Temporal Association of Rotavirus Vaccine Introduction and Reduction in All-Cause Childhood Diarrheal Hospitalizations in South Africa

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Abstract

Background.—The public health impact of rotavirus vaccination in African settings with a high human immunodeficiency virus (HIV) infection prevalence is yet to be established. We

evaluated trends in all-cause diarrheal hospitalizations in Soweto, Johannesburg, before and after the introduction of rotavirus vaccine into South Africa's national immunization program in August 2009.

Methods.—Hospitalizations in children <5 years of age with a diagnosis of diarrhea, defined by *International Classification of Diseases, Tenth Revision* codes A00–A05, A06.0–A06.3, A06.9, A07.0–A07.2, A07.9, and A08–A09, were identified at the Chris Hani Baragwanath Academic Hospital from 1 January 2006 to 31 December 2014. The median annual prevaccine (2006–2008) hospitalization incidence was compared to that of the vaccine era (2010–2014), and stratified by age group and HIV infection status.

Results.—Incidence reductions (per 1000 population) were greatest in children aged <12 months: 54.4 in the prevaccine era vs 30.0, 23.6, 20.0, 18.8, and 18.9 in the postvaccine years 2010–2014, respectively (a 44.9%–65.4% reduction). Lower incidence reductions (39.8%–49.4%) were observed among children aged 12–24 months from the second year post–vaccine introduction onward. Reductions were observed in both HIV-infected and HIV-uninfected children. There was a change in the seasonal pattern of diarrheal hospitalizations post–vaccine introduction, with flattening of the autumn–winter peaks seen in the prevaccine years.

Conclusions.—An accelerated and sustained decline in all-cause diarrheal hospitalizations, temporally associated with rotavirus vaccine introduction, was observed in children <2 years of age. However, the impact of other interventions such as improved sanitation and changes in HIV management cannot be discounted.

Keywords

rotavirus vaccine; diarrhea; HIV; children

Rotavirus is the leading cause of diarrhea among children <5 years of age, accounting for approximately 27% of all severe diarrhea episodes worldwide in 2011. Rotavirus vaccines have the potential to reduce diarrheal morbidity and mortality, especially in Africa where almost half of the global rotavirus deaths occur [1, 2]. Following demonstration of high vaccine efficacy of Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and RotaTeq (Merck Vaccines, Whitehouse Station, New Jersey) in prelicensure clinical trials in Latin America, Europe, and the United States, introduction of rotavirus vaccines into national immunization programs resulted in a substantial decrease in diarrhea-related hospitalizations and deaths in these countries [3–9]. Lower vaccine efficacy was, however, observed in clinical trials in low- to middle-income countries in Africa, and there are limited data evaluating the impact of rotavirus vaccines on the burden of diarrheal hospitalizations in African settings [10, 11].

The effectiveness of rotavirus vaccines in Malawi and South Africa has been evaluated by case-control studies, but these studies were not able to fully address the public health impact of this intervention [12, 13]. Sentinel surveillance in children aged <5 years in South Africa showed that diarrheal hospitalizations decreased by about a third in 2010 and 2011 compared to 2009, the year of vaccine introduction [14]. A study from Ghana reported a 52%–59% reduction in all-cause diarrhea hospitalizations in children aged <5 years in the year following rotavirus vaccine introduction compared with the immediate prevaccination

year [15]. These studies were, however, limited to the first 2 years postintroduction and did not specifically assess reductions in diarrhea hospitalizations in human immunodeficiency virus (HIV)–infected children, who are at 5-fold greater risk of diarrheal hospitalization compared with HIV-uninfected children [16].

We investigated the impact of routine infant rotavirus vaccination on all-cause diarrheal hospitalizations by comparing the incidence before (2006–2008) and after (2010–2014) vaccine introduction among HIV-infected and HIV-uninfected children <5 years of age in Soweto, South Africa.

