Vaccine-derived Rotavirus strains in infants in England

Charlotte M. Gower[1], Jake Dunning,[2,3] Sameena Nawaz,[3] David J. Allen[3,4], Mary E. Ramsay[1], Shamez N. Ladhani[1,5]

[1] Immunisation and Counter-Measures Division, National Infection Service, Public Health England, 61 Colindale Avenue, London, NW9 5EQ, UK

[2]Tuberculosis; Acute Respiratory, Gastrointestinal, Emerging and Zoonotic Infections; and Travel and Migrant Health Division (TARGET), National Infection Service, Public Health England, 61 Colindale Avenue, London, NW9 5EQ, UK

[3]Enteric Virus Unit, Virus Reference Department, National Infection Service Laboratories, Public Health England, 61 Colindale Avenue, London, NW9 5EQ, UK

[4]Department of Pathogen Molecular Biology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT

[5] Paediatric Infectious Disease Research Group St. George's University of London, Cranmer Terrace, London SW17 ORE, UK

Corresponding Author: Dr Shamez Ladhani, Immunisation and Counter-Measures Division, National Infection Service, Public Health England, 61 Colindale Avenue, London, NW9 5EQ, UK. E-mail: shamez.ladhani@phe.gov.uk

Abstract

Objective: To describe infants with acute gastroenteritis symptoms in primary and secondary care who have the Rotarix® vaccine-derived G1P[8] rotavirus strain identified in their stools.

Design: Prospective national surveillance conducted by Public Health England (PHE). Rotavirus-positive samples from vaccine-eligible children are routinely submitted to PHE for confirmation and general practitioners are requested to complete a surveillance questionnaire for all cases. The modified Vesikari score was used to assess severity of gastroenteritis

Setting: England, July 2013 to September 2016

Results: 2,637 rotavirus strains were genotyped and 215 (8%) identified as the Rotarix®vaccine-derived G1P[8] strain. There were no Rotarix® vaccine-derived G1P[8] strains detected in unimmunised infants. Rotarix® vaccine-derived G1P[8] strains clustered around the time of rotavirus vaccination and were responsible for 82% (107/130) of rotavirus-positive samples in 2 month-olds and 68% (36/53) in 3 month-olds. However, 14 samples were obtained more than 7 weeks after the last vaccination date; ten of these specimens were from six children who were subsequently diagnosed with severe combined immune deficiency (SCID). Diarrhoea was the single most common presenting symptom (83.0%) in infants with Rotarix® vaccine-derived G1P[8] strains, who were also less likely to present with fever, vomiting, dehydration or severe gastroenteritis.

Conclusions

Rotavirus identified in stools of infants around the time of their routine immunisations is most likely be the Rotarix® vaccine-derived G1P[8] strain. Infants with undiagnosed SCID at the time of rotavirus immunisation may experience prolonged gastroenteritis symptoms. The

46 majority of infants with vaccine strains in their stools more than 7 weeks after immunisation
47 had SCID.
48

Introduction

Rotavirus is the most common cause of diarrhoea leading to hospitalisation in young children and is associated with considerable healthcare utilisation (1-3). Prior to routine immunisation, rotavirus gastroenteritis (RVGE) was associated with more than 80,000 primary care consultations (2) and 13,000 hospitalisations in the UK each year among children under 5 years (3). On 01 July 2013, a two-dose, oral live-attenuated monovalent rotavirus vaccine, Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium), was introduced into the UK national infant immunisation programme at 8 and 12 weeks of age. Despite strict age restrictions for administering both the first and the second dose of vaccine, the programme rapidly achieved a very high vaccine uptake of 93% for the two-dose schedule by 25 weeks of age and was associated with a subsequent 15% decrease in primary care attendance for childhood acute gastroenteritis (AGE) as well as a 77% reduction in laboratory-confirmed rotavirus infections and a 26% decline in all-cause AGE–associated hospitalisations across all age groups (4, 5).

