Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Rotavirus disease and health care utilisation among children under 5 years of age in highly developed countries: A systematic review and *meta*-analysis

Cristina Ardura-Garcia [a,1], Christian Kreis [a,1], Milenko Rakic [a], Manon Jaboyedoff [b], Maria Christina Mallet [a,c], Nicola Low [a], Claudia E. Kuehni [a,d,*]

[a] Institute of Social and Preventive Medicine, University of Bern, Mittlestrasse 43, 3012 Bern, Switzerland
[b] Service of Paediatrics, Department Women-Mother-Child, Lausanne University Hospital and University of Lausanne, Rue de Bugnon 21, 1011 Lausanne, Switzerland
[c] Graduate School for Health Sciences, University of Bern, Mittlestrasse 43, 3012 Bern, Switzerland
[d] Paediatric Respiratory Medicine, Children's University Hospital of Bern, University of Bern, Freiburgstrasse, 3010 Bern, Switzerland

ARTICLE INFO

Article history:
Received 15 December 2020
Received in revised form 16 April 2021
Accepted 17 April 2021
Available online xxxx

Keywords:
Rotavirus
Gastroenteritis
Health care use
Mortality
Systematic review

ABSTRACT

Background: Rotavirus (RV) infection is the leading cause of diarrhoea-associated morbidity and mortality globally among children under 5 years of age. RV vaccination is available, but has not been implemented in many national immunisation plans, especially in highly developed countries. This systematic review aimed to estimate the prevalence and incidence of health care use for RV gastroenteritis (RVGE) among children aged under 5 years in highly developed countries without routine RV vaccination.

Methods: We searched MEDLINE and Embase databases from January 1st 2000 to December 17th 2018 for publications reporting on incidence or prevalence of RVGE-related health care use in children below 5 years of age: primary care and emergency department (ED) visits, hospitalisations, nosocomial infections and deaths. We included only studies with laboratory-confirmed RV infection, undertaken in highly developed countries with no RV routine vaccination plans. We used random effects meta-analysis to generate summary estimates with 95% confidence intervals (CI) and prediction intervals.

Results: We screened 4033 abstracts and included 74 studies from 21 countries. Average incidence rates of RVGE per 100 000 person-years were: 2484 (95% CI 697-5366) primary care visits, 1890 (1597-2207) ED visits, 500 (422-584) hospitalisations, 34 (20–51) nosocomial infections and 0.04 (0.02–0.07) deaths. Average proportions of cases of acute gastroenteritis caused by RV were: 21% (95% CI 16-26%) for primary care visits; 32% (25-38%) for ED visits; 41% (36-47%) for hospitalisations, 29% (25–34%) for nosocomial infections and 12% (8–18%) for deaths. Results varied widely between and within countries, and heterogeneity was high (I^2 > 90%) in most models.

Conclusion: RV in children under 5 years causes many healthcare visits and hospitalisations, with low mortality, in highly developed countries without routine RV vaccination. The health care use estimates for RVGE obtained by this study can be used to model RV vaccine cost-effectiveness in highly developed countries.

Contents

* Corresponding author at: Mittelstrasse 43, 3012 Bern, Switzerland.
E-mail address: claudia.kuehni@ispm.unibe.ch (C.E. Kuehni).
[1] Contributed equally.

https://doi.org/10.1016/j.vaccine.2021.04.039
0264-410X/

1. Introduction

Rotavirus (RV) infection is the leading cause of diarrhoea-associated morbidity and mortality globally among children under 5 years of age [1]. RV-associated deaths are rare in high-income countries, but RV was estimated to account for 4.9 million episodes of diarrhoea among children younger than 5 years in Western Europe in 2016 [1]. The proportion of hospitalisations for acute gastroenteritis in children under 5 years caused by RV varies worldwide but has been reported to be 30–40% in both high- and low-income countries [2]. RV gastroenteritis (RVGE) therefore still poses a considerable burden on health care resources, although it is a vaccine-preventable disease.

Oral RV vaccines have been available since 2006 and have proven clinical efficacy against severe RVGE in different regions of the world, as summarised in a Cochrane review of randomised controlled trials in 2019 [3]. The World Health Organization (WHO) recommended the inclusion of RV vaccine in all national immunisation programmes in 2009, especially for countries at high risk of severe disease and mortality [4]. In Europe, however, only one third of countries had introduced RV vaccination in their national vaccination programmes in 2016 [5]. The low mortality and relatively high costs of the RV vaccine have led public health authorities in high-income countries to question the cost-effectiveness of the vaccine [6,7]. However, the burden on healthcare of RV-related disease includes the morbidity that leads to primary care consultations, emergency care, hospitalisations and nosocomial infections, as well as mortality (Fig. 1).

Previous systematic reviews have described the burden of RV-related health care use [2,8–14]. Most included studies from low and middle-income countries and did not include RV-related disease at all health care levels, from primary care visits to mortality [2,8–11,13]. The most recent review of RV health care use, including studies published up to 2016, also includes countries that have introduced routine RV vaccination [15]. To assess the cost-effectiveness of RV vaccines in high-income countries, we need estimates of RV-related health care use estimates that include all levels of care. We conducted a systematic review and meta-analysis to estimate the incidence and prevalence of primary and emergency care visits, hospitalisations, nosocomial infections and deaths for RVGE among children under 5 years in highly developed countries that had not introduced routine RV vaccination by 2018.

2. Methods

The protocol for this systematic review has been registered in the PROSPERO repository (CRD42019118069). We used the Preferred Reporting Items for Systematic Reviews and meta-Analyses statement (PRISMA, research checklist online) [16] to report our findings.

2.1. Eligibility criteria

We searched for scientific manuscripts reporting on health care use for RVGE in children under 5 years old in highly developed countries, before routine RV vaccination introduction. To obtain accurate estimates, we included only studies that included children seen or hospitalised for acute gastroenteritis and that used specific and reliable tests to diagnose RVGE and specified age ranges. We defined highly developed countries as those with a good healthcare system (WHO mortality strata A: low adult mortality, very low child mortality [17]), a democratic government and a high-income economy (Organization for Economic Cooperation and Development (OECD) member [18]). The list of eligible countries is shown in Supplementary Table 1. To reduce the risk of biases from studies with small sample sizes, misclassification of diagnosis and limited study period, we defined exclusion criteria based on sample size, year of publication and study duration. The detailed inclusion and exclusion criteria are described in the Supplementary Material (p. 10).

2.2. Information sources and search strategy

We searched the Embase and MEDLINE databases on December 17, 2018. Our search strings included medical subject headings (MeSH) or thesaurus terms and free text key words pertaining to (1) rotavirus, (2) disease outbreak, surveillance or epidemiology, (3) names of major geographic regions or cities in eligible countries and (4) infancy and childhood. The complete search strings are presented in the Supplementary Material (p. 5). We used an automated procedure to eliminate duplicates and generated an EndNoteX8 (Clarivate Analytics, Philadelphia, Pennsylvania, United States of America, USA) library to screen retrieved records.