METHODS

Study Setting

The Chris Hani Baragwanath Academic Hospital was the only public hospital serving the urban community of Soweto, Johannesburg, South Africa, among whom <10% had private medical insurance. As a result, the majority of children who required hospitalization were admitted to this hospital, where care was provided free of charge to children <5 years of age. The prevalence of HIV infection among mothers attending antenatal clinics in the Gauteng province remained steady at 30% since 2006; however, due to improvement in the prevention of mother-to-child transmission of HIV, the HIV prevalence among children aged <5 years decreased from 5.0% in 2006 to 3.8% by 2013 [17, 18]. Access to antiretroviral therapy (ART) has improved since its introduction into the public sector in 2004, with the estimated coverage in HIV-infected children requiring treatment being 54% in 2009 and 63% in 2012 [19, 20]. Rotarix was introduced into the national immunization program on 1 August 2009, and is provided at no cost at primary healthcare facilities. Two doses are recommended at 6 and 14 weeks of age, and children received trivalent oral polio vaccine (OPV-Merieux; Sanofi Pasteur, Lyon, France) concurrent with rotavirus vaccine at the 6-week immunization visit. District health information systems estimates of coverage rates for the second dose of rotavirus vaccine increased from 67% in 2010 to 96% in 2011 [21].

Study Participants

Children presenting with diarrhea either came directly from the community or were referred from community clinics. Decisions regarding hospitalization, investigations, and treatment were at the discretion of the attending physicians. Patient discharge diagnoses were obtained from a discharge summary completed by the attending physician on discharge/death of the child or the ward admission registry. A study physician coded the discharge diagnoses using the *International Classification of Diseases, Tenth Revision* (*ICD-10*). HIV infection status was obtained from HIV test results recorded in the discharge summary, ward registry, or from the hospital laboratory. Children 9 months of age were considered to be HIV infected if either the HIV enzyme-linked immunosorbent assay (ELISA) or HIV polymerase chain reaction (PCR) test was positive; and HIV uninfected if HIV ELISA or HIV PCR test was negative. Children aged <9 months were considered to be HIV-infected if the HIV PCR test was positive and HIV uninfected if the HIV ELISA or HIV PCR test was negative. If

a child was hospitalized more than once, results of any HIV test performed during these hospitalizations were used to assign HIV status to that child.

Data Analysis

All-cause diarrheal hospitalizations were defined by the following *ICD-10* diagnosis codes: A00–A05, A06.0–A06.3, A06.9, A07.0–A07.2, A07.9, and A08–A09. Children <5 years of age hospitalized with a primary or secondary diagnosis of diarrhea from 1 January 2006 to 31 December 2014 were included in this study. Any hospitalizations with a codiagnosis of nosocomial infection (*ICD-10* code Y95) or occurring within 14 days of the discharge date of a previous admission in the same child were excluded. All data were anonymized for personal identifiers of patients.

Monthly counts of all-cause diarrheal hospitalizations were plotted against time for age groups 0–11, 12–23, and 24–59 months for the period 2006–2014. A general strike of hospital staff occurred during a 3-week period in June 2007, resulting in only 1 pediatric ward remaining functional during this time. We adjusted for the resulting decrease in hospitalizations by calculating the ratio of hospitalizations, by age group, in June compared to May in 2006 and 2008, and multiplying the number of hospitalizations in May 2007 by this factor. Annual incidence of all-cause diarrheal hospitalizations (per 1000 population) was estimated using the annual number of children hospitalized for diarrhea in the numerator and the midyear population estimate in the denominator. Population denominators for Soweto (subdistrict D and G, Johannesburg) were obtained from Statistics South Africa, and HIV prevalence was estimated from projections of the Actuarial Society of South Africa's 2008 AIDS and Demographical model [17]. The median annual incidence during the prevaccine years 2006–2008 was compared to the incidence in the vaccine era (2010–2014), and stratified by age group and HIV status. Children who were not tested for HIV infection were assumed to be HIV uninfected, on the assumption that physicians were less inclined to test for HIV in the absence of clinical stigmata. We assessed the incidence of hospitalization for bronchiolitis (*ICD-10* codes J21.0, J21.1, J21.8, J21.9), for which there were no preventive intervention strategies implemented over the same period, to determine whether there were any changes in hospital admission practices. Confidence intervals for incidence estimates were calculated using the Poisson distribution.

Ethics Statement

Approval for the study was obtained from Human Research Ethics Committee (HREC approval number: M110528) of the University of the Witwatersrand. There was a waiver of consent for this observational study.