In England**,** hospital laboratories commonly employ a number of different rotavirus antigen tests with variable sensitivities and specificities to confirm the diagnosis of rotavirus gastroenteritis in children (6). A few of the larger specialist hospitals use more sensitive enzyme immunoassays and, less commonly, reverse-transcriptase polymerase chain reaction (RT-PCR) to confirm the diagnosis. Because of the variable testing practices, and as part of enhanced national surveillance to monitor the impact, effectiveness and safety of the infant rotavirus immunisation programme, Public Health England (PHE) requested hospital laboratories across England to submit all rotavirus-positive stool samples from children in the vaccine-eligible cohort to the national reference laboratory (Enteric Virus Unit; EVU) for confirmation and molecular characterisation. Surveillance of circulating rotavirus genotypes

before and since vaccine introduction has shown that the incidence of the previously most prevalent strain, G1P[8], on which the vaccine is based, has declined most significantly (7). At the same time, the genotype diversity of the remaining wild type rotavirus strains causing gastroenteritis has increased (7). Laboratory surveillance also identified a substantial proportion of samples as Rotarix®vaccine-derived-G1P[8] strains (7). Here we describe the characteristics of infants with confirmed Rotarix®vaccine-derived-G1P[8] strain identified in their stools following the introduction of the rotavirus vaccine into the national immunisation programme and discuss the implications of our findings for frontline clinicians assessing infants with acute gastroenteritis in primary and secondary care.

Methods

Hospital laboratories routinely report all clinically significant infections, including rotavirus, electronically to PHE through the second-generation surveillance system (SGSS). PHE conducts enhanced national surveillance of all reported rotavirus cases in the vaccine-eligible cohort in England. As part of enhanced surveillance, a questionnaire is sent to general practitioners (GPs) for each case, requesting the rotavirus immunisation history; between 01 July 2013 and 30 June 2015, the questionnaire also requested information to complete a modified Vesikari score for cases (8, 9).

Since the introduction of the rotavirus immunisation programme, all NHS laboratories have also been asked to routinely submit rotavirus-positive stool samples in vaccine-eligible children (i.e. those born since 01 May 2013) to the PHE EVU for confirmation (10-12) and molecular characterisation (13, 14). Samples from vaccine-eligible cases reported through SGSS and not submitted to PHE are actively followed-up with the reporting hospital virology department. Unlike hospital laboratories, methodologies used at PHE EVU determines wild-

type rotavirus genotypes according to binomial classification using the virus VP4 (P) and VP7 (G) sequences (as GxP[x]) and further differentiates G1P[8] type viruses between wild-type and vaccine-derived strains. Rotarix®vaccine-derived-G1P[8] strains were defined either: (1) where the sequences of the VP4 and VP7 encoding genes (segments 4 and 9, respectively) demonstrated highest homology with Rotarix® sequences (accession numbers JX943612 and JX943614, respectively); and/or (2) through detection of the Rotarix® sequence using a previously published and validated qRT-PCR assay, specifically targeting the NSP2 gene (segment 8) of the Rotarix® strain (13).

For this study, all cases identified with a Rotarix®vaccine-derived-G1P[8] strain between 01 July 2013 and 30 September 2016 were included in the analysis. For each case, the interval between the date of sample and the last dose of rotavirus vaccination was used to estimate the duration of shedding of the Rotarix®vaccine-derived-G1P[8] strains. Infants with a shedding interval greater than seven weeks were considered as outliers based on the distribution of the data, and investigated further by requesting additional clinical details and underlying conditions from their GP and, if needed, hospital clinicians. Infants confirmed with Rotarix®vaccine-derived-G1P[8] strains who were reported by their GP as unimmunised and those where the date of sample collection preceded the reported vaccination date were also followed-up to investigate the potential source of the Rotarix®vaccine-derived-G1P[8] strain.

Data Analysis

Data are mainly descriptive. Non-normal data are presented as medians with interquartile ranges and compared using the Mann Whitney U test. Proportions are compared using the chi-squared or Fisher's exact test, as appropriate.

Ethical Approval

PHE has legal permission, provided by Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002, to process confidential information for national surveillance of communicable diseases. (http://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made). This includes PHE's responsibility to monitor the safety and effectiveness of vaccines, and as such, individual patient consent is not required.