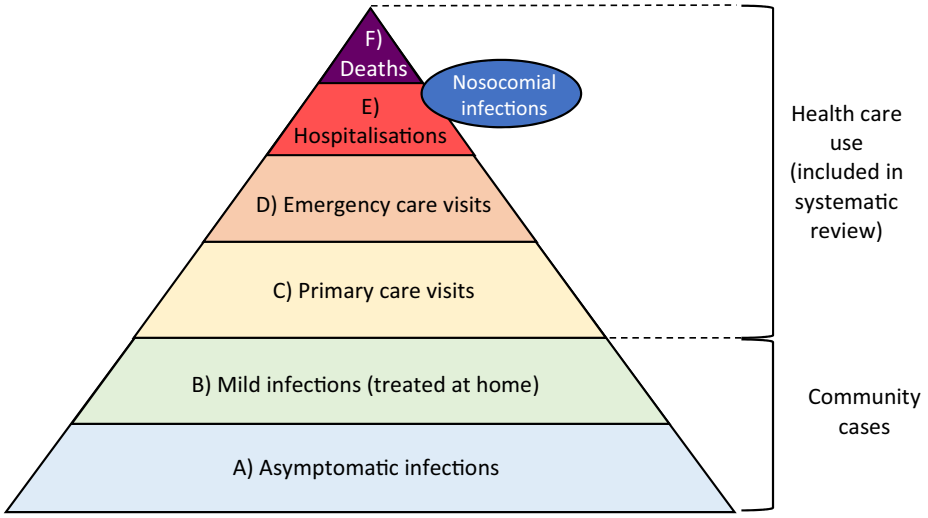

Fig. 1. Contributions to rotavirus burden of health care use. Levels C through F were estimated in our study.

2.3. Study selection

We screened titles and abstracts to assess eligibility using an accelerated process (screening by one reviewer, followed by confirmation of records for exclusion by a second reviewer) [19]. Two reviewers then independently screened the full-texts of potentially eligible studies in duplicate. Disagreements were settled by consensus or by discussion with a third researcher.

2.4. Data extraction

We extracted the data from all eligible publications into a prepiloted standard data extraction form in a secure online database (Research Electronic Data Capture, REDCap, Vanderbilt University, Tennessee, USA). Data extraction was done by one reviewer and checked by a second reviewer (e.g. missing details or to confirm important data). We extracted information on the publication, study characteristics and the number and characteristics of the participants, the authors' definitions of the outcome measure, numerical results and the specific laboratory procedure for identification of causal pathogens. A detailed list of items extracted is described in the Supplementary Material (p. 10).

2.5. Risk of bias assessment

We assessed the risk of bias in individual studies by adapting the tool proposed by Hoy et al. [20] to asses population based prevalence studies. The checklist contains 10 items classified as: Yes (low risk) or No (high risk). Questions 1–4 assess external validity and 5–10 internal validity. Further details can be found in the Supplementary Material (p. 11).

2.6. Synthesis of results and analysis

For each study and outcome, we used the number of positive RV stools samples and the person-years of the population at risk to calculate incidence rates, and the number of cases of acute gastroenteritis and the number of RV positive stool samples to calculate pooled proportions. When the number of RVGE cases were not reported, we calculated it based on person-years and incidence rates. Similarly, if the number of person-years was not reported, we calculated it based on the incidence rate and 95% confidence interval. For proportions, if only the numerator (RV positive stool samples) or the denominator (number of all cases of acute gastroenteritis) were reported, we used the reported proportion of RVGE to calculate the other number. For nosocomial infections, we only included those reported to occur during hospitalisation.

We performed random effects *meta*-analysis to calculate summary estimates of average incidence rates or proportions (with 95% CI). We used the Freeman-Tukey Double arcsine transformation to calculate the overall incidence rate or proportion [21]. We examined heterogeneity graphically, using forest plots, statistically by calculating the I^2 and Tau-squared statistics [22], and in subgroup analyses at the country level. We calculated the prediction interval to indicate the range of the predicted proportion or incidence rate in a new study conditional on the previous studies [22,23]. However, if the heterogeneity between studies was so large as to render the prediction interval uninformative, the prediction interval was not plotted along with the forest plots. We did not test the included studies for potential risk of publication bias because the relevance for studies of prevalence or incidence is uncertain. We used the R language for statistical computing for all analysis, using the metaprop and metarate functions of the package 'meta' [24] and package 'epitools' [25].

We performed three sensitivity analyses to explore possible causes of heterogeneity. First, we assessed incidence rates and proportions in studies that included only children under 2 years of age, as severe RVGE affects particularly children of this age range. For this, we selected studies that included children aged between 0 and 24 months. In a second sensitivity analysis we assessed if the risk of bias in the studies affected the pooled estimates for children under 5 years old. For this analysis, we selected studies with a low risk of bias score for selection and non-response bias, i.e. items 3 and 4 on the Hoy et al. risk of bias tool [20]. In the third sensitivity analysis we assessed if studies that tested the stools only for RV and not for multiple pathogens, might be attributing RV as the cause for the acute gastroenteritis, when the child is only excreting RV, and the symptoms are caused by another pathogen. For this, we included only studies that tested stool samples also for other gastrointestinal pathogens apart from RV.

3. Results

Our electronic search identified 4033 records after removing duplicates, of which we selected 1336 based on screening of titles and abstracts. Of these, we included 77 full-text manuscripts reporting on 74 studies in the systematic review [26–100]

(Fig. 2). The included studies were conducted in 21 different countries in North America, Europe, Asia and Oceania.

We describe results for different levels of health care use: primary care, emergency care, hospitalisations, nosocomial infections and deaths. For each level of health care use, we present summary estimates of incidence rates and proportions of acute gastroenteritis caused by RV infection in children under 5 years of age (Table 1).

3.1. Primary care visits

The summary incidence rate for primary care visits, estimated from 3 studies was 2484 (95%CI: 697–5366) per 100 000 person-years (I^2: 99%) (Supplementary Figure 1). The proportion of primary care visits for acute gastroenteritis caused by RV infection was 21% (95% CI: 16–26%; prediction interval: 5–44%; I^2: 98%) estimated from 14 studies from 9 countries that ranged between 9 and 45% (Fig. 3).

3.2. Emergency care visits

The incidence rate of RVGE emergency care visits in one study was 1890 per 100 000 children per year (95% CI: 1597–2207) [82]. The estimated proportion of emergency care visits for acute gastroenteritis caused by RV infection was 32% (95% CI: 25–38%; prediction interval: 6–65%; I^2: 98%), based on 19 studies from 11 countries (Fig. 4).

3.3. Hospitalisations

The summary incidence rate of RVGE hospitalisations was 500 (95%CI: 422–584; prediction interval 221–892; I^2: 100%) per 100 000 children per year, based on 13 studies from 9 countries (Fig. 5). An estimated 41% of hospitalisations for acute gastroenteritis were caused by RV infection (95% CI: 36–47%; prediction interval: 9–79%; I^2: 100%) based on 45 studies from 16 countries (Fig. 6). Summary estimates by country are in Supplementary Figure 2.