RESULTS

Trends in Diarrheal Hospitalizations

A total of 16 800 diarrheal hospitalizations occurred in children aged <5 years from 1 January 2006 to 31 December 2014. There was a downward trend in the number of diarrheal hospitalizations after rotavirus vaccine introduction, especially in children aged 0–11 months (Figure 1). Before rotavirus vaccine introduction, 68.6% of diarrheal hospitalizations

occurred in children 0–11 months, 20.9% in those 12–23 months, and 10.5% in those 24–59 months of age, compared to the vaccine era where 58.8%, 24.3%, and 16.9% of hospitalizations occurred in the respective age groups ($P < .001$). During the prevaccine period there were distinct annual peaks in the number of diarrheal hospitalizations during the autumn and early winter months of March–May in children aged <24 months, albeit this varied in magnitude and timing from year to year. In contrast, the peaks in diarrheal hospitalizations during the vaccine era were less pronounced and had a bimodal pattern.

Annual Diarrheal Hospitalization Rates

The estimated annual incidence (per 1000 population) of diarrheal hospitalizations among children aged <5 years decreased from 14.7 (median 2006–2008) to 9.7 in 2010—a 33.8% reduction (Table 1). Significant incidence reductions of 47.6%–56.6% (7.0–8.3 per 1000) were maintained through the following 4 years (2011–2014). Reductions were most pronounced in children 0–11 months and were evident from the first year post–vaccine introduction (incidence reduction, 24.4 per 1000; 44.9% in 2010 compared to the prevaccine era; Table 1). Further reduction was seen in 2011, the second postvaccine year (30.8 per 1000 [55.6%]), compared with prevaccine years, and reductions of 63.2%–65.2% (34.4–35.5 per 1000) were maintained during 2012–2014 in this age group. Among children aged 12–23 months, there was a marginal reduction in hospitalization incidence in the first year post–vaccine introduction, and reductions of 39.8%–49.4% were observed during the subsequent 4 years. Hospitalization incidence among children aged 24–59 months remained relatively constant with minimal reductions in the vaccine era compared to prevaccine years (Table 1). In contrast to the vaccine-era declines in diarrheal hospitalizations, the incidence of bronchiolitis hospitalizations remained relatively constant throughout the observation period (Supplementary Figure).

HIV-Infected and HIV-Uninfected Children

Of the total diarrheal hospitalizations, 1743 (10.4%) occurred in children diagnosed with HIV infection. The prevalence of HIV infection among children aged <5 years hospitalized for diarrhea decreased from 14.1% in 2006 to 5.3% in 2014. Overall, only 50% of children were tested for HIV infection, which varied by age group (older children were less likely to be tested) and year of hospitalization (increased testing in the latter years; data not shown).

Among children assumed to be HIV uninfected, significant declines in diarrheal hospitalization incidence in the vaccine era compared with prevaccine years, ranging from 23.2 to 32.8 per 1000 (45.8%–64.9%), were observed in those aged 0–11 months (Figure 2; Supplementary Table 1). In children aged 12–23 months, reductions of 36.5%–49.5% were observed from the second year post–vaccine introduction onward. There were minimal or no incidence reductions in children aged 24–59 months.

The hospitalization incidence among HIV-infected children aged 0–11 months decreased by 102.0 per 1000 (77%) in 2014 compared to the prevaccine years, with reductions ranging from 21.8% to 70.8% during 2010–2013 (Figure 3; Supplementary Table 2). In children aged 12–23 months, reductions in diarrheal hospitalizations in the vaccine era ranged from

45.0% to 64.8% (16.9–24.4 per 1000). There were significant reductions (41.6%–56.7%) in incidence in HIV-infected children aged 24–59 months in most postvaccine years.

DISCUSSION

The introduction of an oral live attenuated rotavirus vaccine into the South African national immunization program was temporally associated with a 34% to 57% decrease in the overall incidence of all-cause diarrheal hospitalizations in children aged <5 years in the urban setting of Soweto, Johannesburg. Reductions were greatest among children aged <12 months and maintained over a 5-year period post–vaccine introduction. A decrease of 45% in incidence was observed in the first year post–vaccine introduction in this age group, with further reductions of 57%–65% maintained through the subsequent 4 years. Among children aged 12–24 months, reductions of 40%–49% were observed from the second year post–vaccine introduction and were also maintained over time. These trends were observed among both HIV-infected and HIV-uninfected children. The incidence of all-cause diarrheal hospitalizations in the postvaccine years remained relatively unchanged or changed minimally among children aged >24 months.