Results

During 01 July 2013 and 30 September 2016, 2,637 rotavirus strains were genotyped by PHE EVU and 215 (8%) identified as the Rotarix®vaccine-derived-G1P[8] strains. Of the 215 strains, eight were from infants who were not UK residents and were, therefore, not followed-up as part of national surveillance as they were not registered with a GP practice. Investigation of seven other cases initially reported as unimmunised by the GP confirmed that all had in fact received the rotavirus vaccine in the six weeks preceding the sample date. In five additional cases, the sample date was reported to be prior to the date of first vaccination, but subsequent investigation revealed that the vaccination date had been reported in error for three cases and the vaccine had in fact been given prior to the sample date. In the remaining two cases, the reported date of vaccination was for the second dose; both infants had been born prematurely and had received their first dose of rotavirus vaccine in hospital at an unspecified date, but prior to the sample date. There were, therefore, no Rotarix®vaccine-derived-G1P[8] strains isolated from unimmunised infants during the surveillance period, despite previous reports (7).

Rotarix®vaccine-derived-G1P[8] strains contributed 32% (12/37) of rotavirus-positive samples in infants aged under 2 months (these infants were immunised at 6-8 weeks; i.e. before they become two months old), 82% (107/130) in 2 month-olds, 68% (36/53) in 3 month-olds, 46% (11/24) in 4-month-olds, 19% (5/26) in 5 month-olds and less than 1% in older infants. There were 158 Rotarix®vaccine-derived-G1P[8] samples detected after a first dose of rotavirus vaccine and before the second dose, with a median of 12 (IQR7-21) days after vaccination (range, 0 days to 96 days). In addition, there were 49 samples with a Rotarix®vaccine-derived-G1P[8] strain detected after the second dose of rotavirus vaccine, with a median of 14 (IQR= 6-48) days after vaccination (range 2 to 420 days) (Figure 1). The interval between the sample date and vaccination was not significant between the first and second dose of Rotarix® (Mann-Whitney U test -8290, p=0.51). In the latter group, 19 samples were identified with a Rotarix®vaccine-derived-G1P[8] strain more than seven weeks after the last rotavirus vaccination (Figure 1). Of these, six had an incorrect sample date recorded and were, therefore, re-classified. Ten of the remaining samples were from six children who were subsequently diagnosed with severe combined immune deficiency (SCID); three additional cases with sample dates of 112 days, 71 days and 57 days after vaccination, respectively, were from infants who did not have any reported underlying condition; one was subsequently diagnosed with intestinal obstruction.

Based on the information in the clinical questionnaire completed by the GP, infants with a Rotarix®vaccine-derived-G1P[8] strain were younger than those with wild-type rotavirus gastroenteritis (Table 1). In the former group, diarrhoea was by far the most prevalent presenting symptom (83.0%) and 54.5% (68/127) presented with diarrhoea only. By comparison, although infants with wild-type rotavirus gastroenteritis (due to any circulating strain) nearly always also presented with diarrhoea (94.6%), other symptoms including fever

(48.4% vs. 20.2%, p<0.001) and vomiting (74.2% vs. 32.0%, p<0.001) were more prevalent when compared to infants with a Rotarix®vaccine-derived-G1P[8] strain. Notably, infants with wild-type rotavirus infection were less likely than those with a Rotarix®vaccine-derived-G1P[8] strain to present with diarrhoea only (without vomiting) (95/407 [23.3%] vs. 68/127 [54.5%]; P<0.001). Infants with wild-type rotavirus gastroenteritis were also more likely to be dehydrated (25.1% vs. 11.4%, P=0.001) and have severe gastroenteritis according to the modified Verikari score (37.5% vs. 9.8%, P=0.001) compared to those with a Rotarix®vaccine-derived-G1P[8] strain (Table 1).

Discussion

During the first three years of the infant rotavirus immunisation programme in England, one in twelve rotavirus strains detected in stool samples from infants in the vaccine-eligible cohort were Rotarix®vaccine-derived-G1P[8] strains. More than 93% of samples containing Rotarix®vaccine-derived-G1P[8] virus were found in infants within 7 weeks of their first or second Rotarix® vaccination at 8 and 12 weeks of age. Detection of Rotarix®vaccine-derived-G1P[8] strains in infants older than 5 months of age was associated with an underlying diagnosis of SCID; these infants continued to excrete the vaccine-derived for a long period. Infants with Rotarix®vaccine-derived-G1P[8] strains presented predominantly with diarrhoea and, compared to those with wild-type rotavirus gastroenteritis, were less likely to be dehydrated or have severe gastroenteritis as assessed by the modified Vesikari score.

