Impact of rotavirus vaccine on all-cause diarrhea and rotavirus hospitalizations in Madagascar

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Abstract

Background—Rotavirus vaccine was introduced into the Extended Program on Immunization in Madagascar in May 2014. We analyzed trends in prevalence of all cause diarrhea and rotavirus hospitalization in children < 5 years of age before and after vaccine introduction and assessed trend rotavirus genotypes circulating at Centre Hospitalier Universitaire Mère Enfant Tsaralalàna (CHU MET).

Methods—From January 2010 to December 2016, we reviewed the logbook admission to observe the rate of hospitalization caused by gastroenteritis among 19619 children < 5 years of age admitted to hospital In June 2013–Dec 2016. Active rotavirus surveillance was also conducted at CHUMET with support from WHO. Rotavirus was detected by EIA from stool specimen of children with gastroenteritis eligible surveillance at sentinel site laboratory and rotavirus positive specimens were further genotyped at Regional Reference Laboratory by PCR.

Results—Diarrhea hospitalizations decreased after rotavirus vaccine introduction. The median proportion of annual hospitalizations due to diarrhea was 26% (range: 31% to 22%) before vaccine

introduction; the proportion was 25% the year of vaccine introduction, 17% in 2015 and 16% in 2016. Rotavirus positivity paralleled patterns observed in diarrhea. Before vaccine introduction, 56% of stool specimens tested positive for rotavirus; the percent positive was 13% in 2015, 12% in 2016. 21 distinct genotypes were detected in the pre-vaccine period; the most common were G3P[8] (n=53; 66%), G2P[4] (n=12; 15%), and G1P[8] (n=11; 14%). 6 distinct genotypes were found in 2015; the most common genotype was G2P[4] (n=10; 67%).

Conclusions—Following rotavirus vaccine introduction all-cause diarrhea and rotavirus-specific hospitalizations declined dramatically.

Keywords

Rotavirus vaccine; rotavirus; surveillance; genotype

Background

Diarrheal diseases remain one of the most common causes of child mortality in the world, with the majority of this burden in developing countries (1). In 2009, the World Health Organization (WHO) recommended all countries include rotavirus vaccine in their routine immunizations programs (2, 3, 4). In Madagascar, the two-dose oral monovalent human rotavirus vaccine, Rotarix(RV1, GSK Biologics), was introduced into the routine Expanded Program on Immunization (EPI) in May 2014 with support from WHO and funding from Gavi. Madagascar's vaccine schedule recommends rotavirus vaccine administration to infants at 2 and 4 months of age. Rotarix contains a G1P[8] human rotavirus strain and has been found to be effective in preventing severe rotavirus disease caused by the vaccine strain as well as genotypes not included in the vaccine (5, 6,7).

Laboratory-based rotavirus gastroenteritis sentinel surveillance was initiated in Madagascar in June 2013 at one sentinel hospital site in the capital city of Antananarivo. Diarrhea and rotavirus surveillance was important for making decisions regarding whether to introduce rotavirus vaccine into a country's routine immunization program and is essential to enable monitoring of vaccine impact and for selective pressure of rotavirus genotypes by the vaccine. The circulating genotypes can change over seasons and regions. Rotavirus vaccine impact evaluations in many countries have shown significant reduction of rotavirus hospitalizations since licensure in 2006including: Brazil, US, Panama, Mexico, Austria, Australia, Belgium, El Salvador, Rwanda, Ghana (8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18). Little is known about rotavirus disease burden and the impact of rotavirus vaccine introduction in Madagascar.

The objective of this analysis is to describe the impact of rotavirus vaccine introduction on the burden of severe all-cause diarrhea and rotavirus hospitalizations among children 59 months of age admitted to one sentinel surveillance hospital site in Madagascar. We also describe the trends in circulating rotavirus genotypes causing severe disease in Madagascar among children 59 months of age before and after rotavirus vaccine introduction.

Methods

Centre Hospitalier Universitaire Mère Enfant Tsaralalàna (CHUMET), an 82 bed public referral pediatric hospital located in the capital of Madagascar, primarily serves local patients, though some patients come from elsewhere in the country. CHUMET is the only rotavirus gastroenteritis surveillance site in Madagascar that reports to the WHO sentinel hospital surveillance network.

Retrospective hospital log book review

We reviewed hospital admission logbooks from CHUMET for children <5 years of age hospitalized for acute gastroenteritis with or without dehydration from January 1, 2010 to December 31, 2016; we compared diarrhea hospitalizations from the pre-vaccine period (January 2010 to December 2013 with the post-vaccine period (January 2015 to December 2016).

Active Rotavirus surveillance

Rotavirus surveillance-eligible stool specimens collected at CHUMET from children 59 months of age were tested for rotavirus antigen by enzyme immunoassay (EIA). Children were included if they were admitted with acute gastroenteritis defined as 3 or more watery, non-bloody stools within a 24 hour period lasting less than 7 days, and stool was collected within 48hours of admission. Surveillance data for this reported was collected from June 2013 to December 2016; we compared rotavirus prevalence detected by EIA from June 2013 to April 2014 as the pre-vaccine period with January 2015 to December 2016 as the post-vaccine period.