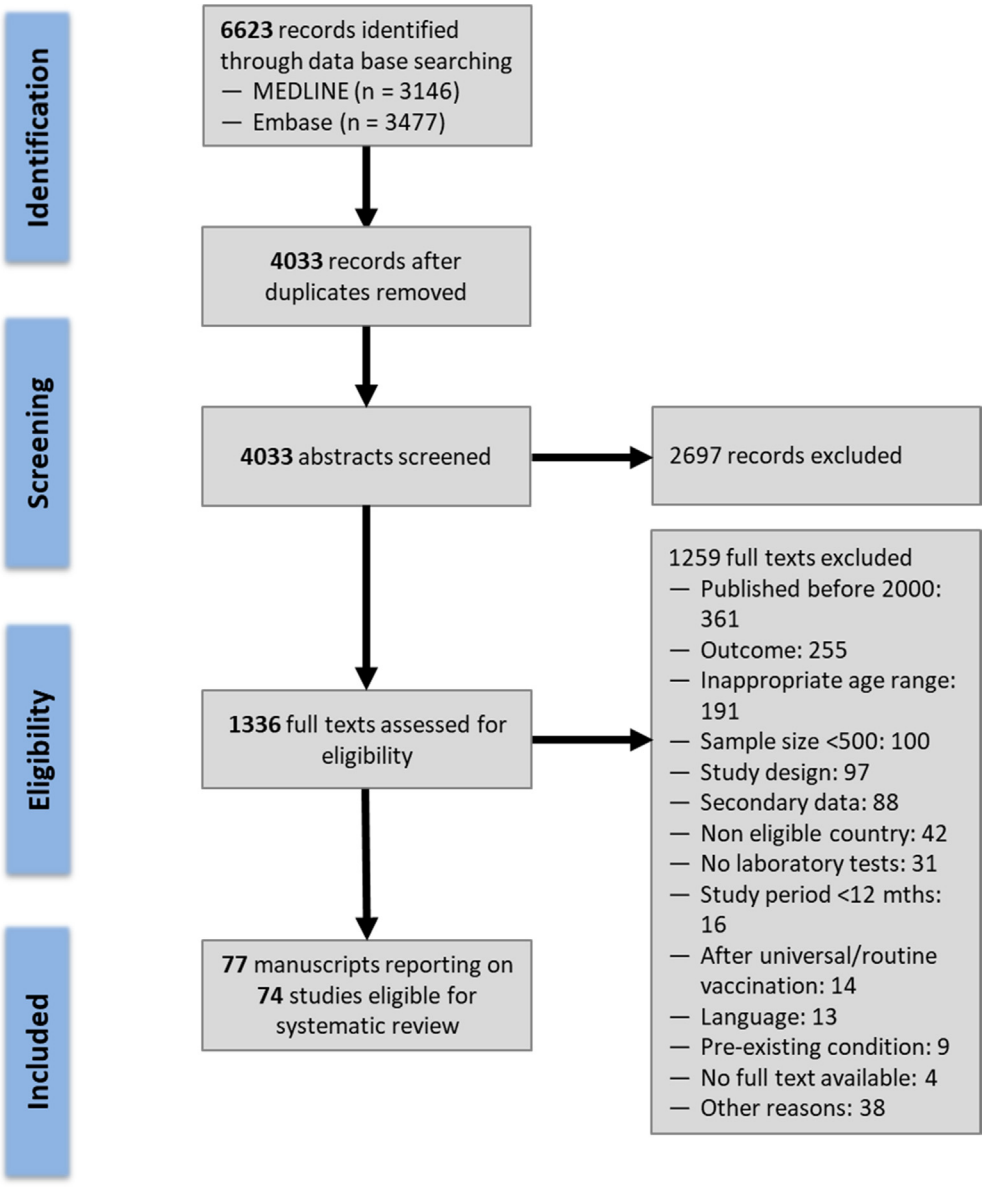

Fig. 2. Rotavirus burden of health care use: flow diagram of study selection.

Table 1
Summary table with summary estimates of health care use for rotavirus gastroenteritis in children in highly developed countries with no routine rotavirus vaccination programmes.

	Outcome measure, number of studies (n)	Under 5 years old	Under 2 years old	Under 5 years, low risk of bias*	Under 5 years, multiple pathogens tested
Primary care visits	Proportion (95% CI)	21% (16–26%), 14	24% (14–35%), 2	17% (10–26%), 7	16% (7–28%), 4
	Incidence per 100 000 person-years (95% CI)	2484 (697–5366), 3	4390 (2916–6161), 2	–	1036 (814–1285), 1
Emergency care visits	Proportion (95% CI)	32% (25–38%), 19	34% (9–66%), 2	29% (20–39%), 11	22% (18–26%), 7
	Incidence per 100 000 person-years (95% CI)	1890 (1597–2207), 1	1205 (193–3072), 2	–	–
Hospitalisa-tions	Proportion (95% CI)	41% (36–47%), 45	50% (32–68%), 8	40% (32–47%), 30	38% (31–44%), 16
	Incidence per 100 000 person-years (95% CI)	500 (422–584), 13	826 (650–1024), 9	544 (470–623), 10	333 (41–905), 2
Nosocomial infections	Proportion (95% CI)	29% (25–34%), 3	53% (46–60%), 3	29% (25–34%), 3	30% (26–35), 2
	Incidence per 100 000 person-years (95% CI)	34 (20–51), 3	95 (90–100), 1	43 (36–50), 2	26 (20–33), 1
	Incidence per 1000 hospital-days (95% CI)	0.63 (41–90), 3	7.09 (1–17), 4	0.61 (0.33–0.98), 2	0.79 (0.68–0.91), 1
	Incidence per 1000 hospitalisations (95% CI)	1.5 (1–2.1), 1	18 (3–46), 3	–	–
Mortality	Proportion (95% CI)	12% (8–18%), 1	–	–	–
	Rate per 100 000 person-years (95% CI)	0.04 (0.02–0.07), 2	–	0.04 (0.02–0.07), 2	–
	Rate per 100 000 hospitalisations (95% CI)	129 (81–187), 1	–	–	–

* Summary estimates including only studies with low risk of bias score for selection and non-response bias, i.e. items 3 and 4 on the Hoy et al. risk of bias tool.

3.4. Nosocomial infections

The summary incidence rate of RVGE nosocomial infections was 34 (95% CI: 20–51) per 100 000 children under 5 years old per year, with high heterogeneity (I^2: 91%, 3 studies) (Supplementary Figure 3).The incidence rate of RVGE nosocomial infections per 1000 hospital-days reported by 3 studies [31,55,79], was 0.63 cases (95% CI: 0.41–0.90; prediction interval: 0–7.3; I^2: 91%) per 1000 hospital-days (Supplementary Figure 4). One study reported the incidence proportion of RVGE nosocomial infections per 1000 hospitalisations as 1.5 (95% CI: 0.96–2.15) [91]. The proportion of nosocomial infections of acute gastroenteritis caused by RV in children under 5 years old hospitalised for reasons other than acute gastroenteritis was 29% (95% CI: 25–34%; prediction interval: 2–72%; I^2: 31%), as estimated from 3 studies (Supplementary Figure 5).

3.5. Mortality

The summary mortality rate for RVGE in children under 5 was 0.04 deaths (95% CI: 0.02–0.07; I^2: 0%) per 100 000 person-years [35,93], as reported in 2 studies from Germany (Supplementary Figure 6). The proportion of deaths for acute gastroenteritis caused by RV was reported by one study from the UK as 12% (95% CI: 8–18%) [88]. The same study also reported mortality for RVGE as 129 (95% CI 81–187) deaths per 100 000 hospitalisations in children under 5 years.