Currently available point-of-care (POC) or rapid diagnostic tests for rotavirus do not differentiate between rotavirus strains as they are directed toward an antigen (VP6) common across all group A rotaviruses and/or utilise polyclonal reagents which do not discriminate between virus genotypes. Nucleic-Acid Amplification Test (NAAT)-based approaches are

capable of distinguishing genotypes, and – in the case of G1P[8] – wild from vaccine-derived strains. At present, commercial kit-based platforms do not offer this distinction as part of the multiplex designs, although laboratories may incorporate the test into any in-house methodologies after appropriate validation. The diagnostic tests commonly used by NHS hospital laboratories do not differentiate between wild-type and Rotarix®vaccine-derived-G1P[8] strains; this has important clinical implications.

Vaccine-strains causing symptoms: clinical implications

In our cohort, stool samples were submitted from symptomatic infants who were assessed in primary or secondary care because of parental concerns. In clinical trials, reported adverse events associated with Rotarix® vaccines include vomiting and diarrhoea. In a recent integrated analysis of the safety and reactogenicity of Rotarix® among >100,000 infants enrolled in 28 phase II and III clinical trials, the rates of any vomiting (17.8% vs. 17.0%) or diarrhoea (7.8% vs. 7.5%) as well as severe (Grade 3 intensity) vomiting (2.7% vs. 2.4%) or diarrhoea (4.9% vs. 4.5%) was similar among recipients of Rotarix® and the placebo group (15). Of the serious adverse events within 30 days of Rotarix® immunisation, however, gastroenteritis (0.27% vs. 0.39%; relative risk 0.65; 95% CI, 0.52-0.82; P=0.0002) and severe diarrhoea (0.03% vs. 0.06%; relative risk 0.48; 95% CI, 0.24-0.94; P=0.03) were both significantly less common in vaccinated infants compared to the placebo group.

In Japan, where two live attenuated oral rotavirus vaccines (Rotarix® and Rotateq®) have been used voluntarily since 2011, analysis of 1,824 stool samples from children at outpatient clinics with acute gastroenteritis identified the Rotarix®vaccine-derived-G1P[8] strain in six of 372 (1.6%) rotavirus-positive samples and no Rotateq® vaccine-derived strains (16). Wild-type rotavirus strains and other pathogens such as norovirus, *Escherichia coli* and enterovirus were also detected in two and four of the six samples, respectively, that were positive for the

Rotarix®vaccine-derived-G1P[8] strain (16). The authors concluded that the contribution of the vaccine-derived strains to the children's symptoms was unclear, although all six had been vaccinated 2-14 days before sample collection. In another study, diarrhoea post-vaccination was reported in 21% (13/61) of infants admitted to hospital within two weeks of receiving the Rotateq® vaccine (17).

Given that both vomiting and diarrhoea (especially severe symptoms warranting medical attention) are uncommon adverse events following oral rotavirus vaccination, even when solicited in clinical trials, a key question that remains as to whether the vaccine-derived strains identified in the stool samples of symptomatic infants in this study was responsible for the illness or whether another pathology was involved. Additional assessments to identify the cause of the gastrointestinal symptoms, including identification of other pathogens in the stool sample, may help elucidate the role of the Rotarix®vaccine-derived-G1P[8] strains in such infants. In the meantime, clinicians should be cautious when assessing infants presenting with symptoms of acute gastroenteritis during the period after their rotavirus immunisations (typically, 2-5 months of age). In particular, a rotavirus-positive stool sample in a recently immunised infant should be interpreted with caution unless, for G1[P8] strains, the presence of a Rotarix®vaccine-derived G1[P8] has been discounted, particularly in infants who are severely unwell, as there may be another cause of the illness. Another important consideration regarding oral rotavirus vaccination which has previously been reported is that clinicians should be aware of the small but significant increased risk of intussusception during the first week – and up to three weeks – after rotavirus immunisation, especially after the first dose of Rotarix® (18).