Samples submitted to surveillance site laboratory were screened for group A rotavirus using EIA prospect TM kit. Rotavirus antigen-positive fecal samples were stored at −20 °C until transfer to the regional reference laboratory (RRL) in Medunsa, South Africa for confirmation by polymerase chain reaction (PCR) and genotyping.

At the RRL, rotavirus antigen-positive samples were tested for determination of G and P types, using semi-nested multiplex PCR method performed with consensus- and genotype-specific primers. The first-round PCR products were purified; the sequencing was performed using consensus primers for the VP7 and VP4 genes and the sequence data were analyzed with the bioinformatics software packages. The rotavirus 11 genomic segments were separated by polyacrylamide gel electrophoresis (PAGE) to display two major distinctive RNA migration patterns. Genotyping results are presented for three periods: June 2013–April 2014, May–December 2014, and January–December 2015.

Analysis

All analyses were performed and figures generated using Microsoft Excel 2013. The Pearson chi square results were calculated using R 3.2.4.

Results

Retrospective hospital log book review

From January 2010 to December 2013, 12,026 children 59 months were admitted to hospital; diarrhea hospitalizations represented a median of 26% (range: 31% to 22%) of annual hospitalizations during this period (Figure 1). In 2014, the year of rotavirus vaccine introduction, 3,362 children 59 months were admitted to hospital, of which 25% were due to diarrhea. In the years following vaccine introduction, 5821 children were admitted to hospital with 16% due to diarrhea, compared with the pre-vaccine median, this is a 36% (p<0.001) reduction in the percent diarrhea hospitalizations in the post vaccine period. We noted increased diarrhea hospitalizations during two annual seasons: April–June and October-November. In 2015 and 2016, two seasonal peaks in diarrhea admissions are observable but reduced compared to earlier years (Figure 2). Before rotavirus vaccine introduction, 54%, 36%, and 10% of diarrhea hospitalizations included in this analysis were among children 0–11 months, 12–23 month, and 24–59 months of age, respectively (Figure 2); after rotavirus vaccine introduction, this distribution changed to 39%, 42%, and 19% of diarrhea hospitalizations, respectively.

Active Rotavirus surveillance

The number of stool specimens tested and EIA rotavirus positive results are shown by month from June 2013 to December 2016 in Figure 3; the seasonality and reduction observed in the number of stool specimens and rotavirus positivity parallels patterns observed in diarrhea hospitalizations (Figure 2). During this period of rotavirus surveillance, we collected and analyzed by EIA 203 (30% of all diarrhea admissions) stool specimens before rotavirus vaccine introduction and 449 (47% of all diarrhea admissions) stool specimens after rotavirus vaccine introduction. The remaining children did not meet the case definition for rotavirus or were not able to provide a stool specimen. From June 2013 to April 2014, rotavirus was detected in 114 (56%) stool specimens. The proportion of rotavirus positive stool specimens was 12% (n=56) in the post vaccine period (2015–2016), a reduction of 78% (p<0.01). Before vaccine introduction, 67%, 32%, and 1% of all rotavirus detected in stool specimens was among children aged 0–11 months, 12–23 months, and 24–59 months. In contrast, 48%, 43%, and 9% of all rotavirus detected in stool specimens was among children aged 0–11 months, 12–23 months, and 24–59 months after vaccine introduction, respectively (Figure 4).

Genotype testing

A total of 195 (69%) rotavirus positive specimens were genotyped at RRL (Table 1). Indeed, a limited number of rotavirus positive specimens were further tested for genotype according to RRL and WHO recommendations; the rest (n= 317) were not tested. We detected 21 distinct genotypes during the surveillance period. Before vaccine introduction, 7 different genotypes were detected in 80 specimens (Figure 5). The most commonly detected genotypes were G3P[8] (n=53; 66%), G2P[4] (n=12; 15%), and G1P[8] (n=11; 14%). Other genotypes were detected in the additional 4 specimens (5%). Of the genotyped specimens from the pre-vaccine introduction period, 68% were from children 0–11 months of age (Figure 6). During the first eight months after rotavirus vaccine introduction in 2014, 13

rotavirus genotypes were detected in 100 specimens. The most common detected genotypes were G3P[8] (n=20, 20%) and G9P[6], G9P[8], and G9P[4]P[8] with 9 specimens each. There were 9 additional genotypes detected in 53 specimens. In 2015, 6 distinct rotavirus genotypes were found in 15 specimens. The most common genotype was G2P[4] (n=10, 67%). The remaining 5, G3P[8], G9P[4]P[8], G1G3P[4], G1G3P[NT], G3G12P[4]P[8], had one positive specimen each. Compared with the genotypes detected pre-vaccination period, G1P[8], G3P[NT], G4P[6], G12P[6], and GNTP[8] were not detected in 2015. Of the genotyped specimens from 2015, 60% were from children 12–23 months of age.

