Burden of rotavirus disease in young children in Iceland – Time to vaccinate?

Iris Kristinsdottir [a,b], Asgeir Haraldsson [a,b], Arthur Löve [a,c], Tinna Laufey Asgeirsdottir [d], Valtyr Thors [a,b,*]

[a] Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[b] Children's Hospital Iceland, Landspitali University Hospital, Reykjavik, Iceland
[c] Department of Clinical Microbiology, Division of Virology, Landspitali University Hospital, Reykjavik, Iceland
[d] Faculty of Economics, University of Iceland, Reykjavik, Iceland

ARTICLE INFO

ABSTRACT

Background: Acute gastroenteritis poses a significant burden on young children, families, health care facilities and societies. Rotavirus is the most common pathogen, but rotavirus infections are vaccine preventable. Information on the epidemiology of gastroenteritis in Icelandic children has until now not been available and rotavirus vaccination is currently not offered to Icelandic infants. The objective of this study was to assess the burden of rotavirus acute gastroenteritis in young children in Iceland and determine the potential benefit of adding rotavirus vaccine to the Icelandic childhood immunization schedule.

Methods: For a two-year period, children < 6 years old attending a children's emergency department for acute gastroenteritis were recruited at the Children's Hospital in Reykjavík, Iceland. Demographic information and Vesikari scores were registered. Stool samples were analyzed for pathogens. Duration of symptoms, treatment given, and secondary household infections were among the collected information. Annual cost of the infections in young children was estimated based on health care expenditures and lost days of parental work.

Results: 325 children were included in the study, 75% of which were $\leq$ 24 months old. A pathogen was identified in 80% of cases, of which rotavirus was identified in 54%. Rotavirus caused a more severe disease than other pathogens, more often leading to fluid treatment in the emergency department and admissions. Median duration of rotavirus-illness was six days and caused a median of four days lost from work by parents. The estimated annual cost of rotavirus acute gastroenteritis was €2.9 million.

Conclusions: Rotavirus causes significant disease burden in young children. Although rarely life-threatening in high income countries, the costs for society are substantial. The inclusion of rotavirus vaccine in the national immunization schedule will reduce the disease burden and would be cost-saving in Iceland.

© 2021 Published by Elsevier Ltd.

1. Introduction

Rotavirus is an important cause of acute gastroenteritis (AGE) in young children and the majority of children have already been infected by the age of five [1–3]. The annual number of rotavirus infections in Western Europe is high, with an estimated incidence of 219 infections per 100 000 children under the age of five, leading to nearly 5 million cases each year [4,5]. Rotavirus infections seldom lead to death in high-income countries but place a significant burden on children, families and health care systems [4,6,7].

The World Health Organization (WHO) has recommended the inclusion of a rotavirus vaccine in all childhood vaccination schedules since 2009 [8]. Four rotavirus vaccines are prequalified by WHO [9] and two have been licensed by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), one monovalent and the other pentavalent [10–13]. Both are live attenuated vaccines, given orally in two- and three-dose schedules, respectively, in the first year of life and have both been shown to be safe and effective [10,14,15]. Rotavirus vaccination is not included in the national immunization program in Iceland.

The introduction of rotavirus vaccines has led to a significant reduction in diagnosed infections, visits to emergency departments and hospital admissions due to rotavirus [7,16–18]. Furthermore, rotavirus vaccinations have been shown to be cost-effective in

* Corresponding author at: Children's Hospital Iceland – Landspitali University Hospital, Hringbraut, 101 Reykjavik, Iceland.
E-mail address: valtyr@landspitali.is (V. Thors).

high-income countries, and may even be cost-saving [19–22]. Financial benefits may vary between countries due to differences in cost of care [19,23,24]. Neither epidemiological studies, estimates of disease burden, nor cost-effectiveness calculations of rotavirus vaccination have previously been done in Iceland. This study was designed to estimate the burden of pediatric RVAGE in Iceland.

2. Methods

2.1. Study design, setting and data collection

The study was a two-year prospective study on AGE leading to an emergency department (ED) visit at the Children's Hospital, Iceland from 1st January 2017 to 31st December 2018. Parents of children aged < 6 years presenting to the ED with AGE (ICD-10 diagnoses A08/A09) and fulfilling the inclusion criteria of acute gastroenteritis (three or more loose stools and/or two or more forceful vomiting within 24 h and onset in the last 14 days), were approached and offered participation in the study. Participation was contingent upon written informed consent of a parent/legal guardian. At the time of ED visit, the following information was registered: date of ED visit, age (in months), sex, day-care attendance, Vesikari score[25] of the AGE episode, number of days with symptoms before the ED visit, and need for treatment at the ED (oral fluid, intravenous fluid, antiemetics).