3.6. Risk of bias

One fifth of the studies (17) met all 10 items; 23 (31%) fulfilled all the items for external validity and 50 (68%) all for internal validity items. When assessing external validity (Supplementary Figure 7), 41 (55%) studies had a study population that was a good representation of the national population; 74% of studies tested all children with acute gastroenteritis seen during the study period in the study population, or tested a random sample of children for RV; 73% of studies had a low risk of non-response bias. Internal validity: 58 (78%) studies used the same method to test all the stool samples for RV.

3.7. Sensitivity analyses

Our first sensitivity analysis selected only studies that included children 0–24 months old (Table 1 & Supplementary Figure 8–16). In this population, the incidence rates of RVGE were higher for primary care visits, hospitalisations and nosocomial infections, but not for emergency care visits. No study reported mortality in children under 2 years of age. The summary estimated proportions of primary and emergency care visits for gastroenteritis caused by RV were slightly higher, whereas for hospitalisations it reached 50% (compared to 41% in under-5 s) and for nosocomial infections 53% (compared to 29% in under-5 s). The second sensitivity analysis included only studies with low risk of bias (Table 1 & Supplementary Figures 17–23). Overall, the summary incidence rate and proportion of the five different health care outcomes changed little when we excluded studies with lower external validity. The third sensitivity analysis included only studies that looked for other pathogens in the stool samples (29 of 74). Very few studies reporting on incidence of RVGE tested for multiple pathogens, and those that did reported a lower incidence of primary care visits and hospitalisations than all studies in under-5 s (1036 vs 2484 and 333 vs 500 per 100 000 per year, respectively) (Table 1 & Supplementary Figure 24–28). The summary estimated proportions of primary care and emergency visits caused by RV were lower compared to the main analyses (16% vs 21%, and 22% vs 32%), while that of hospitalisations was similar. Results for nosocomial infections were similar and none of the studies reporting on mortality tested for multiple pathogens.

4. Discussion

This systematic review and *meta*-analysis of RVGE in children aged under 5 years found that, in highly developed countries with no RV routine vaccination, every year an average of 500 children are hospitalised per 100 000 children. Emergency care visits and primary care visits occurred 4 to 5 times more often than

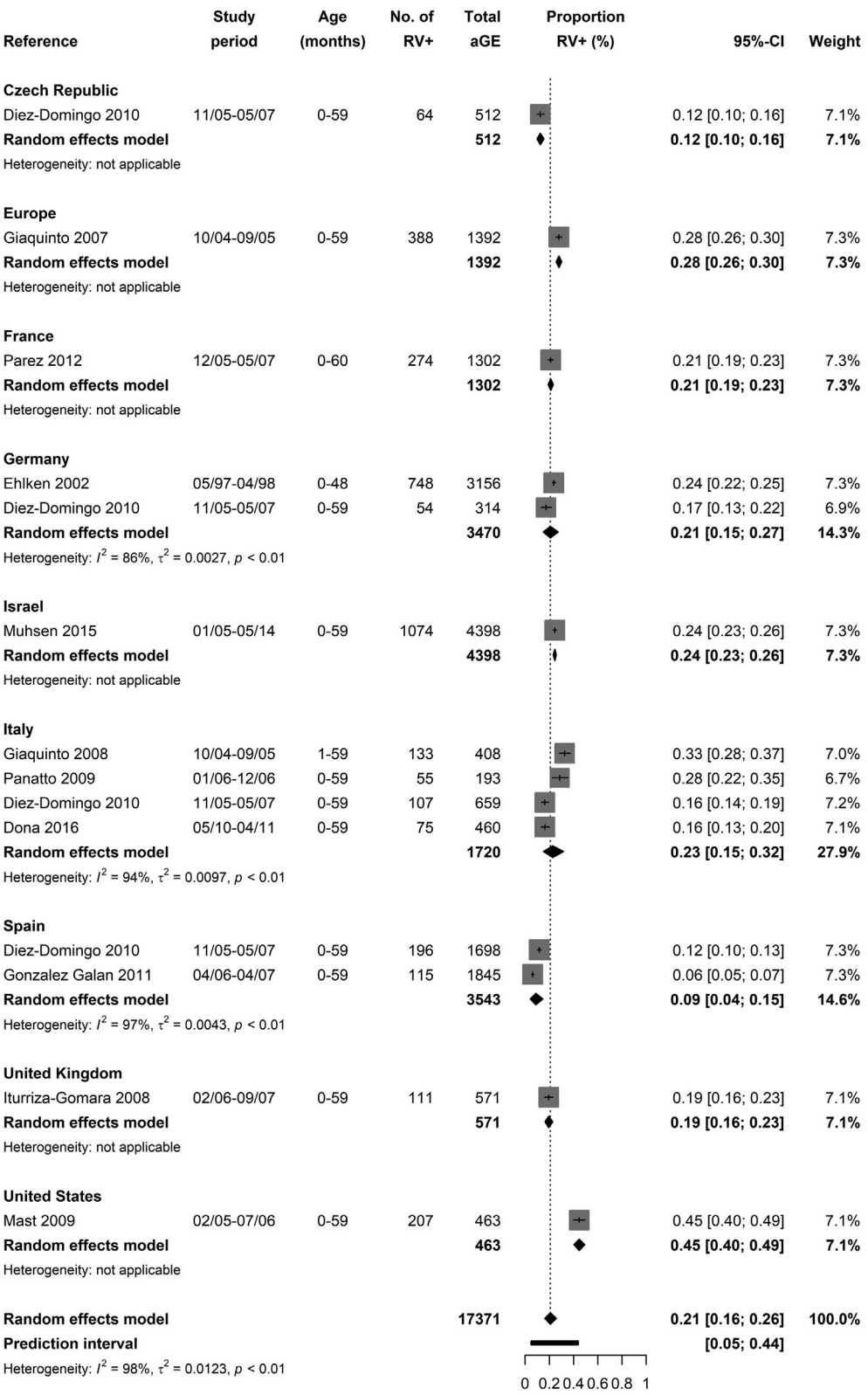

Fig. 3. Proportion of primary care visits for RVGE among all visits for acute gastroenteritis of children aged 0–5 years (forest plot). RVGE: Rotavirus gastroenteritis; RV+: stools samples that tested positive for rotavirus; AGE: acute gastroenteritis; CI: Confidence Interval.

hospitalisations. Mortality for RVGE was very low (0.04 deaths per 100 000 person-years; 95% CI: 0.02–0.07). The proportion of acute gastroenteritis caused by RV was highest for hospitalisations (40%) and lowest for primary care visits (21%). For nosocomial acute gastroenteritis, an average of 29% was caused by RV. In children aged under 2 years, the incidence rates of all outcomes were higher than in children under 5 years old, while the proportions of RVGE among all acute gastroenteritis were similar. There were large

