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Catching-up with pentavalent vaccine: Exploring reasons behind lower rotavirus vaccine coverage in El Salvador☆

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ABSTRACT

Rotavirus vaccine was introduced in El Salvador in 2006 and is recommended to be given concomitantly with DTP–HepB–*Haemophilus influenzae* type b (pentavalent) vaccine at ages 2 months (upper age limit 15 weeks) and 4 months (upper age limit 8 months) of age. However, rotavirus vaccination coverage continues to lag behind that of pentavalent vaccine, even in years when national rotavirus vaccine stock-outs have not occurred. We analyzed factors associated with receipt of oral rotavirus vaccine among children who received at least 2 doses of pentavalent vaccine in a stratified cluster survey of children aged 24–59 months conducted in El Salvador in 2011. Vaccine doses included were documented on vaccination cards (94.4%) or in health facility records (5.6%). Logistic regression and survival analysis were used to assess factors associated with vaccination status and age at vaccination. Receipt of pentavalent vaccine by age 15 weeks was associated with rotavirus vaccination (OR: 5.1; 95% CI 2.7, 9.4), and receipt of the second pentavalent dose by age 32 weeks was associated with receipt of two rotavirus vaccine doses (OR: 5.0; 95% CI 2.1–12.3). Timely coverage with the first pentavalent vaccine dose was 88.2% in the 2007 cohort and 91.1% in the 2008 cohort ($p = 0.04$). Children born in 2009, when a four-month national rotavirus vaccine stock-out occurred, had an older median age of receipt of rotavirus vaccine and were less likely to receive rotavirus on the same date as the same dose of pentavalent vaccine than children born in 2007 and 2008. Upper age limit recommendations for rotavirus vaccine administration contributed to suboptimal vaccination coverage. Survey data suggest that late rotavirus vaccination and co-administration with later doses of pentavalent vaccine among children born in 2009 helped increase rotavirus vaccine coverage following shortages.

1. Introduction

Diarrhea due to rotavirus is one of the leading causes of death in children under 5 years of age internationally [1]. Since 2006, second generation live orally administered rotavirus vaccines have been recommended as a two-dose monovalent rotavirus vaccine (RV1; Rotarix, GlaxoSmithKline Biologicals) or three-dose pentavalent rotavirus vaccine (RV5; RotaTeq, Merck & Co., Inc.) regimen by the World Health Organization (WHO) [1]. The El Salvador Expanded Programme on Immunization (EPI) introduced a 2-dose oral rotavirus vaccination series in October 2006 entirely with government funds, as a low-middle income but non-Gavi eligible country, and recommended administration at 2 and 4 months of age, concurrently with injected diphtheria–tetanus–pertussis–hepatitis B–*Haemophilus influenzae* type b (pentavalent) vaccine and live oral poliovirus vaccine (OPV) [2,3]. Studies have shown a positive impact of rotavirus vaccine in El Salvador: a 2010 vaccine effectiveness study demonstrated a four-fold reduction (OR: 0.24) in hospitalizations for rotavirus infection among children who

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC).

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received two doses of vaccine [4]; and a 2011 study found an overall reduction in rotavirus diarrhea hospitalizations by age group in children under five years of age, with the most significant benefits in birth cohorts that had been eligible for vaccination [5].

When second generation rotavirus vaccines were introduced, the WHO Strategic Advisory Group of Experts (SAGE) recommended upper age limits of 15 weeks of age for the first dose and 8 months of age for completion of the two- or three-dose series [1,6–8]. In 2012, WHO updated its recommendations supporting co-administering rotavirus vaccine with diphtheria–tetanus–pertussis (DTP)-containing vaccine regardless of the child's age [1]; the same year, the Technical Advisory Group on Vaccine-preventable Disease (TAG) of the Pan American Health Organization (PAHO) recommended that countries of the Americas work to improve adherence to the national routine vaccination schedule to ensure timely vaccination, with a consideration of possible benefits of late rotavirus vaccination under some circumstances [9]. Before these modified recommendations, rotavirus vaccines were the only vaccines in the routine infant vaccination schedule with upper age limits for administration [1,7]. The upper age limit recommendations were informed by experiences with the first licensed rotavirus vaccine, which was withdrawn in 1999 because of an increased risk of intussusception, a potentially fatal bowel obstruction caused by telescoping of one part of the intestine into an adjacent segment, especially among older infants [6,10,11]. Based on large safety and efficacy trials and observational studies [1,6–8,12,13], the risk of intussusception following receipt of second generation rotavirus vaccines was shown to be greatly reduced compared to the earlier vaccine, although continued monitoring of this risk is still warranted.