A stool sample from the child was obtained. If a stool sample was not attainable, an anal skin swab was done [26]. When symptoms or medical history could indicate a bacterial infection, samples were also sent for bacterial culture. Within one week from the ED visits, parents/legal guardians were contacted by telephone and asked about total duration of illness, number of days the child missed from day-care, number of days lost from work or school for parents/guardians, number of other infected household members and their stance on rotavirus vaccination. If the symptoms were still ongoing, another phone call was made two weeks from the ED visit.

2.2. Virology – laboratory methods

Stool samples were transferred to the national laboratory for virological analysis. Processing of samples including DNA extraction and subsequent PCR was performed according to standardized laboratory methods [27]. A cycle threshold (CT) lower than 40 was considered positive (between 37 and 40 as weakly positive).

2.3. Definitions, data analysis and statistics

All AGE episodes, in which rotavirus was one of the identified pathogens, were considered RVAGE when comparing RVAGE to non-rotavirus AGE. All episodes, in which another pathogen or no pathogen was detected, were categorized as non-rotavirus AGE. A weakly positive result from PCR was included if it was the only detected pathogen but excluded if another pathogen was detected in the same sample. If children visited the ED on three or more consecutive days, it was defined as an admission.

Mann-Whitney U test was used for comparison of numerical variables and χ^2 test for categorical variables. A p-value of <0.05 was considered statistically significant. Analysis was done using R (version 3.6.3).

2.4. Cost - calculations

All costs were converted from Icelandic kronur (ISK) to EUR (€), using the average exchange rate in 2018 (1 EUR = 127.73 ISK) [28].

The cost of RVAGE was estimated by analyzing the direct cost due to healthcare, as well as indirect cost in the form of loss of productivity due to parental sick leave (not including secondary cases). Data on hospital costs (ED visits and admissions) was retrieved from hospital registry.

We assumed that 10% (reported range 10–20%)[1,29] of all children < 6 years of age were infected with rotavirus annually. Days lost from work were assumed to be three days (reported range in other studies 2.5–7.5) [6,18,24,29] for each primary infection. The value of lost work days was based on average salary including wage related expenses of working people in Iceland (€367/day), retrieved from Statistics Iceland [30].

2.5. Ethics

The study was approved by The National Bioethics Committee (ref. no. VSN-16–152) and the Medical Director at Landspitali University Hospital (ref. no. LSH 77–16).

3. Results

During the two-year study period 1081, children < 6 years old visited the ED at the Children's Hospital due to AGE, 468 in 2017 and 613 in 2018. Participation was approved for 348 children (32.2%) with signed informed consent. No samples were retrieved from 14 patients, six reported symptoms (diarrhea or vomiting) for > 14 days prior to ED visit and no data on duration of symptoms was available for three participants. They were therefore excluded from the analysis. Thus, 325 children were included in the study, of which 126 presented to the ED in 2017 and 199 in 2018 (26.9% and 32.5% respectively of AGE ED visits). Males were 194, females 131, and the median age was 16 months (Table 1). The majority (75.7%) of patients were ≤ 24 months of age. Median days with symptoms prior to ED visit was four (range 1–14) days (Table 1). Sixty percent of patients received treatment in the ED, of which oral fluid was the most common treatment. Twenty-nine patients (8.92%) were admitted to the Children's Hospital due to AGE. A quarter of non-admitted patients had at least one subsequent visit to the ED in the three days following the first ED visit. Of those, most patients had one subsequent visit (62/296) but nine had two visits and five three visits. Transmission of AGE to household members occurred in 56.7% of families (169/298, data missing for 27 households), with a median of one secondary infection in a family (range 0–7).

Pathogens were isolated from 80.3% of patients (261/325). One pathogen was isolated from most samples (198/325), two pathogens were isolated from 16.9% of samples (55/325) and three from 2.5% (8/325). Rotavirus was the most common pathogen, isolated from 142 patients (54.4% of positive samples), followed by adenovirus and norovirus (Fig. 1). Rotavirus was more prevalent in 2018 compared to 2017 (Fig. 2). In 2017, rotavirus was isolated from stool samples from 36 patients (28.6% of patients included in the study in 2017) but from 106 patients in 2018 (53.3% of patients included in 2018). Most episodes of RVAGE occurred in late winter and spring, from January to May (Figs. 2 and 3). Norovirus and adenovirus were more common in the autumn (Fig. 3). Bacterial infections were found in four cases, three cases of *Salmonella* spp. and one of *Campylobacter jejuni*.