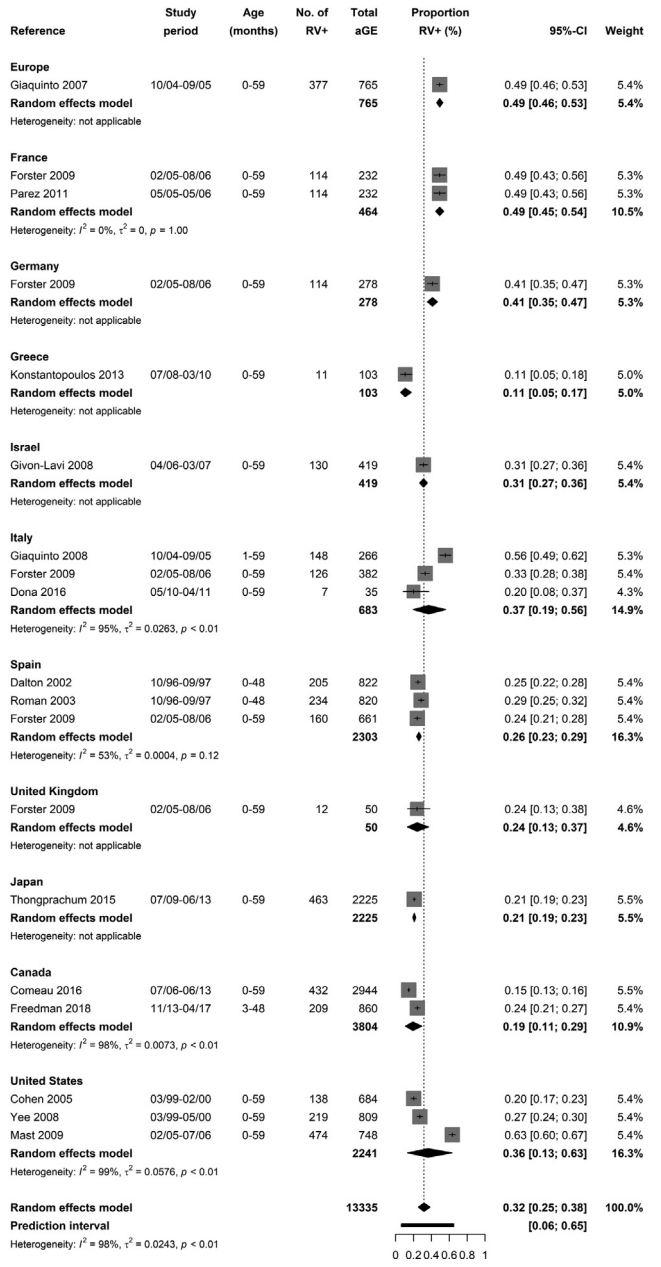

Fig. 4. Proportion of emergency department consultations for RVGE among all consultations for acute gastroenteritis of children aged 0–5 years (forest plot). RVGE: Rotavirus gastroenteritis; RV+: stools samples that tested positive for rotavirus; AGE: acute gastroenteritis; CI: Confidence Interval.

variations between and within countries, and heterogeneity was high (>90%) in most models.

4.1. Strengths and limitations

This systematic review summarised incidence rates and proportions of RVGE disease across all levels of health care use, from primary care to hospitalisations, including nosocomial infections and mortality (Fig. 1). This gives a complete picture of the burden of RVGE in highly developed countries with no routine RV vaccination programmes. Our inclusion criteria attempted to reduce small study and measurement biases. We also attempted to identify causes of heterogeneity, such as age, risk of bias and testing solely for RV, in sensitivity analyses.

This review has also limitations. We found high heterogeneity, both between and within countries. This may be due to differences in health care systems and climate, so the average summary estimates may not be applicable to all settings. Second, some of the included studies had a high risk of bias, especially concerning external validity. However, the summary estimates did not vary greatly when excluding these studies. Finally, the proportion of children that had received RV vaccination may have varied between studies. We excluded studies undertaken after RV vaccine introduction in national immunisation programmes, but some parents might still have opted to vaccinate their children and pay privately. We extracted these data from the studies when available, but it was rarely reported.

4.2. Findings in relation to other studies

For every hospitalisation for RVGE, we estimated an average of 4 emergency care visits and 5 primary care visits. The ratio between primary care visits and hospitalisations was similar for children aged under 2. A 2017 European Centre for Disease Prevention and Control (ECDC) report on RV burden in the European Union also found that there are 2–4 times more visits to the emergency department or other outpatient facilities caused by RVGE than hospitalisations [14]. However, the proportion of acute gastroenteritis caused by RV were half as high for primary care than for hospitalisations (21% vs 40%). Indeed, RV may lead to more severe disease with a higher degree of dehydration than other pathogens. One previous *meta*-analysis of studies from China reported on RVGE burden estimates for different levels of health care. They found that 33% of outpatient visits for acute gastroenteritis were caused by RV, and 43% of hospitalisations, similar to our findings [12].

The higher incidence of RVGE in children under 2 years of age, especially severe RVGE requiring hospitalisations, has been reported [11] and is explained by the higher risk of dehydration in infants. This could account for part of the variation in incidence and proportions found between studies depending on the age distribution, which was not reported by all studies.

Hospitalisations for RVGE have been studied worldwide. Two reviews including high and low-income countries found hospitalisation rates for RVGE similar to our study. The ECDC report of 49 studies from the European Union and the European Economic Area, reported that the hospitalisation incidence rates ranged from 100 to 1190 per 100 000 person years (most of which were between 300 and 600) and the proportion of all acute gastroenteritis hospitalisations ranged between 26 and 69% [14], comparable to our findings. A worldwide review including 242 studies found also a similar overall proportion of RV-attributable hospitalisations for acute gastroenteritis in children aged under 5 (38%; 95% CI: 36–40%) [11]. However, this proportion was lower in studies that tested for multiple pathogens rather than for RV alone (20% in studies with 5–13 pathogens vs 39% in single-pathogen studies, $p < 0.0001$) [11]. This was not the case in our study for the proportion of hospitalisations, though we also found a lower incidence of hospitalisations for RVGE in the two studies that tested for multiple pathogens. Worldwide reviews found that the incidence of RV hospitalisations does not vary much with the level of economic development (median RV admissions per 1000 children under 5 years per year: 2.0 vs 1.9 in low- and high-income regions, respectively) [13].

4.3. Implications for health care and future research

The results from this *meta*-analysis can be used to model the cost-effectiveness of RV vaccine introduction into national immunisation plans in highly developed countries. Economic evaluations