Rotavirus testing was not conducted, either routinely or as part of a surveillance program, until diarrheal surveillance was established at Chris Hani Baragwanath Academic Hospital in May 2009. We could, therefore, not access the impact of rotavirus vaccine introduction on rotavirus-specific diarrheal hospitalizations and used all-cause diarrheal hospitalizations as a proxy. Our findings do, however, support the hypothesis that the observed decline in all-cause diarrheal hospitalizations can be attributed partly to the introduction of rotavirus vaccination into the routine immunization program. The reductions in incidence that we observed occurred specifically in the age groups that received the vaccine and were consistent with increasing vaccine coverage. Children aged <12 months would have been eligible to receive rotavirus vaccine from August 2009, and a 45% reduction was observed in the first postvaccination year (2010). As coverage increased to >90% at the end of 2010, consistent reductions of approximately 65% were observed from 2011 to 2014. Some of the children aged 12–23 months and hospitalized in the latter half of 2010 may have received rotavirus vaccine, and there is a small incidence reduction observed in the first postvaccination year, with greater reductions observed from the second postvaccination year in this age group. Previous South African studies showed that rotavirus disease occurred early in life, with 90%–95% of children hospitalized for severe rotavirus diarrhea being <18 months of age; hence, we would expect that the major public health impact of vaccination would be in children aged <24 months [22, 23]. We did not see any clear evidence of indirect protection (ie, protection in older unvaccinated children), as has been observed in some high-income settings [24, 25]. In our setting, very little rotavirus-associated hospitalization occurred in children >2 years of age prior to vaccine introduction, so any indirect protection in this age group would likely be minimal. Encouragingly, we did not see a shift toward increased incidence of diarrheal hospitalizations in these older children either.

There was a change in the epidemiology of diarrheal disease after rotavirus vaccine introduction. The prevaccine years were characterized by peaks in diarrheal hospitalizations among children aged <24 months during the autumn–winter months of March to May.

This seasonal pattern is consistent with what was known about rotavirus epidemiology in South Africa prior to vaccine introduction. Although rotavirus disease occurred year round, increases in rotavirus shedding had been observed during the cool, drier months, resulting in autumn–winter peaks in rotavirus-associated hospitalizations [23]. We observed a diminished peak in all-cause diarrheal hospitalizations during 2010, and these peaks were less pronounced during 2011–2014, where a bimodal pattern was observed.

The phase 3 clinical trial, which included both HIV-infected and HIV-uninfected children, demonstrated efficacy of the rotavirus vaccine against all-cause severe gastroenteritis of 44% (95% confidence interval, 19%–61%) during the first year of life, whereas our trend analysis showed reductions of 57%–65% in children aged <12 months [10].Although the confidence intervals do overlap, the point estimates we observed were higher. A decrease in transmission due to an overall decrease in circulation of rotavirus in the population could not be accounted for in the efficacy study design, and may account for the greater reductions that we observed in children aged <12 months. Our observed reductions are also greater than estimates of the reductions in all-cause diarrheal hospitalizations in children <12 months obtained from sentinel surveillance conducted in South Africa: 38% in the first and 43% in the second year after vaccine introduction [14]. However, these data were based on comparison with prevaccine estimates from 2009, the year of vaccine introduction, with no data available prior to vaccine introduction, and analyses were also limited to the months of May–December.