Children with RVAGE were older than children with non-rotavirus AGE (median 18 vs. 14 months, p = 0.002) and presented to the ED sooner in the course of the illness, with a median of three days with symptoms compared to four days for children with non-rotavirus AGE (p = 0.005) (Table 1). Eighty percent of RVAGE episodes were classified as severe (Vesikari score ≥ 11) compared to 52.7% of non-rotavirus AGE (p < 0.001). Only one episode of RVAGE was classified as mild (Vesikari score < 7) compared to 14 (7.7%) of

Table 1

Characteristics of patients attending the ED with acute gastroenteritis. The table shows comparison of characteristics between those with RVAGE and non-rotavirus AGE.

	All acute gastroenteritis episodes, N = 325	Rotavirus acute gastroenteritis, N = 142	Non-rotavirus acute gastroenteritis, N = 183	p-value
Sex, male	194 (59.7)	83 (58.5)	111 (60.7)	0.773
Age, months	16 (1–71)	18 (1–69)	14 (1–71)	0.002
≤24 months of age, n (%)	246 (75.7)	100 (70.4)	146 (79.8)	0.069
Attending day care*				0.284
Yes	230 (72.3)	106 (75.7)	124 (69.7)	
No	88 (27.7)	34 (24.3)	54 (30.3)	
Vesikari score†				<0.001
Severe (≥11)	210 (64.8)	114 (80.3)	96 (52.7)	
Moderate (7–10)	99 (30.6)	27 (19.0)	72 (39.6)	
Mild (<7)	15 (4.6)	1 (0.7)	14 (7.7)	
Days with symptoms prior to ED visit	4 (1–14)	3 (1–12)	4 (1–14)	0.005
Duration of illness, days	6 (1–28)	6 (1–18)	8 (1–28)	<0.001
Days missed from day care*	5 (0–21)	5 (0–13)	5 (0–21)	0.676
Parental absence from work/school, days	4 (0–21)	4 (0–14)	4 (0–21)	0.476
Cases leading to secondary infections‡	169 (56.7)	78 (59.5)	91 (54.5)	0.450
Number of secondary cases within a family‡	1 (0–7)	1 (0–5)	1 (0–7)	0.835
Treatment in ED				
Any AGE treatment	196 (60.3)	119 (83.8)	77 (42.1)	<0.001
p.o. fluid	163 (50.1)	98 (69.0)	65 (35.5)	<0.001
i.v. fluid	82 (25.2)	56 (39.4)	26 (14.2)	<0.001
antiemetics	102 (31.4)	67 (47.2)	35 (19.1)	<0.001
Admissions	29 (8.9)	20 (14.1)	9 (4.9)	0.007

Numbers presented as n (%) or median (range). * Data on day care attendance missing for seven participants, two in the RVAGE group and five in the non-rotavirus AGE group. Those not attending day care excluded from analysis of days missed from day care. †Data missing on Vesikari score for one child (in the non-rotavirus AGE group). ‡Data missing on secondary infections for 27 cases (11 in the RVAGE group and 16 in the non-rotavirus AGE group).

non-rotavirus AGE. The duration of illness was shorter for RVAGE than non-rotavirus AGE (median 6 vs. 8 days, p < 0.001) (Table 1). More patients with RVAGE needed treatment, compared to patients with non-rotavirus AGE. Intravenous fluid was required for 39.4% of patients with RVAGE, compared to 14.2% of those with non-rotavirus AGE (p < 0.001) and admission was more often needed in RVAGE (14.1% vs. 4.9%, p = 0.007). There was no difference in loss of parental productivity or days missed from daycare between the two groups. Furthermore, there was no difference in infectivity of RVAGE compared to non-rotavirus AGE.

When asked about their stance towards rotavirus vaccinations, 91% of parents were in favor of including rotavirus vaccinations in

Icelandic vaccination schedules, 6.3% were against rotavirus vaccinations and 2.5% were undecided.