Discussion

Our analysis of retrospective diarrhea hospitalization admissions and laboratory-confirmed rotavirus from a sentinel hospital surveillance site Madagascar following rotavirus vaccine introduction showed an important decrease diarrhea hospitalizations and rotavirus positive stool specimens, particularly in the 0–11 month age group. Prior to vaccine introduction, we identified two annual peaks for diarrhea hospitalizations in April–June and October–November. In the first 2 years following rotavirus vaccine introduction, a peak in diarrheal hospitalizations was observed in June, but with much fewer hospitalizations than the previous years and a less distinct peak was observed later in the year. Although the number of months of laboratory surveillance from before vaccine introduction are limited, the decrease in rotavirus hospitalizations are dramatic and concur with those from diarrhea hospital admissions. To the best of our knowledge, this is the first published description of severe diarrhea and rotavirus disease burden in the pre- and post-rotavirus vaccine introduction in Madagascar.

As rotavirus vaccine was introduced to Madagascar's national immunization schedule in 2014, we expected a reduction in diarrhea and rotavirus illness among children 0–11 months of age in 2015 and 2016, since this cohort was eligible for vaccination. We also expected a reduction in diarrhea and rotavirus illness children 12–23 months of age in 2016, since they would have been eligible for vaccination as infants the previous year. The nation-wide coverage of rotavirus vaccination estimated by WHO/UNICEF was 39% in 2014 and 69% in 2015(19). We observed the greatest reduction in diarrhea and rotavirus illness in age groups targeted for rotavirus vaccination. These findings are similar to several other countries that have introduced rotavirus vaccine, including Ghana, Rwanda, Malawi, South Africa, Brazil, Mexico, Panama and El Salvador (8, 9, 11, 12, 13, 17, 18, 19, 21, 22, 23, 23). Reductions in diarrhea and rotavirus in age groups not eligible for vaccination, have also been reported by several high-income and middle-income countries, including the USA, Australia, Austria, and El Salvador (10, 11, 17, 25, 26, 27). Rwanda showed also indirect protection of groups not eligible for vaccination two years only after introduction, although indirect effects were not found in Zambia and South Africa (17, 22, 29). In Madagascar, there were very few hospitalized children ages 24–59 months and we did not observed a reduction in diarrhea hospitalizations or rotavirus stools in the 12–23 and 24–59 month old age group. This cohort was not targeted for vaccination during this surveillance period.

Before vaccine introduction, the most common genotypes were G1P[8], G2P[4], andG3P[8], which is similar to findings from the USA and the majority of the countries in Europe (29,

30, 31). In 2015, G2P[4] became the most common genotype in Madagascar. Rotarix has been demonstrated to have high levels of protection against homotypic (G1P[8]) and partially heterotypic G1 strains or P[8]-expressing strains; many studies have also found high levels of protection against heterotypic strains (35,36, 37, 38, 39, 40, 41, 42, 43, 44, 45). While this analysis has limited data following vaccine introduction, the rotavirus genotype G1P[8] was not observed after vaccine introduction and genotype G3P[8] also decreased in first year after vaccine implementation. Ongoing surveillance of circulating rotavirus genotypes is important to observe for selective pressure, which could lead to diminished vaccine effectiveness.

This descriptive analysis has several limitations. First, during the surveillance period, not all children hospitalized for diarrhea were tested for rotavirus (758/2168); as decisions about stool testing were made based on the rotavirus case definition, we do not believe this will bias the results. Second, there was only one surveillance sentinel site in the country located in the capital so our results may not be representative of all children in Madagascar. Third, laboratory sentinel hospital surveillance was initiated only 11 months prior to rotavirus vaccine introduction, consequently we are limited in the information we have about rotavirus disease burden prior to vaccine introduction. Additionally, 11 months of surveillance is an imperfect comparison for 12 month periods; nonetheless, we did observe significant reductions in rotavirus positive stools. Finally, data about molecular epidemiology of rotavirus are limited, making it difficult to draw conclusions about the post-vaccine introduction situation in Madagascar.

In summary, hospital admissions for diarrhea and rotavirus declined during the first two years after introduction of rotavirus vaccine in Madagascar among groups targeted for vaccination. These findings are similar to those reported by other countries that had previously introduced rotavirus vaccine. These promising results may be built upon as Madagascar works to improve routine vaccination coverage in future years and as the cohorts of vaccine-eligible children ages.

Acknowledgments

References

1. World Health 0rganization. Weekly epidemiological record No 47. 2008; 83:421–4282.

2. Babji S, Kang G. Rotavirus vaccination in developing countries. Curr Opin Virol. 2012; 2:443–448. [PubMed: 22698800]

3. WHO. Rotavirus vaccines: an update. Wkly Epidemiol Rec. 2009; 84:533–540. [PubMed: 20034143]

4. Rotavirus vaccines. WHO position paper—January 2013. Wkly Epidemiol Rec. 2013; 88:49–64. [PubMed: 23424730]

5. Glass RI, et al. Rotavirus vaccines: Current prospects and challenges. Lancet. 2006; 368:323–332. [PubMed: 16860702]

6. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006; 354:11–22. [PubMed: 16394298]

7. Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. N Engl J Med. 2010; 362(January 4):289–298. [PubMed: 20107214]

8. doCarmo GM, Yen C, Cortes J, et al. Decline in diarrhea mortality and admissions after routine childhood rotavirus immunization in Brazil: a time-series analysis. PLoS Med. 2011:8.