The oral rotavirus vaccine has been shown to be safe and immunogenic in HIV-infected children, but vaccine efficacy against diarrhea has never been specifically assessed in this subgroup [26]. The rotavirus vaccine effectiveness study conducted in South Africa observed similar effectiveness in HIV-exposed but uninfected and HIV-unexposed children, but was not able to assess effectiveness specifically among HIV-infected children [12].To our knowledge, this is the first study to show the impact of rotavirus vaccine introduction on diarrheal hospitalizations in HIV-infected children. The reductions we observed may have been confounded by interventions other than rotavirus vaccine introduction, most notably the expanded use of ART. During the study period there was increased uptake of ART among HIV-infected children as well as several changes in the South African guidelines for ART use. In 2010 and 2013 the HIV management guidelines were revised to include initiation of ART in all children <12 months and <5 years of age, respectively, irrespective of immunological status [27, 28]. The monitoring of ART access and usage in South Africa is challenging, with changes in reporting practices, lack of data on age of patients, changes in treatment guidelines leading to changes in the denominator for estimation of treatment coverage, and debate over the best measures to use to assess coverage. It is thus difficult to tease out the specific impact of ART vs rotavirus vaccine among these children, and it is likely that both interventions contributed to the reduced diarrheal hospitalizations observed in HIV-infected children.

An ecological study such as this has inherent limitations, including the ability to attribute causality. We used all-cause diarrheal hospitalizations as a proxy for rotavirus-associated hospitalizations, but without pathogen-specific testing it is difficult to definitively conclude on a causal relationship between rotavirus vaccine introduction and reductions in diarrheal

hospitalizations. We cannot exclude other possible reasons for the decline in diarrheal hospitalizations such as changes in the socioeconomic factors in the population or variability in the natural occurrence of rotavirus or other enteric pathogens, most notably norovirus and bacteria. Furthermore, vaccine coverage data were not available specifically for the Soweto population, only on a national level. Comparing census data from 2001 and 2011, respectively, there were improvements in the proportion of households with access to tap water (84.5% to 91.6%) and flush toilets (86.5% to. 90.5%), as well as a decrease in the average household size (3.1 to 2.9) in the Johannesburg region, although no subdistrict-level or year-on-year data were available [29]. One would assume that changes in sanitation would improve consistently over the years, leading to a steadier decline in annual diarrheal hospitalizations, rather than the more accelerated decline that we observed in the vaccine era.

Our incidence calculations relied on population estimates that are based on census data (2001 and 2011) with extrapolation to other years, and this may have led to under- or overestimation of the incidence. HIV prevalence was determined using the Actuarial Society of South Africa model with extrapolation of provincial estimates to the Soweto population, which may also have influenced our incidence calculations. Our assumption that children without a documented HIV status were HIV uninfected may have underestimated the disease burden among HIV-infected children. We believe, however, that this assumption likely approximates the true prevalence of HIV among diarrheal hospitalizations in that clinicians generally only tested children they suspected of being HIV infected. An HIV-infected child would most likely have had >1 hospitalization, prompting HIV testing, and if a child tested positive on a subsequent admission, we assumed that the child would have been positive on all admissions. Last, our study was restricted to 1 urban community in South Africa and may not be generalizable to other African settings.

Although the impact of other interventions such as improvement in socioeconomic conditions and changes in HIV management cannot be discounted, the accelerated decline in all-cause diarrheal hospitalizations after rotavirus vaccine introduction and the observed changes in diarrheal epidemiology are suggestive of a significant public health impact of rotavirus vaccine introduction in an African setting with a high prevalence of HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

