



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.

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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

Table 1

Selected characteristics of surveyed children born 2007–2009 with at least 2 documented doses of pentavalent vaccine, their families and communities. El Salvador, 2011.

		Year of birth					
		2007 (N=806)		2008 (N=877)		2009 (N=809)	
		n	%	n	%	n	%
Gender	Female	387	48.0	428	48.8	383	47.3
Parental marital status	Partnered/married	652	80.9	702	80.1	650	80.4
	Divorced/separated	22	2.7	24	2.7	17	2.1
	Single	124	15.4	143	16.3	135	16.7
	Widowed	8	1.0	8	0.9	7	0.9
Parental education level	Less than 7th grade	442	54.8	482	55.0	481	59.5
	7th grade or higher	364	45.2	395	45.0	328	40.5
Parental employment status	Not employed	572	71.1	602	68.6	564	69.7
	Outside the home	234	29.0	275	31.4	245	30.3
Number of people in the household	2–5	503	62.4	564	64.3	503	62.2
	6 or more	303	37.6	313	35.7	306	37.8
Primary mode of transportation	Foot	439	54.5	462	52.7	391	48.3
	Bus	243	30.2	275	31.4	299	37.0
	Personal vehicle	53	6.6	64	7.3	61	7.5
	Other	71	8.8	76	8.7	58	7.2
Area of residence	Urban area	363	45.0	443	50.5	361	44.6
Presence of organized crime	Yes	131	16.3	143	16.3	142	17.6
Region	Central	154	19.1	184	21.0	162	20.0
	Metropolitan	152	18.9	179	20.4	158	19.5
	Occidental	169	21.0	175	20.0	155	19.2
	Oriental	161	20.0	181	20.6	160	19.8
	Paracentral	170	21.1	158	18.0	174	21.5

2011 national vaccination coverage survey born during 2007–2009, 2492 (99.8%) had received at least two doses of pentavalent vaccine. Among these, 2338 (93.8%) of 2492 had documentation of receipt of the first dose of oral rotavirus vaccine and 2162 (86.3%) had completed the two-dose rotavirus vaccination series. Median age at receipt of first dose of pentavalent vaccine (penta1) was 62.4 days (range: 0–1234 days) and median age at receipt of the second dose (penta2) was 125.3 days (range: 58–1398 days), close to the recommended ages of 2 and 4 months, respectively. Similarly, oral rotavirus vaccine doses were received at a median age of 63.7 days (range: 0–1183 days) for the first dose (rota1) and 126.8 days (Range: 58–1463 days) for the second dose (rota2). Among 2338 children who received the first dose of rotavirus vaccine, 1814 (77.2%) received rota1 and penta1 on the same date, and 453 (19.9%) received rota1 a median of 55.2 days after penta1 (Table 2). Among 2162 children who received the second dose of rotavirus vaccine, 1613 (74.8%) received rota2 and penta2 on the same date, while 429 (19.9%) received rota2 a median of 40.9 days after penta2. Among children who received rota1 on a different date than penta1 and penta2, 99.1% received OPV1 on the same day as penta1; among children who received rota2 on a different date than penta2 and penta3, 96.8% received OPV2 on the same day as penta2.

Delayed receipt of pentavalent vaccine was strongly associated with non-receipt of rotavirus vaccine or incomplete rotavirus vaccination. Among 154 children with zero doses of rotavirus vaccine despite having received two doses of pentavalent vaccine, 29 (19.7%) had received the first pentavalent vaccine after 15 weeks of age. Among 176 children with only one dose of rotavirus vaccine, 12 (7.3%) had received penta2 after 32 weeks of age. After adjusting for year of birth and maternal education, odds of receipt of oral rotavirus vaccine were lower among children who received penta1 after 15 weeks of age compared with those who received penta1 before 15 weeks of age (OR: 0.2; 95% CI 0.1, 0.4) (Table 3). Among children who received rota1, odds of receipt of rota2 were lower among those who received penta2 after 32 weeks of age compared with those who received the vaccine before 32 weeks (OR: 0.1; 95% CI 0.1, 0.2). Urban residence, maternal employment status, and number of residents in the household were not found to be confounders. Uptake of rotavirus vaccine in children who received pentavalent vaccine before and after the upper age limits of administration are visualized using cumulative incidence curves (Fig. 1).

In the first two birth cohorts to receive oral rotavirus vaccine before national shortages in 2009, we observed significant

Table 2Concurrent administration of rotavirus and pentavalent^a vaccines among children born in 2007–2009. El Salvador, 2011.

