Prior to the active surveillance programme, between 2005 and 2008 KKH submitted ~7 AEFI reports in children per year to HSA as part of passive surveillance. In this paper, we aim to describe the methodology of a hospital-based, active AEFI surveillance system monitoring childhood vaccines in Singapore, and report its early findings.

2. Methods

2.1. Data collection

The hospital-based, active surveillance programme was loosely adapted from the Canadian Immunization Monitoring Programme, Active (IMPACT) [6]. The programme consists of 1 full-time equivalent (FTE) of a surveillance coordinator, ~0.1 FTE for participating paediatric infectious diseases and immunology clinicians and clinical epidemiologist, as well as regulatory specialists from HSA (these were separately funded). The hospital (the largest women's and children's hospital in Singapore with ~800 beds, of which 500 were neonatal/paediatric beds) is primarily a tertiary hospital but also functions as a secondary hospital, and admits ~51% of all paediatric inpatients <15 years in Singapore (based on data from Ministry of Health, Singapore; this is out of a population of ~6,15,200 children <15 years in Singapore in 2013). There were >1,70,000 Children's Emergency attendances per year, with a range of paediatric medical and surgical subspecialty services available caring for a variety of complex care patients [7]. An additional ~10% of paediatric admissions <15 years are seen at the National University Hospital (the only other public sector hospital with paediatric admissions), while the remainder utilize several smaller private hospitals. Healthcare is primarily fee-for-service, with significant subsidies in public sector hospitals [8].

All children who were admitted to KKH between 1st April 2010 and 31st March 2012 were eligible for inclusion in this report. Using electronic healthcare records (and further supported by inpatient clinical notes on paper), all patients admitted with a possible AEFI were identified on a daily basis by manually reviewing their admitting diagnoses and age, followed by recent receipt of immunization; elective admissions (e.g. for surgery, chemotherapy, immunotherapy, diagnostic procedures etc.) were excluded from further screening. Appendix 1 lists relevant criteria used for this initial screen, and the age groups of children eligible for screening essentially reflects the national childhood immunization schedule in Singapore (see Appendix 2). We developed this list based on prior clinical experience, on historical records of reported AEFIs from HSA, and from a review of AEFI literature. Where there was uncertainty regarding whether an admission was an AEFI or not (especially when there was a temporal association with a vaccine), the programme erred on the side of caution by capturing the case and performing further screening.

Apart from demographic information, we collected detailed information on the date and age of vaccination and of symptom onset, date of admission and discharge, and consumption of concurrent medications, from both electronic and paper records (with the exception of the hospital's inpatient clinical notes, all other records (including Emergency department notes, radiology, pharmacy, laboratory data, and discharge summaries) are available electronically). We also collected clinical, laboratory, microbiologic and radiologic details for the admission and presence of any other co-morbidities and concurrent illnesses (especially where there was laboratory confirmation of pathogens that could have led to the admission). Complete vaccination history including vaccination dates, brand, batch numbers, dose, route, site (on the body), and place of vaccination (elicited from patients' Health Booklets [9] or via National Immunization Registry [10]) were also collected. Total numbers of paediatric hospital admissions by month were also extracted for this period.

2.2. Causality and assessment

A standardized clinical and causality assessment framework was developed to classify cases identified, by the type of AEFI and into five categories of causality: Certain, Probable, Possible, Unlikely, Unrelated (see Appendices 3 and 4). For the active surveillance, all potential AEFIs captured after the initial screen would first be reviewed by the primary investigator or participating paediatrician; where necessary, urgent cases could be discussed with the rest of the collaborators by phone or email, and appropriate referrals made to the relevant subspecialty (e.g. neurology or allergy). Subsequently, a multidisciplinary panel composed of paediatricians, regulatory specialists from the Vigilance Branch, HSA and clinical epidemiologist would discuss and review the cases on a monthly basis to ensure agreement with the categories assigned; where there was disagreement, cases were assigned according to majority opinion, and after using criteria from literature for specific conditions or Brighton Collaboration case definition guidelines where available (for AEFI classification). Criteria for causality were modified from WHO-UMC's (Uppsala Monitoring Centre) causality assessment system [11]. Outcomes for each evaluated case were classified according to whether there was recovery without sequelae, recovery with residual sequelae (e.g. disability or chronic infection), death, or unknown/lost to follow-up. All AEFIs that were categorized as Possible, Probable, or Certain (defined