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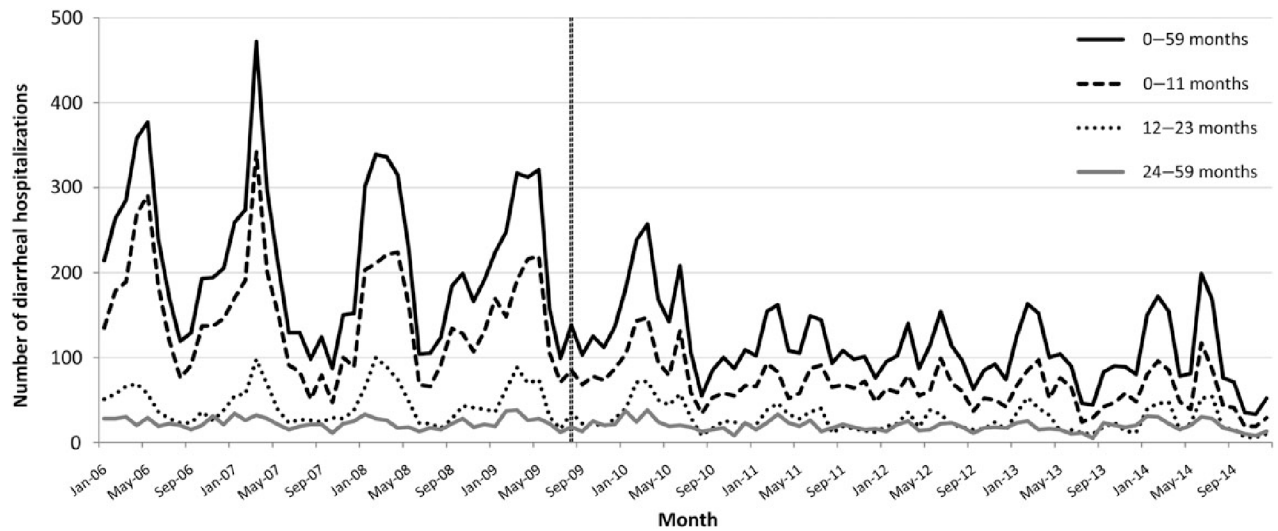
Figure 1.
Monthly count of all-cause diarrheal hospitalizations in children <5 years of age at Chris Hani Baragwanath Academic Hospital, Soweto, South Africa, 2006–2014. Vertical line represents introduction of rotavirus vaccine into the national immunization program in August 2009.
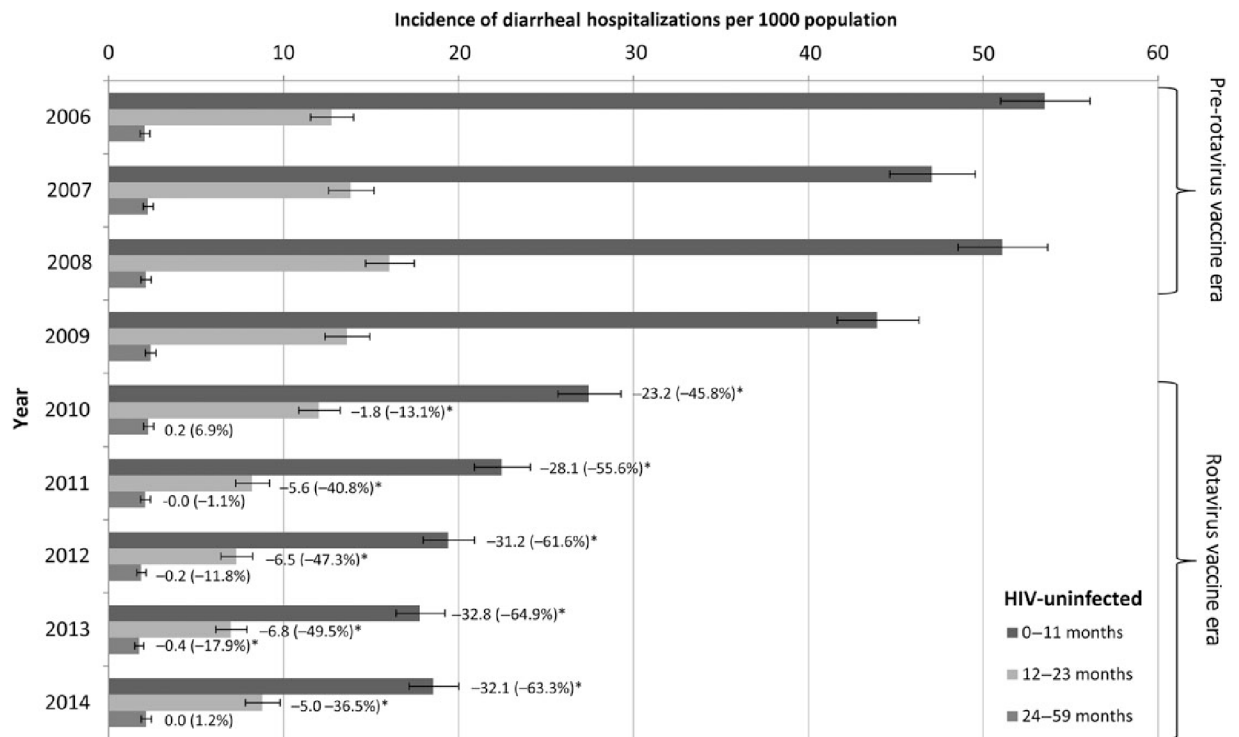
Figure 2.
Annual incidence per 1000 population (95% confidence interval) of diarrheal hospitalizations among