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Evaluating the first introduction of rotavirus vaccine in Thailand: Moving from evidence to policy

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ABSTRACT

Background: We assessed the effectiveness and possible impact of introducing rotavirus vaccine into the routine immunization program.
Methods: Two provinces were selected for an observational study, one where vaccine was introduced and another where vaccine was not available. In these areas, two sub-studies were linked. The prospective cohort study enrolled children 2 month old and followed them to the age of 18 months to detect all diarrhea episodes. The hospital surveillance study enrolled all children up to age 5 hospitalized with diarrhea whose fecal samples were tested for rotavirus. Rates of rotavirus hospitalizations in older children who had not been vaccinated in both settings provided data to determine whether immunization had an indirect herd effect. The key endpoints for the study were both vaccine effectiveness (VE) based upon hospitalized rotavirus diarrhea and herd protection.
Findings: From the cohort study, the overall VE for hospitalized rotavirus diarrhea was 88% (95%CI 76–94). Data from hospital surveillance indicated that for 2 consecutive years, the seasonal peak of rotavirus admissions was no longer present in the vaccinated area. Herd protection was observed among older children born before the rotavirus vaccine program was introduced, who experienced a 40–69% reduction in admission for rotavirus.
Conclusions: Rotavirus vaccine was highly effective in preventing diarrheal hospitalizations and in conferring herd protection among older children who had not been vaccinated.

1. Introduction

In 2009, the World Health Organization recommended that rotavirus vaccine should be included in all national childhood immunization programs as part of a comprehensive strategy to control diarrheal diseases [1]. By May 2016, 81 countries had introduced the vaccine but notably, none of these countries was in Asia [2]. This was surprising because in 1999, the first regional hospital surveillance network for rotavirus diarrhea was established in Asia and documented the high burden of the disease throughout the region [3]. Many studies elsewhere in the world have demonstrated the impressive impact of the introduction of rotavirus vaccine to reduce both hospitalizations and death from this common childhood disease [4–6]. Reasons for this delayed introduction in Asia include concern for the lower efficacy of live oral vaccine in low income countries [7,8], questions about the true burden of this usually mild cause of diarrhea, and the substantial cost of the vaccine for national immunization programs already challenged to introduce other new vaccines for Streptococcus pneumoniae and human papillomavirus [9]. Consequently, seven years after the WHO recommendation, Asia with 40% or more of the world's population is not yet benefitting from the introduction of rotavirus vaccine.

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To address this issue in Thailand, the National Vaccine Committee considered introduction of this vaccine in 2010. Seeking more local evidence to assess this strategy, it recommended conducting a pilot study to ascertain effectiveness of a rotavirus vaccination program [10]. In response to their recommendation, we conducted this study in a province where local health leaders had just decided to introduce the monovalent RIX4144 strain human vaccine (Rotarix®) into the routine program of childhood immunization. Evaluation of the impact of this intervention would provide evidence to inform policy makers in Thailand and throughout Asia on the potential merit of vaccine introduction.

2. Methods

2.1. Study location

We compared data from two provinces, Sukhothai which began a routine immunization program with rotavirus vaccine in October 2011 with three districts of Phetchabun province where immunization had not begun. Sukhothai province in the central plains agricultural area has a population of mostly indigenous Thais who have good access to health service facilities and an annual cohort of about 5000 births per year. Three districts of Phetchabun province (Muang, Lomsak, Nongpai) were selected as the non-vaccinated area because the geography, population, and health service system were similar to those of Sukhothai. For the period 2008–2010, before the vaccine was introduced in Sukhothai, the rate of hospitalization for diarrhea in children under 2 years was comparable between Sukhothai and the three districts of Phetchabun (~3935 vs 4254 per 100,000 populations, respectively) (Health Service Database, retrieved on 19 April 2011).

2.2. Vaccination schedules

Both areas provide free immunization service in public clinics for children less than 5 years according to the National Immunization Program which included BCG, HB, DTP, OPV, JE, and MMR [11]. During the study period, vaccination with DTPw-HB and OPV was provided to children 2 and 4 months of age in both sites, but in Sukhothai, monovalent Rotavirus vaccine (Rotarix®) was added at both visits.