Assuming 10% of children < 6 years old are infected with rotavirus each year (assuming five and a half birth cohorts are susceptible, it's approx. 23,000 susceptible children[31]), there are 2300 RVAGE cases among Icelandic children annually. Fifty percent of cases result in secondary cases, leading to approximately additional 1150 secondary cases in all age groups annually. The primary cases lead to 6900 days lost from work (assuming three days are lost per episode), while parents care for their ill children. Workdays lost from secondary cases were excluded from the analysis. The average annual cost of RVAGE ED visits and hospital admissions at the Children's Hospital during the two study years was €369,677. The cost of days lost from work amounts to €2.5 million annually. The annual societal cost of RVAGE is therefore estimated to be approx. €2.9 million.

4. Discussion

This is the first prospective clinical study on AGE in young children in Iceland and supports findings from other countries that rotavirus is a common cause of AGE in children < 6 years of age and causes a significant disease burden on families and the health care system [2,24,32]. RVAGE is seasonal and usually peaks in late winter and spring, at a similar time of year as respiratory syncytial virus (RSV) and influenza,[33,34] causing considerable burden on health care facilities. Rotavirus was the cause of AGE leading to ED visits in more than half of the cases where a pathogen was identified. The median duration of symptomatic rotavirus infections was six days. Rotavirus has previously been reported as the most common virus causing AGE in children < 5 years of age [2,35]. In our study adenovirus and norovirus were the second and third most common causative organisms, respectively. Bacterial gastroenteritis was rare. Incidences of different pathogens fluctuated between years. Rotavirus infections were more common in 2018 than 2017. More children were recruited to the study in 2018 compared to 2017 (both absolute numbers and percentage of eligible children) which could contribute to this difference. A biennial pattern of RVAGE has been described after introduction of rotavirus
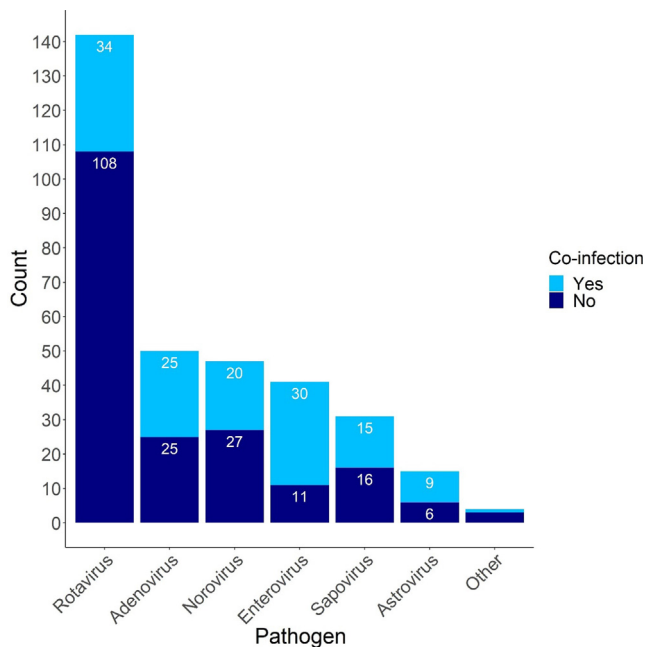

Fig. 1. Pathogens isolated from stool samples, rectal skin swabs and stool cultures. Co-infections occurred in 24.1% of all positive samples, all identified pathogens are shown in this figure. Other: Salmonella spp. and Campylobacter jejuni.
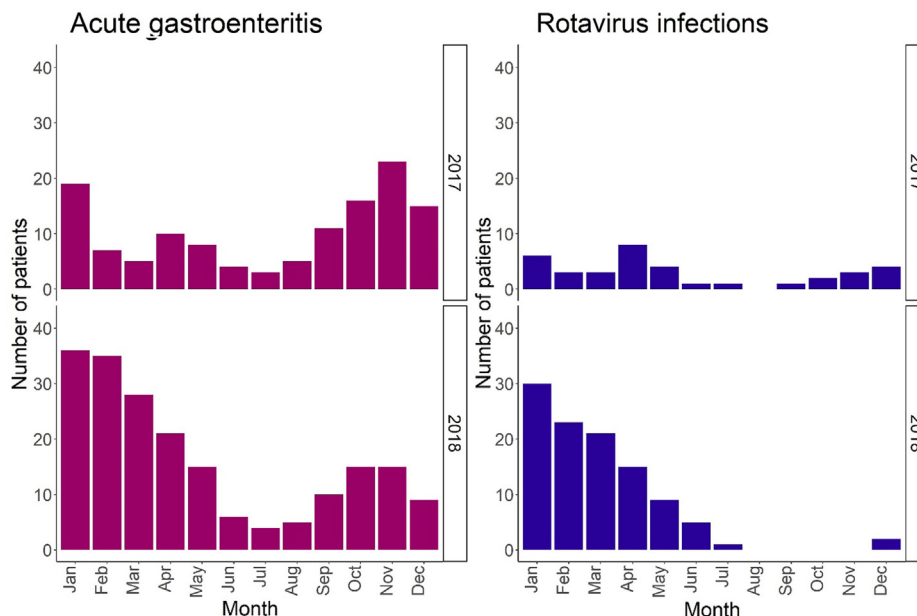
Fig. 2. Distribution of AGE and RVAGE over the study period. AGE leading to ED visits was most common during the winter months, as were RVAGE. AGE was more common in 2018 than 2017, and rotavirus was relatively a more prevalent pathogen in 2018 compared to 2017.