Rotavirus vaccine is highly effective in reducing diarrheal disease hospitalizations [4,5]. However, coverage with rotavirus vaccine is often lower than that of co-administrated vaccines [2,3,14,15]. De Oliveira et al. [3] reported lower coverage with rotavirus vaccine than pentavalent vaccine in El Salvador in 2007, 2008, and 2009. The authors hypothesized that the upper age limits for administration resulted in coverage discrepancies between rotavirus and pentavalent vaccines. There have been no studies investigating the impact of the upper age limits on rotavirus vaccine coverage using data from individual children in low or middle income settings in the Americas.

A national cross-sectional survey of vaccination coverage among children aged 24–59 months was completed in El Salvador in 2011. The primary analysis by Suarez Castaneda et al. [2] showed rotavirus vaccination coverage, estimated at 93.7% for the first dose and 86.3% for the second, to be lower than coverage with the corresponding doses of pentavalent vaccine, estimated at 99.9% for both doses. Additionally, El Salvador experienced a nationwide shortage of rotavirus vaccine between July and October of 2009 [2]. Year of birth was a predictor of rotavirus vaccination timeliness and the primary analysis of that survey concluded that further investigation of the reasons for lower rotavirus coverage was needed [2].

We used the dataset from the 2011 vaccination coverage survey to investigate birth cohort-specific timeliness of rotavirus and pentavalent vaccines, differences in timeliness between doses and vaccines, and co-administration patterns to further understand upper age limits and vaccine shortages as factors in lower rotavirus vaccine coverage in El Salvador.

2. Methods

2.1. Study design

The methods of the study design have been described by Suarez-Castaneda et al. [2]. Briefly, this was a multi-stage stratified cluster survey of all five regions of El Salvador, conducted from 1 November to 2 December 2011. Thirty clusters were sampled via probability proportional to size from each of the 5 regions. Seventeen households within each locality were selected (details described in [2]), and one eligible child was randomly selected in each household, yielding a sample size of 2550 2- to 4-year-old children born between 4 November 2006 and 12 December 2009. Caregivers were interviewed about their child's vaccination status and their attitudes toward vaccination. Vaccination dates were obtained from children's vaccination cards at home (94.4%) or at health facilities if the card was unavailable (5.6%). The survey based coverage estimates on the 2006 national vaccination schedule for children less than two years of age. Only two children had no written record of vaccination and were excluded; both had received vaccines according to parental report. For each missing dose of vaccine, the parent or guardian was asked to recall the reason it was not administered. Parents or guardians were also surveyed about family and community characteristics, such as parental education level and marital status, number of people in the household, levels of community violence (e.g., gang activity), and accessibility of vaccination clinics. These self-reported factors were recorded for each child.

2.2. Analytic methods

The current analysis is limited to the sample of children born in 2007–2009 with at least 2 documented doses of pentavalent vaccine ($N = 2492$); children born in 2006 ($n = 55$) and children who had not received at least 2 doses of pentavalent vaccine ($n = 3$) were excluded. To reflect national policy and facilitate comparisons between the doses, schedule adherence for both vaccines was categorized using the recommended upper age limits for rotavirus vaccine of 104 days for the first dose and 223 days for the final dose of the series. Percentages and (Wald) confidence intervals were calculated accounting for the survey design and the weights provide by the original authors using SAS v9.3 (Cary, NC). These are reported for defined sub-populations overall, and by birth year. The weighted median ages of administration of rotavirus and pentavalent vaccines are presented with absolute ranges. Logistic regression models, also accounting for survey design and weights, were developed for rotavirus vaccination status predicted by the timing of the corresponding dose of pentavalent vaccine, that is administered before or after the upper age limit for rotavirus vaccination, and year of birth; categorical pentavalent timeliness (doses administered within 30 days of the recommended age) was predicted by year of birth. Confounding was assessed using the backwards change in estimate approach [16].

In the time-to-event analysis, children were considered eligible for each dose of vaccine from birth. Children without a written record of the vaccine of interest were censored at their age at the time of the survey. For the second dose of vaccine, children were considered vaccinated if they had a written record for the first and second doses. The results are presented in graphs plotting one minus the proportion of unvaccinated children by age in months. These images were generated using *R* (3.0) survey method survival analysis package to account for the sample weights and survey design.

The survey was reviewed by the national and PAHO ethical committees and considered non-research. This secondary analysis was approved by Emory University's Institutional Review Board and the Centers for Disease Control and Prevention.

3. Results

Table 1 describes the characteristics of the surveyed children and their households. Of 2495 children included in El Salvador's

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