2.3. Observational cohort study

From September 2012 to June 2013, all 204 immunization clinics in the study areas invited parents of the infants arriving for their 2-month old visit to join the study and give their informed consents (Fig. 1). The initial visit was followed by four face-to-face interviews when children came back for their 4, 6, 9, and 18-month visits and an additional telephone contact when children were 13 months of age. At each visit, parents were queried about the occurrence of episodes of diarrhea, treatment and its cost since the last visit (the economic study is reported separately). A diarrheal episode was defined as the occurrence of 1 watery or 3 or more loose stool in a 24 h period. A new diarrheal episode had to be separated by at least 14 days from a patient's full recovery from a previous diarrhea illness.

In Sukhothai, children had to have received at least one dose of rotavirus vaccine with the first dose administered between 6 and 15 weeks of age to be included in the study. In Phetchabun, the non-vaccinated area, the children who received rotavirus vaccine were excluded. We estimated the sample size for the study using a study power of 80%, an alpha error of 0.05, vaccine efficacy of 71% [12], and a rate of hospitalized rotavirus diarrhea among the non-vaccinated group of 1.2%, with 30% lost to follow up and/or lost from case detection at hospitals. Using cohorts of equal size [13], we would require approximately 2696 children in each group to document a significant reduction in rotavirus hospitalization.

2.4. Hospital surveillance study

Hospital surveillance for diarrhea among children 2–59 months of age was conducted in all 12 public hospitals in the study areas from the day the first cohort volunteer was recruited in September 2012 until the end of follow up in October 2014 (Fig. 1). This data allowed us to detect rotavirus diarrhea admissions among infants enrolled in the cohort study and provided information on the epidemiology of severe rotavirus leading to hospital admissions among all children less than 5 years. We could then look for herd protection as evidenced by a decrease in hospitalization from rotavirus among older children in both areas who had not been vaccinated against rotavirus because they were born before the vaccination program began in Sukhothai. All children hospitalized with diarrhea between 2 and 59 months of age were invited to participate in the surveillance study. If parents consented, we queried them for information on the diarrheal episode and treatment. One fecal sample was collected on admission and sent for rotavirus detection. The ward staff who conducted the hospital surveillance were neither aware of the rotavirus vaccination status of the patients nor whether patients were participants in the cohort study.

2.5. Rotavirus laboratory tests

Each month, fecal specimens (5 ml) collected in the hospitals were kept frozen and sent to the Department of Medical Science at the Ministry of Public Health. Rotavirus was tested by polyacrylamide gel electrophoresis (PAGE) [14] and positive samples were characterized further to identify G- and P-types by reverse transcription-PCR (RT-PCR) [15,16]

2.6. Data analysis

The incidence of diarrhea was calculated in the cohort study as the number of episodes per 100 person-year (P-Y) of follow up. The time period began from the initial interview and stopped on the day of the last follow up visit. We excluded the 14 days after the 2- month vaccinations as well as the 14-day period after each diarrheal episode. Multiple Poisson regression was used to control for confounding factors and the "Adjusted Odds Ratio" (adjOR) with 95% confidence interval was used to compare the diarrheal risk between vaccinated versus non-vaccinated children. Vaccine effectiveness (VE) was $((1 - \text{adjOR}) \times 100)$. Statistical analysis was performed using SPSS 20.

3. Results

3.1. Observational cohort study

Since vaccination was conducted in only one province, Sukhothai, and the results were to be compared with a similar province where vaccination was not offered, Phetchabun, we first assessed the comparability of children at these two locations (Appendix 1). The 2893 infants enrolled in Sukhothai and 1937 in Phetchabun, were comparable in terms of their distribution of gender, gestational age, birth weight, family income. Groups did not differ significantly in their age of enrollment (73 ± 10 day old in both groups) or the end of follow up (533 ± 118 vs 541 ± 103 day old), and 90–92% participated until the end of the follow up time. The non-vaccinated group from Phetchabun came