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Post-authorization safety surveillance of a liquid pentavalent vaccine in Guatemalan children

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ABSTRACT

Objective: Combination vaccines have improved the efficiency of delivery of new vaccines in low and middle-income countries. Post-authorization monitoring of adverse events (AEs) after vaccination with a liquid pentavalent DTwP-HepB-Hib combination vaccine was conducted in Guatemalan infants.
Methods: A prospective observational safety study of the incidence of medical attended events (MAEs) and serious adverse events (SAEs) in children who received pentavalent and oral polio vaccines at 2, 4 and 6 months of age was conducted in two clinics at the Institute of Guatemala. Parents were contacted by telephone after each dose. All outpatient, emergency department visits, and hospitalizations were monitored. A self-controlled analysis was conducted to determine if there was evidence of increased risk of MAEs or SAEs following vaccines as compared to control time windows.
Results: Of 3000 recruited infants, 2812 (93.7%) completed the third dose and 2805 (93.5%) completed follow-up. Ten AEs in eight infants, of which four SAEs in four infants, were classified as related to the vaccine. Thirteen deaths were reported due to common illnesses of infancy, and none were judged to be related to the vaccine. The mortality rate (4.4 per 1000) was lower than expected for the population. The incidence-rate-ratio for healthcare visits was lower in post-vaccination time windows than for control windows; after the first vaccine dose, the rate ratios for the risk periods of 0–1, 2–6, and 7–30 days post-vaccination were 0.3, 0.5, and 0.7, respectively (all statistically significantly different from the reference value of 1.0 for the 31–60 day control period).
Conclusion: The liquid pentavalent vaccine was associated with lower rates of health care visits and not associated with increases in SAEs or hospitalizations. Systems can be set up in low to middle income countries to capture all health care visits to monitor the safety of new vaccines.

1. Introduction

Since 1990, the global coverage for diphtheria, tetanus toxoid and pertussis vaccines (DTP) has steadily increased up to 85% [1,2]. In 1992, WHO recommended the addition of hepatitis B vaccine (HBV), and in 2005, *Haemophilus influenzae* type b conjugated vaccines into the expanded program of immunization. With the increasing number of vaccine antigens administered in early infancy, combination vaccines for children's immunization programs have helped reduce the number of injections, reduce the number of clinic visits, and increase parental compliance [3]. For low and middle-income countries, fully liquid combination vaccines that are ready to use simplify and improve the efficiency of immunization delivery and avoid programmatic errors associated with reconstitution of separate products [4].

Vaccine safety monitoring prior to registration or licensure is reviewed by national, regional and global regulatory authorities. However, at the time of registration, limited safety data are available. To detect rare or unexpected adverse events following immunization (AEFI) surveillance studies are required after deployment in the population. In low and middle-income countries, the

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lower accessibility to the health care system and limited capacity for pharmacovigilance surveillance can limit collection of safety data; therefore perceptions of vaccine safety arising when serious AEFIs are reported, even when events are coincidental and expected, may derail immunization programs [4,5]. New post-licensure study methods have been developed in upper income countries that provide data to help identify rare SAEs and reassure the population and immunization programs about the safety of newly introduced vaccines [6].

The immunogenicity and safety of a fully liquid pentavalent vaccine Quinvaxem® was demonstrated in clinical trials of healthy infants [7–9]. Nevertheless, in Sri Lanka, after introduction of this liquid pentavalent vaccine by the national program, individual case reports of deaths and hypotonic-hyporesponsive episodes (HHEs) were reported and vaccination was interrupted. The incidence of HHE of 14.9 cases per 100,000 doses was found to be well within the reported estimated rate of HHE incidence following vaccination with whole-cell pertussis-containing vaccines (21–250 cases per 100,000 doses). The program in Sri Lanka was later reinitiated as the clinical and epidemiological data showed no evidence of an unexpected safety profile of Quinvaxem® and no significant increase in the incidence of recognized adverse events when compared with the previous whole-cell pertussis vaccine in use [10].

This observational study was designed as part of the WHO prequalification post-registration process to provide further information on important safety outcomes for infants receiving a primary immunization series with Quinvaxem® as it was delivered as part of the public immunization system in Guatemala. We set up a monitoring system to examine patterns of clinic and emergency department (ED) visits, hospitalizations and deaths following vaccination using a self-controlled case series design that has been shown to be useful in higher income countries [11–13].