9. Gurgel RG, Bohland AK, Vieira SC, et al. Incidence of rotavirus and all-cause diarrhea in northeast Brazil following the introduction of a national vaccination program. Gastroenterology. 2009; 137:1970–1975. [PubMed: 19632228]

10. Gastañaduy PA, Curns AT, Parashar UD, Lopman BA. Gastroenteritis hospitalizations in older children and adults in the United States before and after implementation of infant rotavirus vaccination. JAMA. 2013; 310:851–853. [PubMed: 23982372]

11. Molto Y, Cortes JE, De Oliveira LH, et al. Reduction of diarrhea-associated hospitalizations among children aged <5 years in Panama following the introduction of rotavirus vaccine. Pediatr Infect Dis J. 2011; 30:S16–S20. [PubMed: 21183835]

12. Quintanar-Solares M, Yen C, Richardson V, Esparza-Aguilar M, Parashar UD, Patel MM. Impact of rotavirus vaccination on diarrhea-related hospitalizations among children < 5 years of age in Mexico. Pediatr Infect Dis J. 2011; 30:S11–S15. [PubMed: 21183834]

13. Paulke-Korinek M, Kundi M, Rendi-Wagner P, et al. Herd immunity after two years of the universal mass vaccination program against rotavirus gastroenteritis in Austria. Vaccine. 2011; 29:2791–2796. [PubMed: 21320539]

14. Raes M, Strens D, Vergison A, et al. Reduction in pediatric rotavirus-related hospitalizations after universal rotavirus vaccination in Belgium. Pediatr Infect Dis J. 2011; 30:e120–e125. [PubMed: 21436757]

15. Zeller M, Rahman M, Heylen E, et al. Rotavirus incidence and genotype distribution before and after national rotavirus vaccine introduction in Belgium. Vaccine. 2010; 28:7507–7513. [PubMed: 20851085]

16. Yen C, Armero Guardado JA, Alberto P, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. Pediatr Infect Dis J. 2011; 30:S6–10. [PubMed: 21048524]

17. Ngabo FideleTate Jacqueline E, Gatera MauriceRugambwa CelseDonnen PhilippeLepage PhilippeMwenda Jason M, Binagwaho AgnesUmesh D Parashar. Effect of pentavalent rotavirus vaccine introduction on hospital admissions for diarrhoea and rotavirus in children in Rwanda. The Lancet Global Health. 2016; 4(2):e129–136. [PubMed: 26823214]

18. Enweronu-Laryea Christabel C, Boamah IsaacSifah EricDiamenu Stanley K, Armah George. Decline in severe diarrhea hospitalizations after the introduction of rotavirus vaccination in Ghana: a prevalence study. BMC Infectious Diseases. 2014; 14:431.doi: 10.1186/1471-2334-14-431 [PubMed: 25100574]

19. WHO and UNICEF estimates of immunization coverage: 2015 revision – DRAFT. May, 2016

20. Bar-Zeev N, Kapanda L, Tate JE. … and the VacSurv Consortium. Effectiveness of a monovalent rotavirus vaccine in infants in Malawi after programmatic roll-out: an observational and case-control study. Lancet Infect Dis. 2015; 15:422–428. [PubMed: 25638521]

21. Groome MJ, Page N, Cortese MM, et al. Effectiveness of monovalent human rotavirus vaccine against admission to hospital for acute rotavirus diarrhoea in South African children: a case-control study. Lancet Infect Dis. 2014; 14:1096–1104. [PubMed: 25303843]

22. Mismang VM, Page N, Groome MJ, et al. Impact of rotavirus vaccine on childhood diarrheal hospitalization after introduction into the South African public immunization program. Pediatr Infect Dis J. 2013; 32:1359–1364. [PubMed: 24569308]

23. Sáfadi MA, Berezin EN, Munford V, et al. Hospital-based surveillance to evaluate the impact of rotavirus vaccination in São Paulo, Brazil. Pediatr Infect Dis J. 2010; 29:1019–1022. [PubMed: 20543761]

24. Lambert SB, Faux CE, Hall L, et al. Early evidence for direct and indirect effects of the infant rotavirus vaccine program in Queensland. Med J Aust. 2009; 191:157–160. [PubMed: 19645646]

25. Clarke MF, Davidson GP, Gold MS, Marshall HS. Direct and indirect impact on rotavirus positive and all-cause gastroenteritis hospitalisations in South Australian children following the introduction of rotavirus vaccination. Vaccine. 2011; 29:4663–4667. [PubMed: 21575665]

26. Payne DC, Staat MA, Edwards KM, et al. Direct and indirect effects of rotavirus vaccination upon childhood hospitalizations in 3 US Counties, 2006–2009. Clin Infect Dis. 2011; 53:245–253. [PubMed: 21705316]

27. Lopman BA, Curns AT, Yen C, Parashar UD. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. J Infect Dis. 2011; 204:980–986. [PubMed: 21878425]

28. Mpabalwani Evans M, Simwaka Chibumbya J, Mwenda Jason M, Mubanga Cynthia P, Monze MwakaMatapo BelemParashar Umesh D, Tate Jacqueline E. Impact of Rotavirus Vaccination on Diarrheal Hospitalizations in Children Aged <5 Years in Lusaka. Zambia. 2016; 1(62Suppl 2):S183–7.