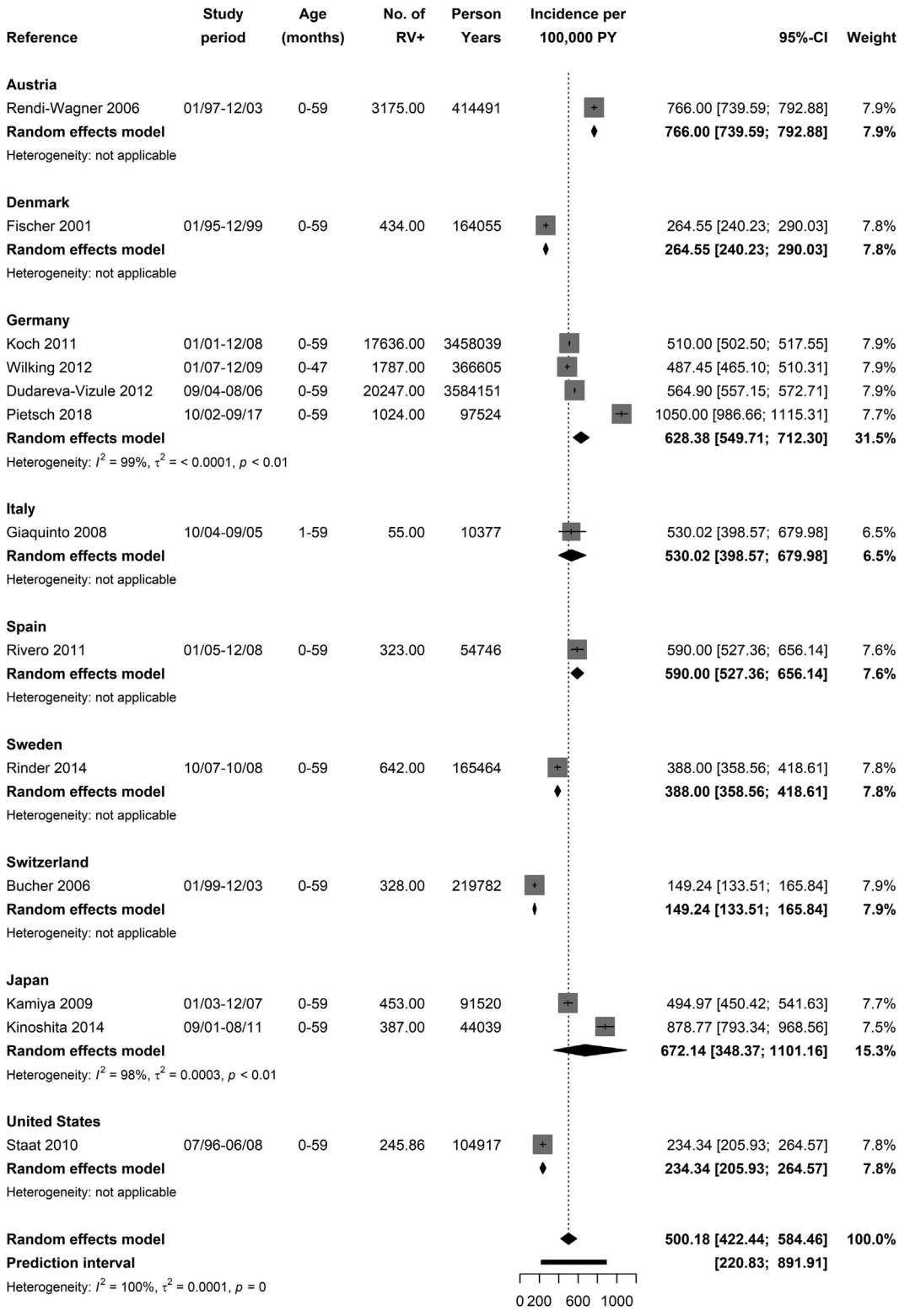

Fig. 5. Incidence rate of hospitalisations for RVGE of children aged 0–5 years per 100,000 person-years (forest plot). RVGE: Rotavirus gastroenteritis; RV+: stools samples that tested positive for rotavirus; PY: person-years; CI: Confidence Interval.

will provide useful information for public health authorities when deciding upon immunisation strategies for RV. We observed a wide variation of estimates of RVGE health care use between and within countries in our review, presumably due to differences in health care systems, climate and prevalence of other gastrointestinal pathogens, but also to differences in study designs (use of hospital records vs cohort studies with invited participants), specific locations (multicentre vs single centre studies) and laboratory methods used (testing for multiple pathogens vs only RV). This has resulted in the high heterogeneity observed in our pooled models.

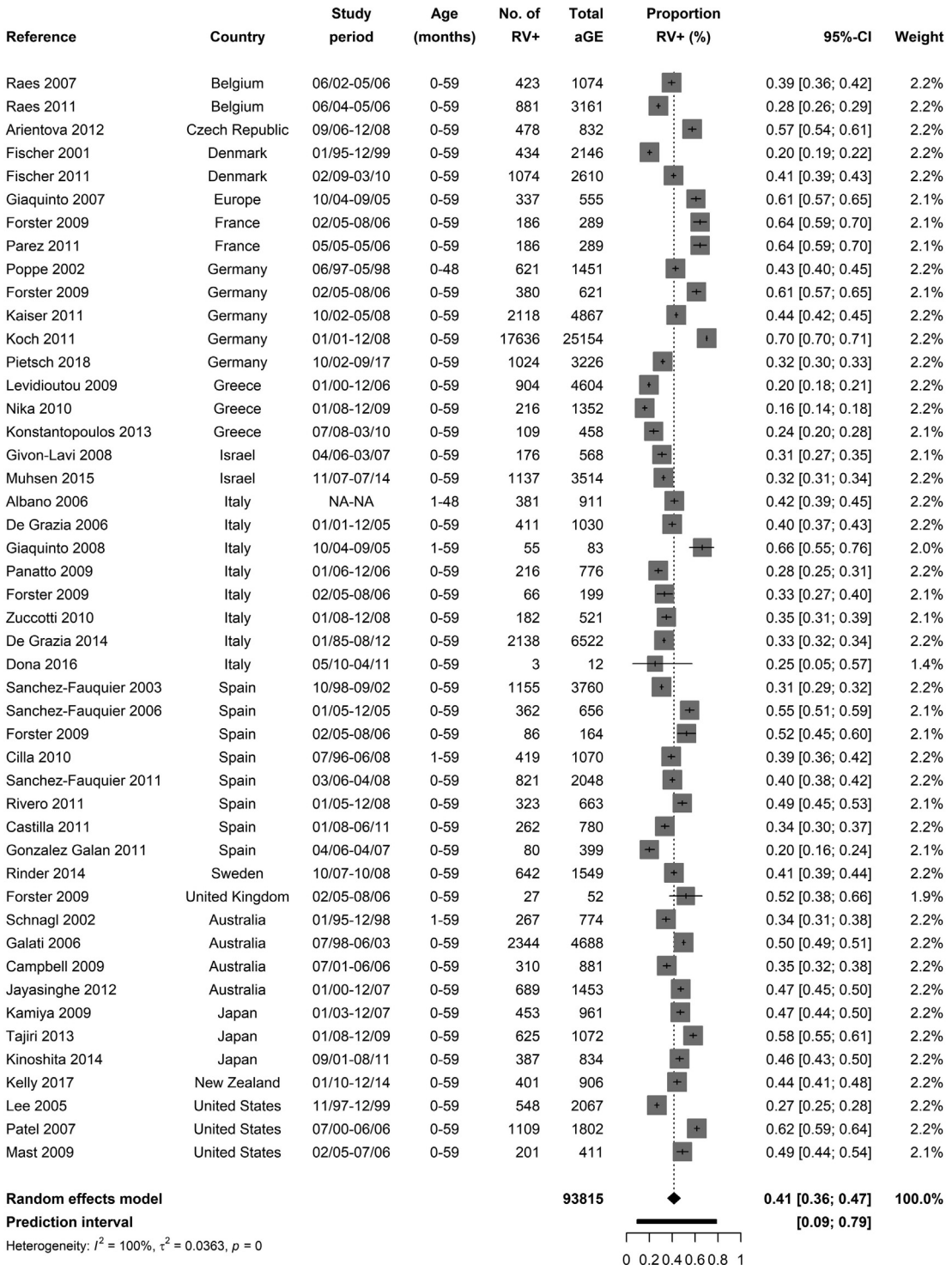

Fig. 6. Proportion of hospitalisations for RVGE among all hospitalisations for acute gastroenteritis of children aged 0–5 years (forest plot without country estimates). RVGE: Rotavirus gastroenteritis; RV+: stools samples that tested positive for rotavirus; AGE: acute gastroenteritis; CI: Confidence Interval.