vaccinations in the USA but not in other countries with a national immunization program [36–38]. The emergence of a biennial pattern has also been described in the Netherlands, a country without a national immunization against rotavirus, but it is hypothesized to be as a result of herd immune effects due to vaccination programs in the neighboring countries [39]. In Iceland, no indirect protection through immunization in neighboring countries nor private market use of vaccine would explain the observed pattern in our study.

Rotavirus is a disease with the highest burden in young children. In our study, the majority of children with RVAGE were aged ≤ 24 months and this is mirrored by other studies [5,32,34]. As described by others, rotavirus infections were more severe than

Fig. 3. Seasonality of identified viruses during the two study years. Rotavirus infections were most common in late winter and spring, while norovirus and adenovirus infections were most common in the autumn.

non-rotavirus AGE and led to significantly more ED treatment and hospital admissions, although overall the disease duration was shorter [5,29,32]. In this cohort, more than half of cases led to a secondary infection in the household, similar to what has previously been reported [6]. This underlines the burden the disease causes on the children and families.

Rotavirus infections have been shown to significantly affect the quality of life of the child and parents during the episode, due to the illness, worries and changes in daily activities, factors often neglected in estimation of disease burden [6,40,41]. Not only does RVAGE cause disease and despair for the children and families, it also imposes substantial cost to the health care system and through lost productivity [24,42]. Loss of productivity, while parents care for their sick children, has previously been described as the main factor of indirect societal cost of RVAGE, accounting for 36–73% of total societal cost, varying between countries [24].

Our analysis of the cost of RVAGE is conservative. Firstly, in our calculation of the societal cost, we estimated that the annual incidence of RVAGE was only 10% in children < 6 years of age. The incidence is likely to be higher, as most children will have been infected at least once by the age of five [1,3,29]. Secondly, we assumed that RVAGE would cause three days lost from work/school. This might be a rather cautious estimate, as other studies have reported lost workdays ranging from 2.5 to 7.5 [6,18,24]. We used an arbitrary assumption, based on reported number of days from the literature, as our study only includes children that present to the ED. They are likely to have a more severe illness than children visiting a GP office or those not seeking any health care at all, resulting in more loss of productivity by parents. Thirdly, we estimated the household secondary attack rate to be 50%, as has been reported [6] but this was not included in our cost analysis. Also, no financial value has been put on GP visits, increased use of diapers, medication, parental anxiety, the loss of free time or health-related quality-of-life reductions. On the other hand, it is likely that in some cases one parent will not be working outside the home and the illness will not lead to any lost days from work. Our cautious estimation of the annual financial burden of RVAGE is €2.9 million; however, we believe that our analysis probably underestimates the true societal cost of RVAGE. Considering that no additional visits need to be added to the standard infant care,
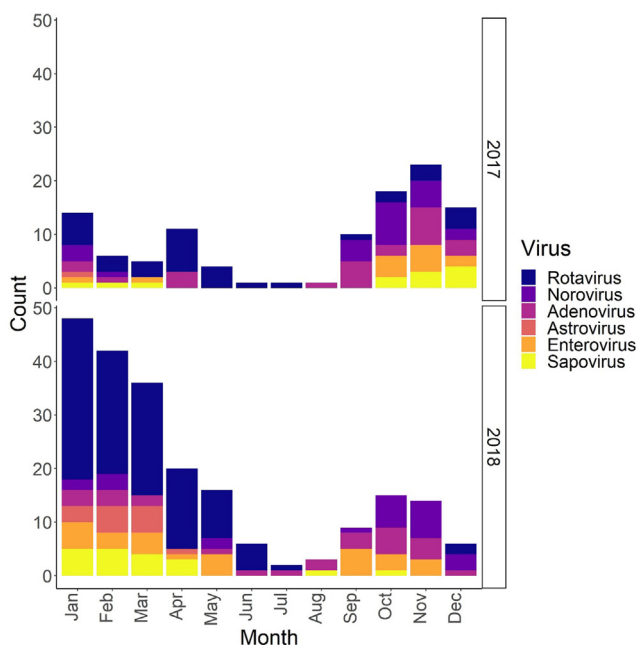
price of vaccine will be the largest factor for policy makers when deciding on inclusion of a rotavirus vaccine in the Icelandic national schedule. Assuming rotavirus immunization would reduce infection rate by 75% and the cost of a full vaccination schedule per child is around €100, the vaccination will be cost-saving according to our analysis.