		Year of birth											
		Total			2007 (N=806)			2008 (N=877)			2009 (N=809)		
		n	%	CI	n	%	CI	n	%	CI	n	%	CI
Rotavirus dose 1 (N=2338)	With penta1 ^b	1814	77.2	(75.0, 79.4)	592	80.6	(77.5, 83.7)	701	84.4	(81.8, 87.0)	521	66.4	(62.2, 70.7)
	With penta2 ^c	166	7.4	(6.1, 8.6)	50	7.2	(5.1, 9.2)	34	4.1	(2.6, 5.7)	83	11.0	(8.5, 13.5)
	In a separate visit	358	15.4	(13.7, 17.2)	90	12.3	(9.5, 15.1)	97	11.4	(9.2, 13.7)	171	22.6	(19.0, 26.1)
Rotavirus dose 2 (N=2162)	With penta2	1613	74.8	(72.8, 76.9)	542	77.9	(74.6, 81.3)	610	80.9	(77.5, 84.2)	461	66.5	(61.6, 69.4)
	With penta3 ^d	95	4.8	(3.7, 5.9)	20	2.9	(1.6, 4.3)	19	2.4	(1.3, 3.6)	56	9.1	(6.2, 12.0)
	In a separate visit	454	20.4	(18.6, 22.2)	138	19.1	(16.0, 22.3)	125	16.7	(13.6, 19.8)	191	25.4	(22.0, 28.9)

^a Diphtheria–tetanus–pertussis–Hepatitis B–*Haemophilus influenzae* type b vaccine.^b Penta1 is the first dose of pentavalent vaccine.^c Penta2 is the second dose of pentavalent vaccine.^d Penta2 is the second dose of pentavalent vaccine.

Table 3
Odds ratios of receiving rotavirus vaccine by pentavalent timing and birth cohort among children born 2007–2009 who received a dose of pentavalent vaccine. El Salvador, 2011.

	Rotavirus dose 1				Rotavirus dose 2			
	Administered		Crude	Adjusted ^a	Administered		Crude	Adjusted ^b
	n	% (CI)			n	% (CI)		
Pentavalent before age limit	2236	94.7 (93.3, 96.1)	1.0 (reference)	1.0 (reference)	2129	87.7 (85.7, 89.7)	1.0 (reference)	1.0 (reference)
Pentavalent after age limit	102	78.3 (69.3, 87.4)	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	85	64.1 (54.0, 74.1)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
Born in 2007	732	90.6 (88.2, 93.1)	1.0 (reference)	1.0 (reference)	700	86.4 (83.5, 89.4)	1.0 (reference)	1.0 (reference)
Born in 2008	832	94.8 (92.9, 97.8)	1.9 (1.3, 2.8)	1.9 (1.2, 2.6)	754	85.2 (82.0, 88.4)	0.9 (0.7, 1.2)	0.8 (0.6, 1.1)
Born in 2009	774	95.7 (94.1, 97.3)	2.3 (1.6, 3.4)	2.3 (1.5, 3.3)	708	87.4 (84.5, 90.2)	1.1 (0.8, 1.4)	1.0 (0.7, 1.3)
Less than 7th grade education	1323	93.9 (92.3, 95.5)	0.9 (0.7, 1.3)	1.1 (0.7, 1.4)	933	85.0 (81.9, 88.1)	1.2 (0.9, 1.6)	1.1 (0.9, 1.5)
7th grade education or higher	1015	93.5 (91.6, 95.6)	1.0 (reference)	1.0 (reference)	1229	87.3 (84.9, 89.6)	1.0 (reference)	1.0 (reference)

^a Adjusted for pentavalent dose 1 categorical timeliness, parental education and birth cohort.

^b Adjusted for pentavalent dose 2 categorical timeliness, parental education and birth cohort.

improvement in timeliness of pentavalent vaccination among children included in the survey. The percentage of children who had received a valid dose of penta1 by 3 months (90 days) of age increased from 88.2% in the 2007 cohort to 91.1% in the 2008 cohort ($p=0.04$), although there was little difference in the median age of penta1: 62.5 compared with 62.3 days. Controlling for maternal

education, odds of penta1 receipt by 3 months of age were 1.6-fold higher among children born in 2008 compared with those born in 2007 (OR: 1.6; 95% CI 1.1, 2.3). The percentage of children who had received penta2 by 5 months of age was 84.6% in the 2007 cohort compared to 87.4% among those born in 2008 ($p=0.10$); odds of timely vaccination was not statistically different (OR: 1.1; 95% CI:

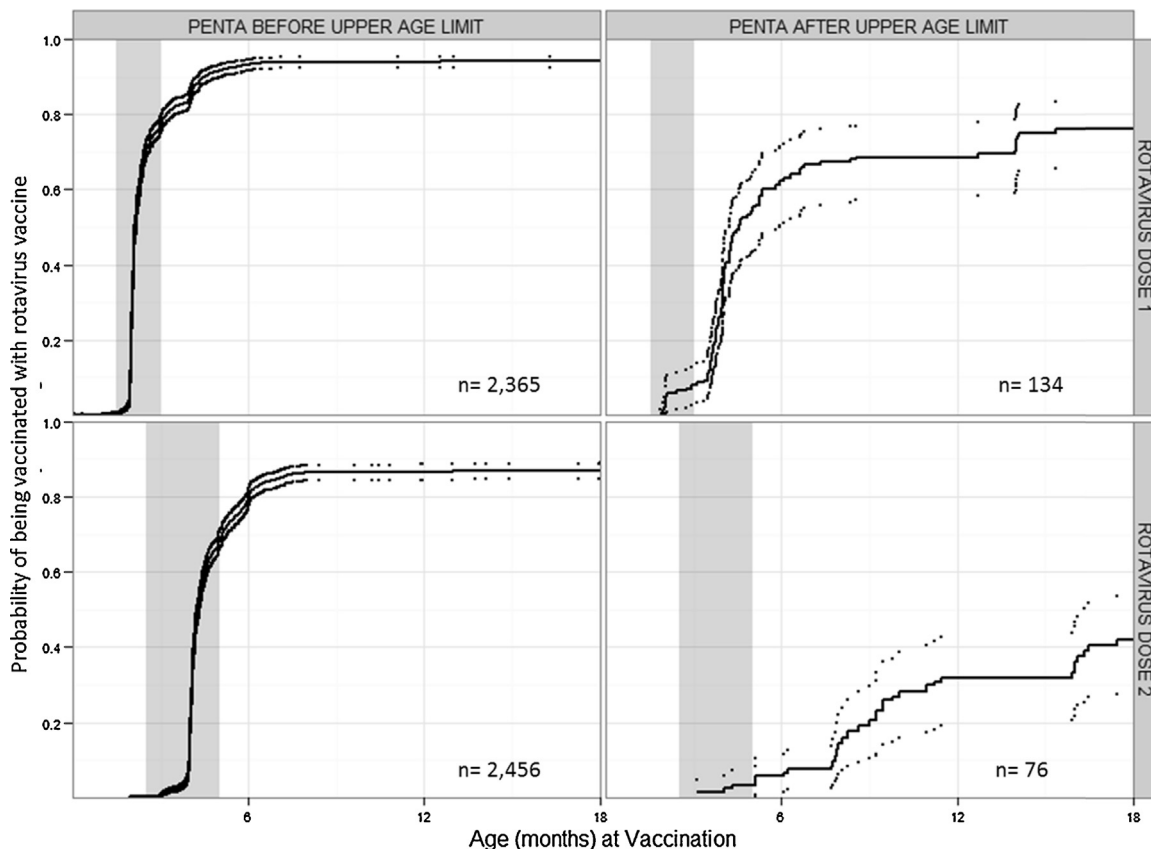


Fig. 1. Cumulative incidence curves showing the probability of rotavirus vaccination for children who received pentavalent vaccine before and after the upper age limit of rotavirus vaccine administration, El Salvador, 2011.

The probability of rotavirus vaccination is shown with solid lines and confidence intervals are shown as dotted lines. The top row shows the probability of vaccination with the first dose of rotavirus vaccine, among children who received the first dose of pentavalent vaccine before the first dose rotavirus vaccine upper age limit (15 weeks of age) in the left column and after the upper age limit in the right column. The bottom row shows the probability of vaccination with the second dose of rotavirus vaccine, among children who received the second dose of pentavalent vaccine before the series rotavirus vaccine upper age limit (8 months of age) in the left column and after the upper age limit in the right column. The gray boxes highlight the minimum acceptable age until 30 days after the recommended age for the rotavirus dose.

0.8, 1.6) after controlling for maternal education, penta1 timeliness, urban residence, maternal employment status, and number of residents in the household.

Despite nationwide shortages of rotavirus vaccine from July to October, 2009, 95.7% (95% CI: 94.1, 97.3) of children born in 2009 received rota1 and 87.4% (95% CI: 84.5, 90.2) received rota2, similar to percentages of children born in 2007 (90.6% and 86.4%) and 2008 (94.8% and 85.2%, respectively). However, the median age of receipt of penta2 was 124.7 days in 2008 compared with 125.9 in 2009, and 22.1% of children born in 2009 received rota1 after 15 weeks of age compared with 9.0% in 2008. Compared with children in the 2007 and 2008 birth cohorts, children born in 2009 were more likely to have received rota2 with the third dose of pentavalent vaccine (penta3) or on separate dates from penta2 and penta3 (2007/2008: 20.6%, 2009: 34.5%; p : 0.001) (Table 2). The primary reason parents gave for their children not receiving rotavirus vaccine was that there was no rotavirus vaccine at the time of their visit, with 63.2, 72.1, and 89.4% of parents citing this reason in the 2007, 2008, and 2009 birth cohort, respectively.