2. Methods

This was an open label, active surveillance prospective cohort study that evaluated the safety of a fully liquid DTwP-HepB-Hib vaccine administered to healthy infants at 2, 4 and 6 months of age under the routine national immunization schedule in Guatemala. This report also includes a post hoc exploratory self-controlled case series analysis. The Center for Health Studies at University del Valle and the Johns Hopkins Bloomberg School of Public Health managed the data collection and analysis. Immunizations, medical care and record management were conducted by the Institute of Social Security in Guatemala (IGSS). The study was performed according to the Declaration of Helsinki, following Good Pharmacovigilance Practices (GPP) with the approval of the institutional review boards of the Johns Hopkins Bloomberg School of Public Health, the University del Valle in Guatemala, and the authorities at IGSS.

2.1. Study population

From December 2008 through January 2010, 3000 healthy infants who came for well-child care to two metropolitan outpatient pediatric clinics of IGSS (Zones 5 and 11) in Guatemala City were enrolled. The fully liquid DTwP-HepB-Hib vaccine (Quinvaxem®, Crucell, Switzerland) was in use by the Ministry of Health of Guatemala, but not by IGSS at the time the study was initiated; therefore these clinics were provided with the study vaccine for all infants coming for their primary series to avoid vaccination errors under the routine schedule. The IGSS system provides free care for children less than 7 years of age of insured workers, and covers 25.8% of the children in Guatemala according to the ENSMI survey of 2008–2009. The Ministry of Health covers an additional 60% of the population, reaching a 3-dose DTwP-HepB-Hib coverage of 78% by 1 year of age in Guatemala City.

Infants were included in the surveillance if they were healthy at the time of their first dose visit, their parents or guardians provided written informed consent for active follow-up and release of medical information, and were accessible by phone. The DTwP-HepB-Hib combination vaccine (Quinvaxem® lot 0451194) is a combination of hepatitis B (Hepavax-Gene®, pre-qualified by WHO since 2006) and DTwP-Hib (Quattvaxem®) vaccines. Quinvaxem® vaccine contained >30 IU of diphtheria toxoid, >60 IU of tetanus toxoid, >4 IU of inactivated *Bordetella pertussis*, 10 μg of purified HBsAg, and 10 μg of Hib oligosaccharide conjugated to CRM_{197} protein, 1.36 mg of aluminum phosphate, 4.5 mg of sodium chloride, and no more than 12.5 μg/dose of residual thiomersal. A 0.5 mL dose of the vaccine was injected intramuscularly into the anterolateral thigh. Oral polio vaccine was administered simultaneously according to the EPI recommendations. Rotavirus or pneumococcal vaccines were not part of the routine schedule at the time of the study.

2.2. Adverse events surveillance system

After each vaccination, infants were observed for 15–30 min for AEFIs according to standard local practice. The parents or guardians were asked to observe their infant's health status and contact the study physician or study nurses if their infant experienced any symptom perceived to be serious. The infant's parent or guardian was contacted by telephone 2 weeks after each vaccination and additionally 4 weeks after the third dose of vaccine to inquire if the infant had had any symptoms that led to a visit to a doctor or clinic, or hospitalization. Per protocol, infants were followed up to 4 weeks after the third dose of vaccine; but we allowed follow up until 12 months of age to record any potential vaccine related AEFI that could have occurred after the indicated period. If the child did have an illness that prompted a health care encounter, the study nurse completed an AEFI form and reviewed the medical record of the visit if available. AEFIs were also captured through active daily monitoring at the IGSS pediatric emergency room and hospital using an electronic mobile database that contained the IGSS affiliation number of the participating infants. Any AE leading to hospitalization, death, or considered life-threatening, resulted in persistent or significant disability/incapacity, or any other medically important event, was considered an SAE and reported within 24 h to the principal investigator and the study nurses at the clinics for follow-up.

Investigators reviewed all AEFIs and the potential causal relationship to the vaccine if the AEFI: (a) was consistent in time and nature to previously reported AEs for any of the vaccine antigens, (b) the event was temporally associated with vaccine administration, and there were no alternative causes for the event, or (c) the event was reproduced upon re-administration of the vaccine. The Brighton Collaboration definitions if available were used to classify any AEFI [14,15].

2.3. Statistical methods

Data from each visit as well as all AEFI were collected using standardized forms that were entered using Teleform (Cardiff, USA). AEFIs were coded and presented using the Medicinal Dictionary for Regulatory Activities (MedDRA) Version 13.0. The sample size of 3000 infants was estimated as sufficient to identify any event occurring at a frequency of $\geq$1 per 1000 population, regardless of seriousness or consequences. All subjects who received at least one dose of vaccine were included in the analysis. Per protocol, the primary endpoint was the proportion of infants with clinically relevant AEFIs and all SAEs during the 5-month primary observation period.