Rotavirus is a highly infectious pathogen[43] with the ability to effectively spread despite general measures of hygiene and the best preventive measure is through immunization. Many countries in Europe have taken up one of the two available vaccines in national immunization schedules [44,45]. The vaccines have been found to be highly effective and cost-effective [18,20,22,46] National rotavirus vaccination schedules shorten and delay the onset of the rotavirus season, as well as reducing its peak [7,47]. Although rotavirus vaccination does not completely eliminate the risk of infection, breakthrough infections in vaccinated children result in a less serious illness with a shorter duration [18]. In addition, some studies indicate that rotavirus vaccinations may reduce childhood seizures, likely due to reduction of both febrile seizures and seizures as a result of direct neurotoxicity of the rotavirus [48,49].

In our study, most parents were in favor of including rotavirus vaccination in immunization schedules in Iceland. However, it is likely that the answers are biased since all children included in the study recently had an episode of AGE. Thus, the answers may not be representative of parental views in Iceland, although general attitude towards vaccinations is very positive [50].

There are some limitations to the study. Although recruiting a third of all children fulfilling the inclusion criteria seems adequate, it may not be representable. Severity of disease may influence willingness to participate and therefore lead to a potential selection bias in the cohort. We studied two consecutive years which may not represent ongoing epidemiology of RVAGE, and we did find fluctuations in individual pathogen incidences. Nevertheless, we maintain that the results provide adequate numbers for our analysis. For cost calculations, we based our estimate of RVAGE incidence and days lost from work from other published studies and in other high-income countries. We believe that these results are similar in Iceland. Finally, we emphasize that cost analyses differ considerably between countries.

5. Conclusions

Rotavirus is the most common pathogen causing AGE leading to ED visits in young children, causing significant illness and burden on health care systems and families. We conclude that implementing rotavirus vaccination for infants in Iceland will reduce the burden of rotavirus disease and be cost-effective. Furthermore, the vaccination is likely to interrupt of transmission and further spread of RVAGE in the community. Finally, the vaccination would improve the quality of life for young children and their families.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003;9 (5):565–72.

[2] Koch J, Wiese-Posselt M. Epidemiology of rotavirus infections in children less than 5 years of age: Germany, 2001–2008. Pediatr Infect Dis J 2011;30 (2):112–7.

[3] Velázquez FR, Matson DO, Calva JJ, Guerrero ML, Morrow AL, Carter-Campbell S, et al. Rotavirus infection in infants as protection against subsequent infections. N Engl J Med 1996;335(14):1022–8.

[4] Troeger C, Khalil IA, Rao PC, Cao S, Blacker BF, Ahmed T, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. JAMA Pediatr 2018;172(10):958. https://doi.org/10.1001/jamapediatrics.2018.1960.

[5] Forster J, Guarino A, Parez N, Moraga F, Roman E, Mory O, et al. Hospital-based surveillance to estimate the burden of rotavirus gastroenteritis among European children younger than 5 years of age. Pediatrics 2009;123(3): e393–400.

[6] Marlow R, Finn A, Trotter C. Quality of life impacts from rotavirus gastroenteritis on children and their families in the UK. Vaccine 2015;33 (39):5212–6.

[7] Marquis A, Koch J. Impact of routine rotavirus vaccination in Germany: evaluation five years after its introduction. Pediatr Infect Dis J 2020.