human immunodeficiency virus (HIV)–uninfected children <5 years of age in Soweto, 2006–2014. Values are incidence difference = incidence in vaccine-era years 2010, 2011, 2012, 2013, and 2014, respectively, minus median incidence in the prevaccine years 2006–2008 (percentage change). A negative value indicates a reduction in incidence; a positive value indicates an increase in incidence. *P < .05. The 95% confidence intervals and P values are provided in Supplementary Table 1.
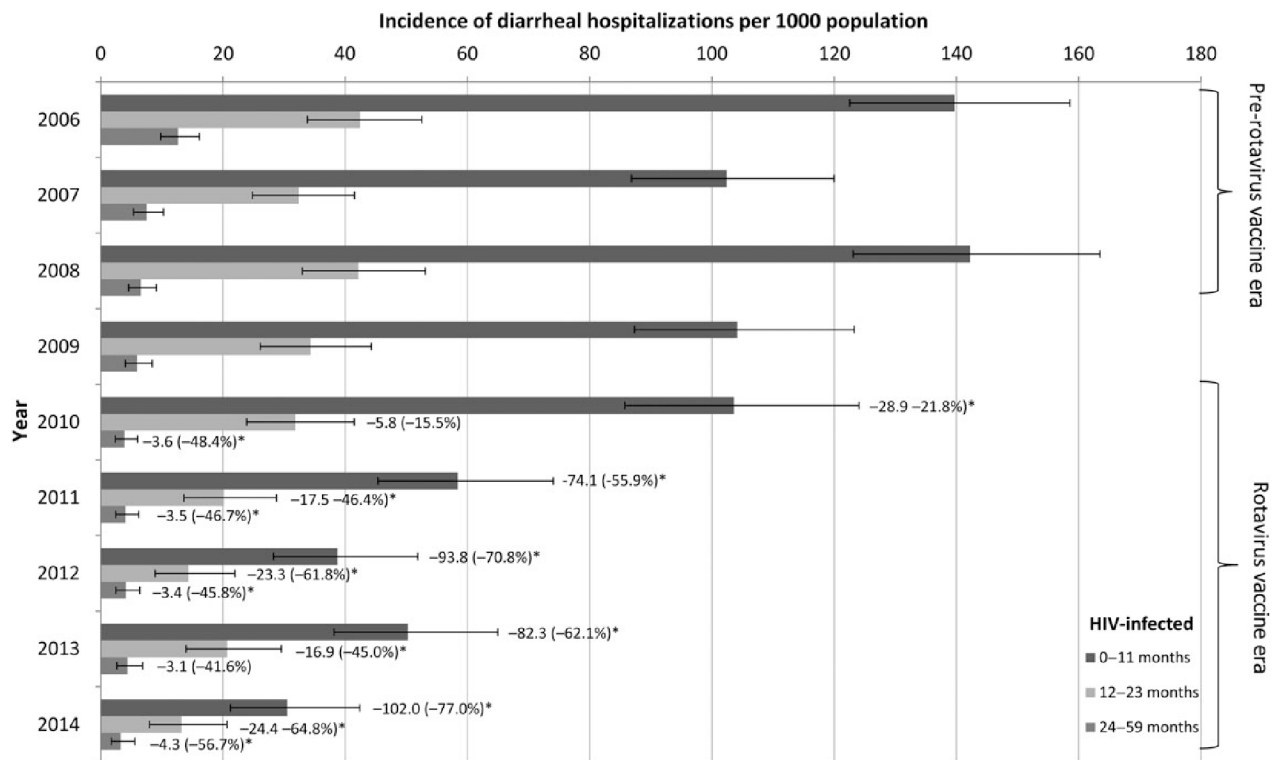
Figure 3.