29. Gentsch JR, Hull J, Teel E, et al. G and P types of circulating rotavirus strains in the United States during 1996–2005: nine years of pre-vaccine data. J Infect Dis. 2009 In press.

30. Iturriza-Gómara M, Dallman T, Bányai K, Böttiger B, Buesa J, Diedrich S, et al. Rotavirus genotypes co-circulating in Europe between 2006 and 2009 as determined by EuroRotaNet, a pan-European collaborative strain surveillance network. Epidemiol Infect. 2011; 139(6):895–909. [PubMed: 20707941]

31. Santos N, Hoshino Y. Global distribution of rotavirus serotypes/genotypes and its implication for the development and implementation of an effective rotavirus vaccine. Rev Med Virol. 2005; 15:29–56. [PubMed: 15484186]

32. Midgley S, Böttiger B, Jensen TG, Friis-Møller A, Person LK, Nielsen L, et al. Human group A rotavirus infections in children in Denmark; detection of reassortant G9 strains and zoonotic P(14) strains. Infect Genet Evol. 2014; 27:114–120. [PubMed: 25038295]

33. Anca IA, Furtunescu FL, Ple ca D, Streinu-Cercel A, Rugin S, Holl K. Hospital-based surveillance to estimate the burden of rotavirus gastroenteritis in children below five years of age in Romania. Germs. 2014; 4(2):30–40. [PubMed: 24967217]

34. Boula A, Waku-Kouomou D, NjikiKinkela M, Esona MD, Kemajou G, Mekontso D, et al. Molecular surveillance of rotavirus strains circulating in Yaoundé, Cameroon, September 2007–December 2012. Infect Genet Evol. 2014; 28:470–475. [PubMed: 25220619]

35. Linhares AC, et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. Lancet. 2008; 371:1181–1189. [PubMed: 18395579]

36. Ruiz-Palacios GM, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006; 354:11–22. [PubMed: 16394298]

37. Tregnaghi MW, et al. Human rotavirus vaccine is highly efficacious when coadministered with routine expanded program of immunization vaccines including oral poliovirus vaccine in Latin America. Pediatr Infect Dis J. 2011; 30:e103–e108. [PubMed: 21378594]

38. Phua KB, et al. Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: randomised, double-blind, controlled study. Vaccine. 2009; 27:5936–5941. [PubMed: 19679216]

39. Lau YL, et al. Efficacy, safety and immunogenicity of a human rotavirus vaccine (RIX4414) in Hong Kong children up to three years of age: a randomized, controlled trial. Vaccine. 2013; 31:2253–2259. [PubMed: 23499605]

40. Vesikari T, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet. 2007; 370:1757–1763. [PubMed: 18037080]

41. Correia JB, et al. Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P[4] strains in Brazil. J Infect Dis. 2010; 201:363–369. [PubMed: 20047501]

42. Steele AD, et al. Human rotavirus vaccine Rotarix provides protection against diverse circulating rotavirus strains in African infants: a randomized controlled trial. BMC Infect Dis. 2012; 12:213. [PubMed: 22974466]

43. Kirkwood CD, Boniface K, Barnes GL, Bishop RF. Distribution of rotavirus genotypes after introduction of rotavirus vaccines, Rotarix® and RotaTeq®, into the National Immunization Program of Australia. Pediatr Infect Dis J. 2011; 30(1, Suppl):S48–S53. [PubMed: 21183840]

44. Carvalho-Costa FA, et al. Rotavirus genotype distribution after vaccine introduction, Rio de Janeiro, Brazil. Emerg Infect Dis. 2009; 15:95–97. [PubMed: 19116062]