Researchers assessing RV-related health care in future could obtain more robust results by using standardised prospective methods across different countries.

5. Conclusion

RV causes a considerable number of health care visits and hospitalisations for gastroenteritis in highly developed countries without routine RV vaccination. RV was one of the main pathogens of severe gastroenteritis requiring hospitalisation in children under 5 years. Even though RVGE mortality is low in highly developed countries, this vaccine-preventable disease poses a considerable burden on health care systems.

Authors contributions

Claudia E Kuehni, Nicola Low, Cristina Ardura-Garcia and Christian Kreis conceptualised and designed the study. Cristina Ardura-

Garcia, Christian Kreis, Milenko Rakic, Manon Jaboyedoff and Christina Mallet performed the screening and data extraction. Christian Kreis analysed the data. Claudia E Kuehni, Nicola Low, Cristina Ardura-Garcia and Christian Kreis interpreted the results. Cristina Ardura-Garcia drafted the manuscript. All authors critically revised the manuscript and approved the final manuscript as submitted.

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.

Acknowledgements

Funding Source: The study was partly supported by a research grant from GlaxoSmithKline Biologicals SA (GSK study identifier HO-18-19250). GlaxoSmithKline Biologicals SA participated in the study design but had no role in the data collection, analysis, interpretation of the results and writing of the manuscript. GlaxoSmithKline Biologicals SA was provided the opportunity to review a preliminary version of this manuscript for factual accuracy, but the authors are solely responsible for final content and interpretation.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.04.039.

References

[1] Troeger C, Khalil IA, Rao PC, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. JAMAPediatrics 2018;172:958–65.
[2] Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:136–41.
[3] Soares-Weiser K, Bergman H, Henschke N, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane database of systematic reviews. 2019.
[4] Organization WH. Rotavirus vaccines: WHO position paper—January 2013. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire, 88 2013 49–64.
[5] Abou-Nader AJ, Sauer MA, Steele AD, Tate JE, Atherly D, Parashar UD, et al. Global rotavirus vaccine introductions and coverage: 2006–2016. Hum Vaccines Immunother 2018;14:2281–96.
[6] Parez N, Giaquinto C, Du Roure C, Martinon-Torres F, Spoulou V, Van Damme P, et al. Rotavirus vaccination in Europe: drivers and barriers. Lancet Infect Dis 2014;14:416–25.
[7] Yen C, Healy K, Tate JE, Parashar UD, Bines J, Neuzil K, et al. Rotavirus vaccination and intussusception–Science, surveillance, and safety: a review of evidence and recommendations for future research priorities in low and middle income countries. Hum Vaccines Immunother 2016;12:2580–9.
[8] Bilcke J, Van Damme P, Van Ranst M, Hens N, Aerts M, Beutels P. Estimating the incidence of symptomatic rotavirus infections: a systematic review and meta-analysis. PLoS ONE 2009;4:e6060.
[9] Bruijning-Verhagen P, Quach C, Bonten M. Nosocomial rotavirus infections: a meta-analysis. Pediatrics 2012;129:e1011–9.
[10] Kawai K, O'Brien MA, Goveia MG, Mast TC, El Khoury AC. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. Vaccine 2012;30:1244–54.
[11] Lanata CF, Fischer-Walker CL, Olascoaga AC, Torres CX, Aryee MJ, Black RE. Global causes of diarrheal disease mortality in children< 5 years of age: a systematic review. PLoS ONE 2013;8.
[12] Liu N, Xu Z, Li D, Zhang Q, Wang H, Duan Z-j. Update on the disease burden and circulating strains of rotavirus in China: a systematic review and meta-analysis. Vaccine 2014;32:4369–75.
[13] Williams C, Lobanov A, Pebody R. Estimated mortality and hospital admission due to rotavirus infection in the WHO European region. Epidemiol Infect 2009;137:607–16.
[14] European Centre for Disease Prevention and Control. Expert opinion on rotavirus vaccination in infancy. Stockholm: ECDC; 2017.
[15] Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD. Global impact of rotavirus vaccination on childhood hospitalizations and mortality from diarrhea. J Infect Dis 2017;215:1666–72.
[16] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62:1006–12.
[17] (WHO) WHO. List of Member States by WHO Region and Mortality Stratum. 2020.
[18] (OECD) OfEC-oaD. OECD. 2020.
[19] Ganann R, Ciliska D, Thomas H. Expediting systematic reviews: methods and implications of rapid reviews. Implementation Sci 2010;5:56.
[20] Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 2012;65:934–9.
[21] Miller JJ. The inverse of the Freeman-Tukey double arcsine transformation. Am Stat 1978;32:138.
[22] Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J Roy Stat Soc Ser A (Statistics in Society). 2009;172:137–59.
[23] Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342:d549.
[24] Schwarzer G. meta: An R package for meta-analysis. R News. 2007;7:40–5.
[25] Aragon TJ. epitools: Epidemiology Tools. R package version 0.5-10.2017.
[26] Zuccotti G, Meneghin F, Dilillo D, Romano L, Bottone R, Mantegazza C, et al. Epidemiological and clinical features of rotavirus among children younger than 5 years of age hospitalized with acute gastroenteritis in Northern Italy. BMC Infect Dis 2010;10:218.
[27] Yee EL, Staat MA, Azimi P, Bernstein DI, Ward RL, Schubert C, et al. Burden of rotavirus disease among children visiting pediatric emergency departments in Cincinnati, Ohio, and Oakland, California, in 1999–2000. Pediatrics 2008;122:971–7.
[28] Wilking H, Hohle M, Velasco E, Suckau M, Eckmanns T. Ecological analysis of social risk factors for Rotavirus infections in Berlin, Germany, 2007–2009. Int J Health Geographics [Electronic Resource]. 2012;11:37.
[29] Vesikari T, Itzler R, Matson DO, Santosham M, Christie CD, Coia M, et al. Efficacy of a pentavalent rotavirus vaccine in reducing rotavirus-associated health care utilization across three regions (11 countries). Int J Infect Dis 2007;11(Suppl 2):S29–35.
[30] Vesikari T, Itzler R, Karvonen A, Korhonen T, Van Damme P, Behre U, et al. RotaTeq, a pentavalent rotavirus vaccine: efficacy and safety among infants in Europe. Vaccine 2009;28:345–51.
[31] Verhagen P, Moore D, Manges A, Quach C. Nosocomial rotavirus gastroenteritis in a Canadian paediatric hospital: incidence, disease burden and patients affected. J Hosp Infect 2011;79:59–63.
[32] Thongprachum A, Takanashi S, Kalesaran AF, Okitsu S, Mizuguchi M, Hayakawa S, et al. Four-year study of viruses that cause diarrhea in Japanese pediatric outpatients. J Med Virol 2015;87:1141–8.
[33] Tajiri H, Takeuchi Y, Takano T, Ohura T, Inui A, Yamamoto K, et al. The burden of rotavirus gastroenteritis and hospital-acquired rotavirus gastroenteritis among children aged less than 6 years in Japan: a retrospective, multicenter epidemiological survey. BMC Pediatrics. 2013;13:83.
[34] Staat MA, Rice MA, Donauer S, Payne DC, Bresee JS, Mast TC, et al. Estimating the rotavirus hospitalization disease burden and trends, using capture-recapture methods. Pediat Inf Dis J. 2010;29:1083–6.
[35] Shai S, Perez-Becker R, von Konig CH, von Kries R, Heininger U, Forster J, et al. Rotavirus disease in Germany–a prospective survey of very severe cases. Pediat Infect Dis J. 2013;32:e62–7.
[36] Sanchez-Fauquier A, Wilhelmi I, Colomina J, Cubero E, Roman E. Diversity of group A human rotavirus types circulating over a 4-year period in Madrid Spain. J Clin Microbiol 2004;42:1609–13.
[37] Sanchez-Fauquier A, Montero V, Moreno S, Sole M, Colomina J, Iturriza-Gomara M, et al. Human rotavirus G9 and G3 as major cause of diarrhea in hospitalized children Spain. Emerg Inf Dis 2006;12:1536–41.
[38] Sanchez-Fauquier A, Montero V, Colomina J, Gonzalez-Galan V, Aznar J, Aisa ML, et al. Global study of viral diarrhea in hospitalized children in Spain: results of structural surveillance of viral gastroenteritis net work (VIGESS-net) 2006–2008. J Clin Virol 2011;52:353–8.
[39] Roman Riechmann E, Wilhelmi de Cal I, Cilleruelo Pascual ML, Calvo Rey C, Garcia Garcia ML, Sanchez-Fauquier A. [Nosocomial gastroenteritis and asymptomatic rotavirus and astrovirus infection in hospitalized children]. Anales de Pediatria 2004;60:337–43.
[40] Roman E, Wilhelmi I, Colomina J, Villar J, Cilleruelo ML, Nebreda V, et al. Acute viral gastroenteritis: proportion and clinical relevance of multiple infections in Spanish children. J Med Microbiol 2003;52:435–40.
[41] Rivero MJ, Roman E, Garcia MI, Zafra M, Gil A, Gonzalez-Escalada A. [Epidemiology of community-acquired rotavirus gastroenteritis in Fuenlabrada (Madrid)]. Enferm Infecc Microbiol Clin 2011;29:432–4.
[42] Rinder M, Tran AN, Bennet R, Brytting M, Cassel T, Eriksson M, et al. Burden of severe rotavirus disease leading to hospitalization assessed in a prospective cohort study in Sweden. Scand J Infect Dis 2014;46:294–302.
[43] Rendi-Wagner P, Kundi M, Mikolasek A, Mutz I, Zwiauer K, Wiedermann U, et al. Active hospital-based surveillance of rotavirus diarrhea in Austrian children, period 1997 to 2003. Wien Klin Wochenschr 2006;118:280–5.
[44] Redondo-Gonzalez O. Validity and reliability of the minimum basic data set in estimating nosocomial acute gastroenteritis caused by rotavirus. Rev Esp Enferm Dig 2015;107:152–61.