The number of surveyed children who received rota1 in November 2009, the month following the nationwide shortage was 134, higher than the number of children aged 2–3 months (n = 80) and exceeding the number of rota1 doses received in any other month children in the study were vaccinated with the first dose of rotavirus vaccine. The increase in rota1 doses received in November 2009 was followed by an increased number of rota2 doses received in January 2010.

4. Discussion

This analysis suggests that shortages of vaccine and missed opportunities led to suboptimal rotavirus vaccine coverage during the first three years following rotavirus vaccine introduction in El Salvador's national immunization program, though first dose rotavirus vaccine coverage was improving by birth cohort. High coverage and timeliness of other routine vaccinations indicate the overall strength of the program at the time of rotavirus vaccine introduction; adherence to upper age limits during the first two years also indicates well-trained vaccination staff. This analysis also showed an increased proportion of infants receiving both doses of rotavirus vaccine after the recommended ages in the 2009 birth cohort, suggesting efforts to provide rotavirus vaccine to infants eligible for vaccination during vaccine shortages. When forecasting vaccination coverage after new vaccine introduction, it is often assumed that a newly introduced vaccine will quickly achieve the same coverage level as established vaccines recommended at the same ages [3] and previous publications have hypothesized that the recommended upper age limits for rotavirus vaccine are related to lower coverage [1,6,14]. This analysis showed that age-specific recommendations contributed to lower coverage, though to a lesser extent than missed opportunities and vaccine shortages. Other variables associated with delayed pentavalent or rotavirus vaccination included child's year of birth and gender, vaccination in the private sector, and mother's education and marital status [2]. Our findings support the revised recommendations from WHO and PAHO advisory bodies to consider the benefits and risks of rotavirus vaccination among older infants, while still working to improve schedule adherence.

This analysis also showed that the timeliness of the first dose of pentavalent vaccine increased significantly as the rotavirus vaccine program matured during the first two years after introduction, before national vaccine shortages. Previous studies found an association between rotavirus vaccine introduction and improved timeliness of other vaccines [15,17] and that new vaccine introduction can strengthen service delivery in existing routine vaccination

programs [18]. As this survey did not include cohorts born before and after rotavirus vaccine introduction, we were unable to assess improved timeliness in administration for other routine infant vaccines as observed in Australia [17] and Paraguay (unpublished data 2011).

Our results also highlight challenges of new vaccine introduction, including the implications of shortages on vaccination coverage and timely administration [3,19–21]. The results of this survey show that the immunization program in El Salvador was flexible in its handling of the national rotavirus vaccine shortages, resulting in a minimal reduction in rotavirus vaccination coverage in 2009 but delayed administration. This was evidenced through adaptability in co-administration and diligent follow-up of children who had not received rotavirus vaccine, or who were partially vaccinated, in the months following the national stock-out. Other subnational shortages likely played a role in lower and less timely coverage with rotavirus vaccine during the study period, as suggested by the reasons parents provided for not having received rotavirus vaccine even before 2009.

This study had several limitations. Because the survey did not include cohorts before the rotavirus vaccine was introduced, we were unable to draw conclusions about the association between rotavirus vaccine introduction and the timeliness of routine infant vaccinations. The 2009 national vaccine shortage also limited our ability to look at improvements in timeliness across birth cohorts. Although the unavailability of the vaccine was identified as a primary reason for non-vaccination [2], we were unable to verify information about local vaccination stock or consider provider attitudes toward vaccinations and contraindications to vaccination for individual children.

This study also has several strengths. The analysis included three birth cohorts of children eligible for rotavirus and pentavalent vaccines with complete documentation of the dates of administration. As receiving pentavalent vaccine was nearly universal, it is clear that there is access to immunization services in this strong program. In addition, because the vaccination and community and family factor data were individually linked, we were able to assess associations based on individual information, rather than ecological and aggregated data. Finally, the overall sample size was sufficiently large to allow us to produce estimates by birth cohort.

Our findings add to the limited literature about the use and coverage of rotavirus vaccine, with a restricted period for valid administration and its impact on timing and coverage. The experience with rotavirus vaccine introduction in El Salvador is unique, but it can provide potentially helpful information for other country programs considering introducing this and other new vaccines, as well as promoting the use of existing survey data to answer specific questions regarding newer vaccines. The findings of this study also add to the growing number of analyses looking at vaccination timeliness and adherence to recommended ages for administration in low and middle income countries [2,22,23] and follows PAHO's new guidance tool for secondary survey analyses created in collaboration with the US Centers for Disease Control and Prevention [24]. El Salvador and other countries that have or will soon introduce new vaccines should continue to carefully monitor availability of vaccine, vaccination coverage, and timeliness and simultaneity of vaccine administration. Vaccination programs should encourage administration of all recommended vaccines during vaccination visits to avoid missed opportunities and rapidly accelerate coverage of new vaccines.

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