45. Gurgel RG, et al. Incidence of rotavirus and all-cause diarrhea in northeast Brazil following the introduction of a national vaccination program. Gastroenterology. 2009; 137:1970–1975. [PubMed: 19632228]
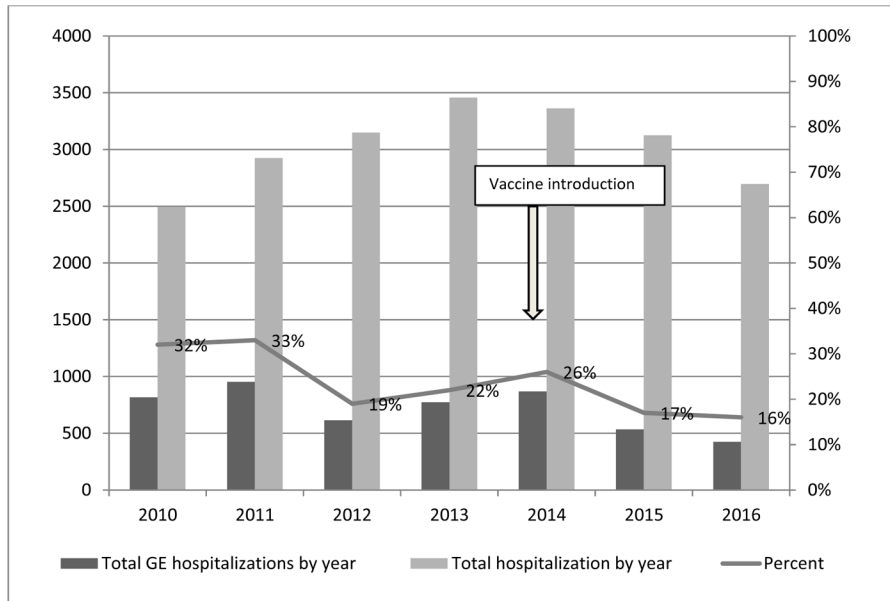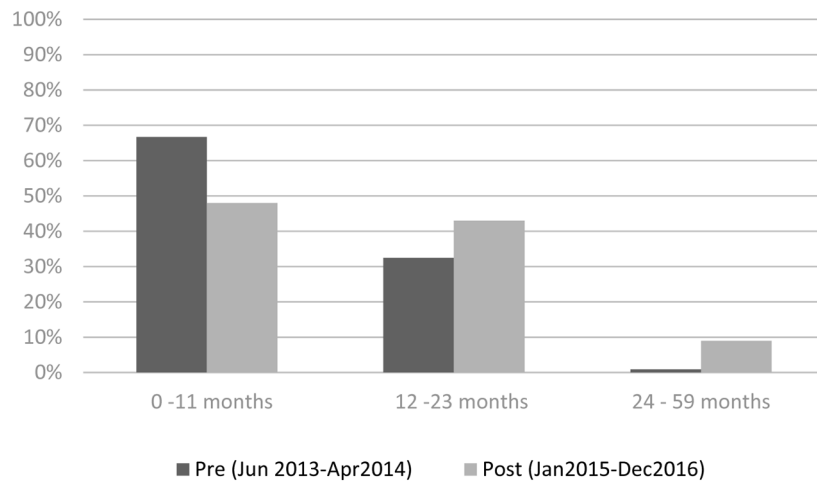
Figure 1.
Number of all diarrhea hospitalizations and total hospital admissions, and percent of total hospital admissions attributed to diarrhea among children 59 months by year 2010–2016, Madagascar.
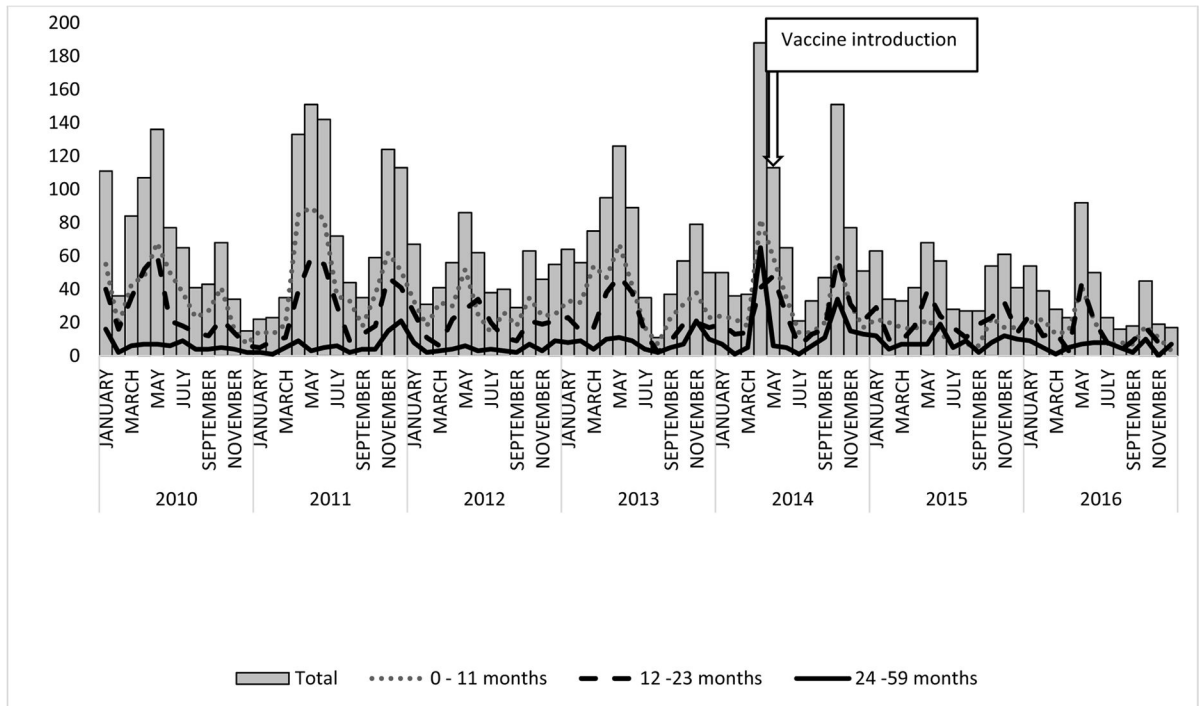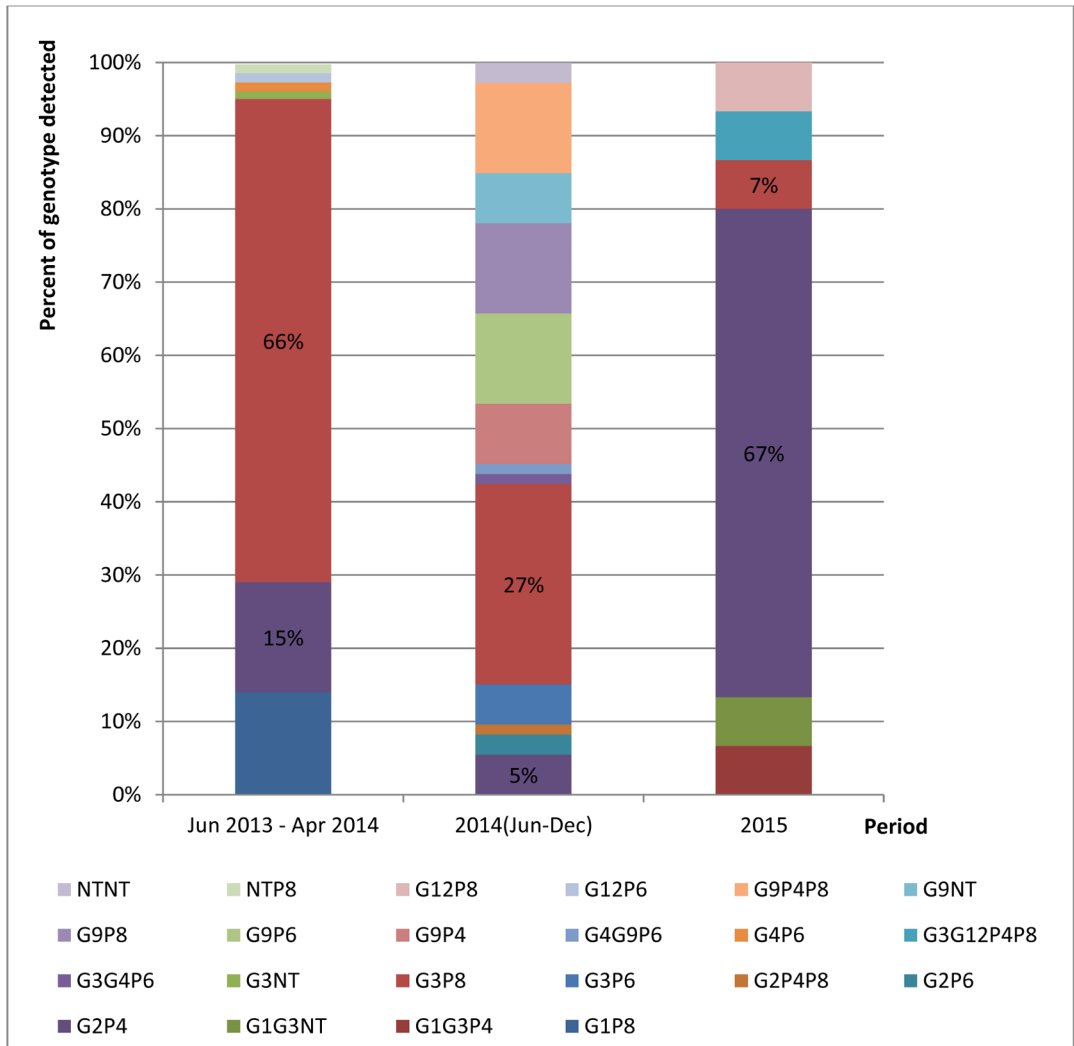
Figure 2.