[8] World Health Organization. Rotavirus vaccination. Wkly Epidemiol Rec 2009;84:232–6.

[9] Prequalified vaccines. World Health Organization; 2021. https://extranet.who.int/pqweb/vaccines/prequalified-vaccines?field_vaccines_effective_date%5B date%5D=&field_vaccines_effective_date_1%5Bdate%5D=&field_vaccines_type %5B0%5D=Rotavirus%20&field_vaccines_name=&search_api_views_fulltext=& field_vaccines_number_of_doses=. Accessed 07.06.2021.

[10] Soares-Weiser K, Bergman H, Henschke N, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev 2019;3: Cd008521.

[11] Rotarix. European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/rotarix. Accessed 09.06.2021.

[12] RotaTeq. European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/rotateq. Accessed 09.06.2021.

[13] Vaccines Licensed for Use in the United States. U.S. Food & Drug Administration. https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states. Updated 08.06.2021. Accessed 09.06.2021.

[14] Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006;354(1):23–33.

[15] Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SAC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354(1):11–22.

[16] 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.

[17] Burnett E, Jonesteller CL, Tate JE, et al. Global impact of rotavirus vaccination on childhood hospitalizations and mortality from diarrhea. J Infect Dis 2017;215(11):1666–72.

[18] Adlhoch C, Hoehne M, Littmann M, et al. Rotavirus vaccine effectiveness and case-control study on risk factors for breakthrough infections in Germany, 2010–2011. Pediatr Infect Dis J 2013;32(2):e82–9.

[19] Heggie R, Murdoch H, Cameron C, Smith-Palmer A, McIntosh E, Bouttell J. Cost-impact study of rotavirus vaccination programme in Scotland. Hum Vaccin Immunother 2019;15(6):1265–71.

[20] Reyes JF, Wood JG, Beutels P, Macartney K, McIntyre P, Menzies R, et al. Beyond expectations: Post-implementation data shows rotavirus vaccination is likely cost-saving in Australia. Vaccine 2017;35(2):345–52.

[21] Leino T, Baum U, Scott P, Ollgren J, Salo H. Impact of five years of rotavirus vaccination in Finland - And the associated cost savings in secondary healthcare. Vaccine 2017;35(42):5611–7.

[22] Hansen Edwards C, de Blasio BF, Salamanca BV, et al. Re-evaluation of the cost-effectiveness and effects of childhood rotavirus vaccination in Norway. PLoS One 2017;12(8):e0183306.

[23] Samdal K, Hagen G, Flem E, et al. Cost-effectiveness of childhood vaccination against rotavirus in norway. In: NIPH Systematic Reviews: Executive Summaries. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2009.

[24] Giaquinto C, Van Damme P, Huet F, Gothefors L, Van der Wielen M. Costs of community-acquired pediatric rotavirus gastroenteritis in 7 European countries: the REVEAL Study. J Infect Dis 2007;195(s1):S36–44.

[25] Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis 1990;22 (3):259–67.

[26] Gibory M, Haltbakk I, Flem E, Vainio K, Salamanca BV, Størdal K, et al. Rotavirus detection in bulk stool and rectal swab specimens in children with acute gastroenteritis in Norway. J Clin Virol 2017;97:50–3.

[27] Wolffs PF, Bruggeman CA, van Well GT, et al. Replacing traditional diagnostics of fecal viral pathogens by a comprehensive panel of real-time PCRs. J Clin Microbiol 2011;49(5):1926–31.

[28] Official exchange rate. The Central Bank of Iceland. https://www.cb.is/? PageId=6909b7bd-5189-45dd-bf5b-c76ea33496ef. Published 2018. Accessed 25.11.2020.

[29] Quee FA, de Hoog MLA, Schuurman R, Bruijning-Verhagen P. Community burden and transmission of acute gastroenteritis caused by norovirus and rotavirus in the Netherlands (RotaFam): a prospective household-based cohort study. Lancet Infect Dis 2020;20(5):598–606.

[30] Laun eftir launþegahópi, starfsstétt og kyni 2014-2019. Hagstofa Íslands. http://px.hagstofa.is/pxis/pxweb/is/Samfelag/Samfelag__launogtekjur__1_laun__1_laun/VIN02002.px/. Accessed 25.11.2020.

[31] Lifandi og andvana fæddir eftir kyni 1951-2019. Hagstofa Íslands. http://px.hagstofa.is/pxis/pxweb/is/Ibuar/Ibuar__Faeddirdanir__Faeddir__faedingar/MAN05100.px/. Accessed 31.01.2021.