Prolonged shedding and SCID

Infants with the Rotarix®vaccine-derived-G1P[8] strains identified more than 7 weeks after they were given rotavirus immunisation ~~period~~ often had underlying SCID. Prolonged shedding of the Rotarix®vaccine-derived-G1P[8] strain is well-reported in infants with SCID (19) and vaccination of SCID patients with live rotavirus vaccines, including Rotarix®, is contra-indicated. Infants with SCID can be diagnosed early through national newborn screening programmes but this is not universally implemented (20-22), including in England, although a pilot study is being planned. In countries without such a screening programme, infants with prolonged gastrointestinal symptoms after rotavirus vaccination and/or shedding of Rotarix®vaccine-derived strain, particularly more than seven weeks following the most recent immunisation, should be assessed for underlying immune deficiency, especially SCID (20).

Transmission of vaccine-derived strains in the community

Another important finding in our study was the lack of Rotarix®vaccine-derived-G1P[8] strains in the stools of unimmunised, symptomatic children during the first three years of the national immunisation programme. Recent studies in neonatal intensive care units also did not identify any transmission of Rotarix®vaccine-derived-G1P[8] strains from immunised to unimmunised infants (23-25). Transmission of the vaccine strain to unimmunised children has been reported, albeit infrequently, and is not associated with any symptoms in the recipients, which is reassuring (26-28). Evidence of such horizontal transmission events is important because it could help explain the indirect (population) protection afforded by the infant programme to unvaccinated children and adults in England (4) and elsewhere (29).

Strengths and Limitations

The strength of this study lies in the enhanced national surveillance conducted by PHE that began prior to introduction of the rotavirus vaccine into the national immunisation programme (4). In addition to demonstrating population impact, we were able to monitor changes in circulating rotavirus strains following vaccine introduction (7). One limitation, however, was that sample submission rates from vaccine-eligible infants to PHE was relatively poor at the beginning of the programme but increased rapidly once the hospital laboratories implemented local protocols to prospectively submit positive samples to PHE. Additionally, stool samples were taken at the clinicians' discretion and only from infants whose parents were sufficiently concerned about their child to seek medical attentions. It is also possible that clinicians may be more likely to submit stool samples from immunised infants because they would expect such infants to be protected against rotavirus gastroenteritis. Finally, the information needed to calculate the modified Vesikari score, was poorly completed because the individual parameters of the Vesikari score are not routinely recorded in the clinical records and the surveillance questionnaire was sent to GPs several weeks after the diagnosis was confirmed in the infant.

Conclusions and Clinical Implications

Clinicians should be aware that infants may develop acute gastroenteritis symptoms, especially diarrhoea, and have positive rotavirus stool tests after rotavirus vaccination. SCID remains the major contraindication to rotavirus vaccination; those with prolonged gastrointestinal symptoms and/or rotavirus-positive stools after vaccination should be investigated for underlying immunodeficiency, including SCID.

Acknowledgements

We are grateful to the microbiologists and local authorities, general practitioners, health protection and environmental health specialists who have contributed data and reports to national surveillance systems and the epidemiologists and information officers who have worked on the national surveillance of intestinal infectious diseases for Centre for Infectious Disease Surveillance and Control and Health Protection Services Colindale. We are grateful to the scientists within the PHE Enteric Virus Unit, who perform the confirmatory and characterisation tests for the national surveillance programme, and also Prof David Brown, for his help in establishing the programme.

What is already known

1. Rotavirus is the most common cause of acute gastroenteritis leading to hospitalisation in young children worldwide
2. The live attenuated oral rotavirus vaccines are highly effective in preventing severe rotavirus gastroenteritis and hospitalisations due to rotavirus gastroenteritis
3. Hospital laboratories generally do not distinguish between wild-type rotavirus strains and vaccine strains in stool samples of symptomatic infants

What this study adds

1. After implementation of the rotavirus immunisation programme, 8% of rotavirus-positive stool samples in vaccine-eligible infants were vaccine strains