Total and age group-specific number of diarrhea hospitalizations among children ≤ 59 months of age at sentinel hospital from January 2010 to December 2016, Madagascar.
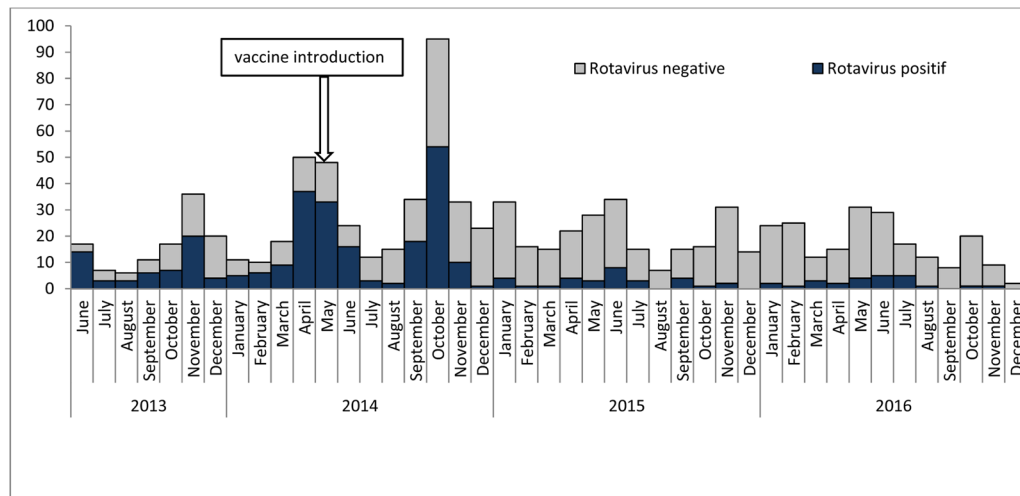
Figure 3.
Number of rotavirus positive stool samples among children 59 months of age by month from June 2013 to December 2016, Madagascar.
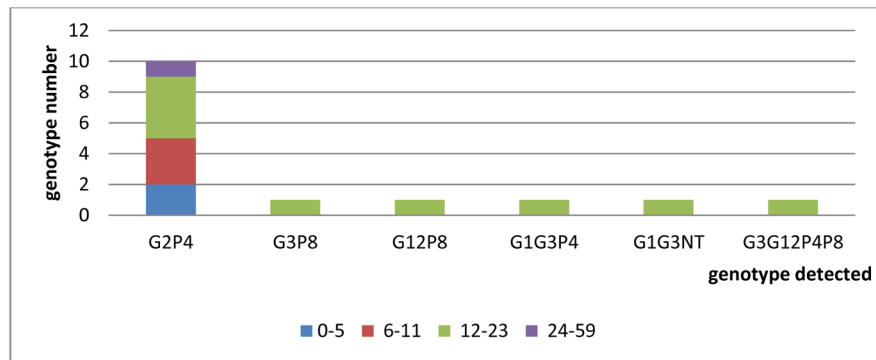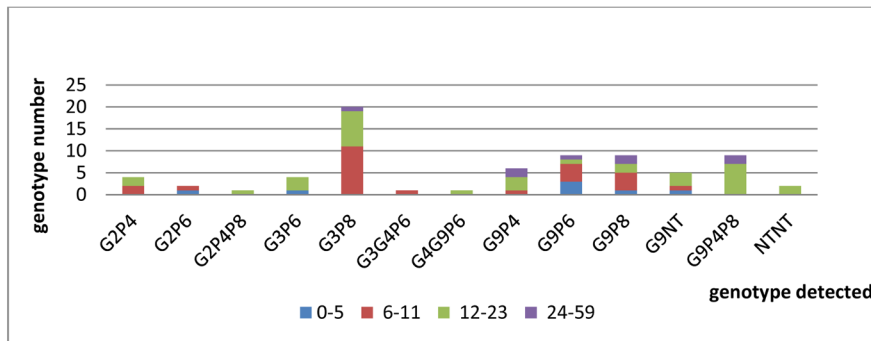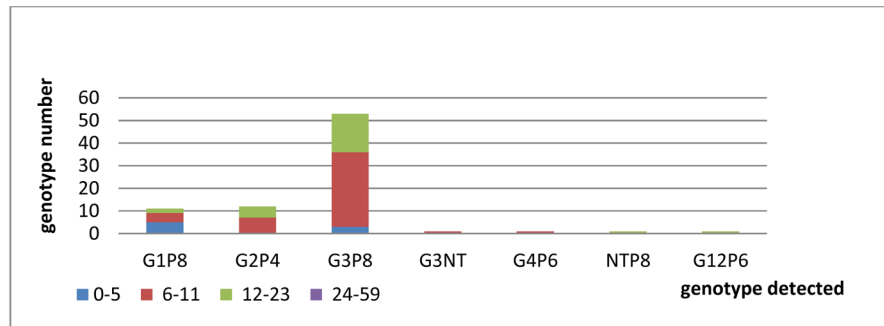
Figure 4.
Percent of total rotavirus positive samples by age group before and after rotavirus vaccine introduction, Madagascar.

Figure 5.
Rotavirus genotype distribution by year, Madagascar.

Figure 6.
Rotavirus genotype according to age groups during pre-vaccine introduction period, in Jun–Dec 2014 and in 2015, Madagascar.

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Table 1

Rotavirus Antigen-positive detected by EIA and genotyping, Madagascar.

	Pre Jun 2013–Apr 2014		Introduction May 2014–Dec 2014		Post Jan 2015–Dec 2016		Total	
	n	%	n	%	n	%	n	%
Specimen tested	203		244		446		893	
Rotavirus+ (EIA)	114	56%	137	56%	56	13%	307	34%
Genotyping at RRL	80	70%	100	73%	15	27%	195	64%