[32] Bruun T, Salamanca BV, Bekkevold T, et al. Burden of rotavirus disease in Norway: using national registries for public health research. Pediatr Infect Dis J 2016;35(4):396–400.

[33] Bloom-Feshbach K, Alonso WJ, Charu V, et al. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PLoS One 2013;8(2):e54445.

[34] Diez-Domingo J, Baldo JM, Patrzalek M, et al. Primary care-based surveillance to estimate the burden of rotavirus gastroenteritis among children aged less than 5 years in six European countries. Eur J Pediatr 2011;170(2):213–22.

[35] Waters V, Ford-Jones EL, Petric M, et al. Etiology of community-acquired pediatric viral diarrhea: a prospective longitudinal study in hospitals, emergency departments, pediatric practices and child care centers during the winter rotavirus outbreak, 1997 to 1998. The Pediatric Rotavirus Epidemiology Study for Immunization Study Group. Pediatr Infect Dis J 2000;19(9):843–8.

[36] Hallowell BD, Parashar UD, Curns A, DeGroote NP, Tate JE. Trends in the laboratory detection of rotavirus before and after implementation of routine rotavirus vaccination - United States, 2000–2018. MMWR Morb Mortal Wkly Rep 2019;68(24):539–43.

[37] Sabbe M, Berger N, Blommaert A, et al. Sustained low rotavirus activity and hospitalisation rates in the post-vaccination era in Belgium, 2007 to 2014. Euro Surveill 2016;21(27).

[38] Hemming-Harlo M, Markkula J, Huhti L, et al. Decrease of rotavirus gastroenteritis to a low level without resurgence for five years after universal rotateq vaccination in Finland. Pediatr Infect Dis J 2016;35(12):1304–8.

[39] Verberk JDM, Pijnacker R, Bruijning-Verhagen P, et al. Biennial pattern of rotavirus gastroenteritis in the Netherlands and a shifting age distribution after a low rotavirus season, 2010–2016. Pediatr Infect Dis J 2018;37(9):e248–50.

[40] Diez Domingo J, Patrzalek M, Cantarutti L, et al. The impact of childhood acute rotavirus gastroenteritis on the parents' quality of life: prospective observational study in European primary care medical practices. BMC Pediatr 2012;12:58.

[41] Brisson M, Sénécal M, Drolet M, et al. Health-related quality of life lost to rotavirus-associated gastroenteritis in children and their parents: a Canadian prospective study. Pediatr Infect Dis J 2010;29(1):73–5.

[42] Shin M, Salamanca BV, Kristiansen IS, et al. Healthcare costs of rotavirus and other types of gastroenteritis in children in Norway. Pediatr Infect Dis J 2016;35(4):e97–e101.

[43] Dennehy PH. Transmission of rotavirus and other enteric pathogens in the home. Pediatr Infect Dis J 2000;19(10 Suppl):S103–105.

[44] Poelaert D, Pereira P, Gardner R, Standaert B, Benninghoff B. A review of recommendations for rotavirus vaccination in Europe: arguments for change. Vaccine 2018;36(17):2243–53.

[45] The ROTA Council - Global Introduction Status. https://preventrotavirus.org/vaccine-introduction/global-introduction-status/. Accessed 03.02.2021.

[46] Karafillakis E, Hassounah S, Atchison C. Effectiveness and impact of rotavirus vaccines in Europe, 2006–2014. Vaccine 2015;33(18):2097–107.

[47] Tate JE, Panozzo CA, Payne DC, et al. Decline and change in seasonality of US rotavirus activity after the introduction of rotavirus vaccine. Pediatrics 2009;124(2):465–71.

[48] Payne DC, Baggs J, Zerr DM, et al. Protective association between rotavirus vaccination and childhood seizures in the year following vaccination in US children. Clin Infect Dis 2014;58(2):173–7.

[49] Sheridan SL, Ware RS, Grimwood K, et al. Febrile seizures in the era of rotavirus vaccine. J Pediatric Infect Dis Soc 2016;5(2):206–9.

[50] Óskarsson Ýmir, Guðnason Þórólfur, Jónsdóttir GuðbjörgA, Kristinsson KG, Briem H, Haraldsson Ásgeir. Public opinion on childhood immunisations in Iceland. Vaccine 2015;33(51):7211–6.