Annual incidence per 1000 population (95% confidence interval) of diarrheal hospitalizations among human immunodeficiency virus (HIV)–infected children <5 years of age in Soweto, 2006–2014. Values are incidence difference = incidence in vaccine-era years 2010, 2011, 2012, 2013, and 2014, respectively, minus median incidence in the prevaccine years 2006–2008 (percentage change). A negative value indicates a reduction in incidence; a positive value indicates an increase in incidence. *$P < .05$. The 95% confidence intervals and P values are provided in Supplementary Table 2.

Table 1.

Incidence of All-Cause Diarrheal Hospitalizations Pre–Vaccine Introduction (2006–2008) Compared With
Vaccine Era (2010–2014) Among Children <5 Years of Age in Soweto, South Africa

Age Group and Year	Hospitalization Incidence (per 1000 Population)	Incidence Difference[a] (95% CI[b])	Change in Incidence[c], % (95% CI[b])	P Value
0–59 mo				
2006–2008[d]	14.7 (14.1–15.3)			
2010	9.7 (9.3–10.2)	−5.0 (−5.7, −4.2)	−33.8 (−37.8, −29.7)	<.001
2011	7.7 (7.3–8.1)	−7.0 (−7.7, −6.3)	−47.6 (−51.0, −44.1)	<.001
2012	6.7 (6.3–7.1)	−8.0 (−8.7, −7.3)	−54.5 (−57.6, −51.3)	<.001
2013	6.4 (6.0–6.8)	−8.3 (−9.0, −7.6)	−56.6 (−59.5, −53.4)	<.001
2014	6.9 (6.6–7.3)	−7.8 (−8.5, −7.1)	−52.9 (−56.0, −49.6)	<.001
0–11 mo				
2006–2008[d]	54.4 (51.9–57.0)			
2010	30.0 (28.2–31.9)	−24.4 (−27.6, −21.3)	−44.9 (−49.0, −40.4,)	<.001
2011	23.6 (22.1–25.3)	−30.8 (−33.8, −27.8)	−56.6 (−60.0, −52.8)	<.001
2012	20.0 (18.6–21.5)	−34.4 (−37.3, −31.5)	−63.2 (−66.3, −59.8)	<.001
2013	18.8 (17.4–20.3)	−35.6 (−38.5, −32.7)	−65.4 (−68.4, −62.2)	<.001
2014	18.9 (17.6–20.4)	−35.5 (−38.4, −32.6)	−65.2 (−68.2, −62.0)	<.001
12–23 mo				
2006–2008[d]	14.9 (13.6–16.2)			
2010	13.0 (11.8–14.2)	−1.9 (−3.6, −.1)	−12.7 (−23.2, −.8)	.035
2011	8.7 (7.7–9.7)	−6.2 (−7.8, −4.6)	−41.6 (−49.4, −32.6)	<.001
2012	7.6 (6.7–8.5)	−7.3 (−8.9, −5.7)	−49.0 (−56.2, −40.9)	<.001
2013	7.5 (6.7–8.5)	−7.3 (−8.9, −5.8)	−49.4 (−56.4, −41.2)	<.001
2014	8.9 (8.0–10.0)	−5.9 (−7.5, −4.3)	−39.8 (−47.7, −30.7)	<.001
24–59 mo				
2006–2008[d]	2.5 (2.2–2.8)			
2010	2.3 (2.1–2.7)	−0.2 (−.6, .3)	−6.2 (−21.2, 11.6)	.461
2011	2.2 (1.9–2.5)	−0.3 (−.7, .1)	−13.0 (−27.1, 3.9)	.116
2012	2.0 (1.7–2.2)	−0.5 (−.9, −.1)	−21.7 (−34.9, −6.1)	.007
2013	1.8 (1.6–2.1)	−0.7 (−1.1, −.3)	−26.5 (−39.0, −11.5)	<.001
2014	2.2 (1.9–2.5)	-0.3 (−.7, .1)	-12.9 (−27.1, 4.0)	.118

[a]Incidence in vaccine-era years 2010, 2011, 2012, 2013, and 2014, respectively, compared with median incidence in the prevaccine years 2006–2008. A negative value indicates a reduction in incidence; a positive value indicates an increase in incidence.

[b]Confidence interval.

[c]A negative percentage change indicates a reduction in incidence; a positive percentage change indicates an increase in incidence.

[d]Median hospitalization incidence 2006–2008.