2. Most vaccine strains were found in infants within 7 weeks of their first or second Rotarix® immunisation at 8 and 12 weeks of age.
3. Infants with vaccine strains presented mainly with diarrhoea and were less likely to have fever, vomiting, dehydration or severe gastroenteritis than infants with wild type rotavirus.
4. The majority of infants with vaccine strains in their stools more than 7 weeks after immunisation had Severe Combined Immune Deficiency

REFERENCES

1. Giaquinto C, van Damme P. Age distribution of paediatric rotavirus gastroenteritis cases in Europe: the REVEAL study. Scand J Infect Dis. 2010;42(2):142-7.
2. Tam CC, Rodrigues LC, Viviani L, Dodds JP, Evans MR, Hunter PR, et al. Longitudinal study of infectious intestinal disease in the UK (ID2 study): incidence in the community and presenting to general practice. Gut. 2012;61:69-77.
3. Harris JP, Jit M, Cooper D, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part I. Estimating the burden of disease. Vaccine. 2007;25(20):3962-70.
4. Atchison CJ, Stowe J, Andrews N, Collins S, Allen DJ, Nawaz S, et al. Rapid Declines in Age Group-Specific Rotavirus Infection and Acute Gastroenteritis Among Vaccinated and Unvaccinated Individuals Within 1 Year of Rotavirus Vaccine Introduction in England and Wales. J Infect Dis. 2016;213(2):243-9.
5. Thomas SL, Walker JL, Fenty J, Atkins KE, Elliot AJ, Hughes HE, et al. Impact of the national rotavirus vaccination programme on acute gastroenteritis in England and associated costs averted. Vaccine. 2017;35(4):680-6.
6. Atchison CJ, Lopman BA, Harris CJ, Tam CC, Iturriza Gómara M, Gray J, J. Clinical laboratory practices for the detection of rotavirus in England and Wales: can surveillance based on routine laboratory testing data be used to evaluate the impact of vaccination?
. Euro Surveillance. 2009;21:19127.
7. Hungerford D, Allen DJ, Nawaz S, Collins S, Ladhani S, Vivancos R, et al. Impact of rotavirus vaccination on rotavirus genotype distribution and diversity in England, September 2006 to August 2016. Euro Surveill. in press.
8. Schnadower D, Tarr PI, Gorelick MH, O'Connell K, Roskind CG, Powell EC, et al. Validation of the modified Vesikari score in children with gastroenteritis in 5 US emergency departments. Journal of pediatric gastroenterology and nutrition. 2013;57(4):514-9.
9. Freedman SB, Eltorky M, Gorelick M. Evaluation of a gastroenteritis severity score for use in outpatient settings. Pediatrics. 2010;125(6):e1278-85.
10. Iturriza Gomara M, Wong C, Blome S, Desselberger U, Gray J. Molecular characterization of VP6 genes of human rotavirus isolates: correlation of genogroups with subgroups and evidence of independent segregation. Journal of virology. 2002;76(13):6596-601.
11. Iturriza Gomara M, Simpson R, Perault AM, Redpath C, Lorgelly P, Joshi D, et al. Structured surveillance of infantile gastroenteritis in East Anglia, UK: incidence of infection with common viral gastroenteric pathogens. Epidemiol Infect. 2008;136(1):23-33.
12. Iturriza-Gomara M, Dallman T, Banyai K, Bottiger 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.
13. Gautam R, Esona MD, Mijatovic-Rustempasic S, Ian Tam K, Gentsch JR, Bowen MD. Real-time RT-PCR assays to differentiate wild-type group A rotavirus strains from Rotarix((R)) and RotaTeq((R)) vaccine strains in stool samples. Human vaccines & immunotherapeutics. 2014;10(3):767-77.
14. EuroRotaNet network m. http://www.eurorota.net/docs.php [
15. Buyse H, Vinals C, Karkada N, Han HH. The human rotavirus vaccine Rotarix in infants: an integrated analysis of safety and reactogenicity. Human vaccines & immunotherapeutics. 2014;10(1):19-24.
16. Kaneko M, Takanashi S, Thongprachum A, Hanaoka N, Fujimoto T, Nagasawa K, et al. Identification of vaccine-derived rotavirus strains in children with acute gastroenteritis in Japan, 2012-2015. PLoS One. 2017;12(9):e0184067.

17. Donato CM, Ch'ng LS, Boniface KF, Crawford NW, Buttery JP, Lyon M, et al. Identification of strains of RotaTeq rotavirus vaccine in infants with gastroenteritis following routine vaccination. J Infect Dis. 2012;206(3):377-83.
18. Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation Ref. No: JVAC-D-16-01124. Vaccine. 2016;34(50):6115.
19. Bakare N, Menschik D, Tiernan R, Hua W, Martin D. Severe combined immunodeficiency (SCID) and rotavirus vaccination: reports to the Vaccine Adverse Events Reporting System (VAERS). Vaccine. 2010;28(40):6609-12.
20. King JR, Hammarstrom L. Newborn Screening for Primary Immunodeficiency Diseases: History, Current and Future Practice. Journal of clinical immunology. 2018;38(1):56-66.
21. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. Jama. 2014;312(7):729-38.
22. Chien YH, Yu HH, Lee NC, Ho HC, Kao SM, Lu MY, et al. Newborn screening for severe combined immunodeficiency in Taiwan. Int J Neonatal Screen 2017;3:16.
23. Hiramatsu H, Suzuki R, Nagatani A, Boda H, Miyata M, Hattori F, et al. Rotavirus Vaccination Can Be Performed Without Viral Dissemination in the Neonatal Intensive Care Unit. J Infect Dis. 2018;217(4):589-96.
24. Hofstetter AM, Lacombe K, Klein EJ, Jones C, Strelitz B, Jacobson E, et al. Risk of Rotavirus Nosocomial Spread After Inpatient Pentavalent Rotavirus Vaccination. Pediatrics. 2018;141(1).
25. Monk HM, Motsney AJ, Wade KC. Safety of rotavirus vaccine in the NICU. Pediatrics. 2014;133(6):e1555-60.
26. Dennehy PH, Brady RC, Halperin SA, Ward RL, Alvey JC, Fischer FH, Jr., et al. Comparative evaluation of safety and immunogenicity of two dosages of an oral live attenuated human rotavirus vaccine. Pediatr Infect Dis J. 2005;24(6):481-8.
27. Miura H, Kawamura Y, Sugata K, Koshiyama N, Yoshikawa A, Komoto S, et al. Rotavirus vaccine strain transmission by vaccinated infants in the foster home. Journal of medical virology. 2017;89(1):79-84.
28. Phua KB, Quak SH, Lee BW, Emmanuel SC, Goh P, Han HH, et al. Evaluation of RIX4414, a live, attenuated rotavirus vaccine, in a randomized, double-blind, placebo-controlled phase 2 trial involving 2464 Singaporean infants. J Infect Dis. 2005;192 Suppl 1:S6-s16.
29. Anderson EJ. Rotavirus vaccines: viral shedding and risk of transmission. The Lancet Infectious diseases. 2008;8(10):642-9.

Table 1: Characteristics of cases by rotavirus strain type, England 2013-2015.

Characteristic	**Wild type strains (n=536)**	**Vaccine derived G1P[8] (n=174)**	**P value**
Age, weeks	54.4 (43.3)	10.9 (4.6)	P<0.001
Age, months	12.5 (10.0)	2.5 (1.1)	P<0.001
Vomiting	305/411 (74.2%)	41/128 (32.0%)	P <0.001
Diarrhoea	401/424 (94.6%)	112/135 (83.0%)	P <0.001
Fever	180/372 (48.4%)	25/124 (20.2%)	P <0.001
Dehydration	97/387 (25.1%)	14/123 (11.4%)	P =0.001
Severity *			
Mild/moderate (1-10)	80/128 (62.5%)	37/41 (90.2%)	P =0.001
Severe (≥11)	48/128 (37.5%)	4/41 (9.8%)	

median (IQR), or n/N (%)

*modified Vesikari Score (based on the information provided by the GP in the clinical questionnaire, a modified Vesikari score could be calculated for 128 infants with wild-type rotavirus infection and 41 infants with a Rotarix®vaccine-derived-G1P[8] strain).

Figure 1

Percentage of 207 Rotarix®vaccine-derived-G1P[8] strains and the time since most recent documented vaccination in weeks. Underlying conditions of individuals with time since vaccination exceeding seven weeks are indicated.