[45] Lee BP, Azimi PH, Staat MA, Louie L, Parada E, Berke T, et al. Nonmedical costs associated with rotavirus disease requiring hospitalization. Pediatr Inf Dis J 2005;24:984–8.
[46] Levidiotou S, Gartzonika C, Papaventsis D, Christaki C, Priavali E, Zotos N, et al. Viral agents of acute gastroenteritis in hospitalized children in Greece. Clin Microbiol Infect 2009;15:596–8.
[47] Lynch M, O'Halloran F, Whyte D, Fanning S, Cryan B, Glass RI. Rotavirus in Ireland: national estimates of disease burden, 1997 to 1998. Pediatr Infect Dis J 2001;20:693–8.
[48] Marc E, Biscardi S, Soulier M, Lebon P, Gendrel D. [Nosocomial rotavirus infections in a pediatric unit: surveillance during four successive winters]. Med et Maladies Infect 2007;37:61–6.
[49] Mast TC, Walter EB, Bulotsky M, Khawaja SS, DiStefano DJ, Sandquist MK, et al. Burden of childhood rotavirus disease on health systems in the United States. Pediatr Infect Dis J 2010;29:e19–25.
[50] Moulin F, Marc E, Lorrot M, Coquery S, Sauve-Martin H, Ravilly S, et al. Hospitalization for acute community-acquired rotavirus gastroenteritis: a 4-year survey. Arch Pediatr 2002;9:255–61.
[51] Muhsen K, Chodick G, Goren S, Anis E, Ziv-Baran T, Shalev V, et al. Change in incidence of clinic visits for all-cause and rotavirus gastroenteritis in young children following the introduction of universal rotavirus vaccination in Israel. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin 2015;20.
[52] Muhsen K, Rubenstein U, Kassem E, Goren S, Schachter Y, Kremer A, et al. A significant and consistent reduction in rotavirus gastroenteritis hospitalization of children under 5 years of age, following the introduction of universal rotavirus immunization in Israel. Hum Vaccines Immunother 2015;11:2475–82.
[53] Nika E, Guajardo T, Papavasileiou K, Makri A, Mammas I, Papavasileiou E, et al. Viral gastrointestinal infections in a paediatric hospital. Clinical Microbiology and Infection. 2010 (2) S320.
[54] Panatto D, Amicizia D, Ansaldi F, Marocco A, Marchetti F, Bamfi F, et al. Burden of rotavirus disease and cost-effectiveness of universal vaccination in the Province of Genoa (Northern Italy). Vaccine 2009;27:3450–3.
[55] Parez N, Mory O, Pozzetto B, Garbag-Chenon A, Pillet S, Texier N, et al. Impact of Rotavirus gastroenteritis requiring hospitalization or presenting to emergency room among children less than 5 years in France. Pathol Biol (Paris) 2012;60:275–81.
[56] Parez N, Pozzetto B, Texier N, Mory O, Garbarg-Chenon A. Tehard B (Incidence of rotavirus gastroenteritis among children under 5 years consulting a paediatrician or a general practitioner in France). Pathol Biol (Paris) 2013;61:99–107.
[57] Patel MM, Tate JE, Selvarangan R, Daskalaki I, Jackson MA, Curns AT, et al. Routine laboratory testing data for surveillance of rotavirus hospitalizations to evaluate the impact of vaccination. Pediatr Inf Dis J 2007;26:914–9.
[58] Pietsch C, Liebert UG. Rotavirus vaccine effectiveness in preventing hospitalizations due to gastroenteritis: a descriptive epidemiological study from Germany. Clin Microbiol Infect 2018;10:10.
[59] Poppe M, Ehlken B, Rohwedder A, Lugauer S, Frank HD, Stehr K, et al. Morbidity and hospital admissions due to rotavirus infection in Germany. [German] Epidemiologie und klinik von rotavirus-gastroenteritiden bei hospitalisierten sauglingen und kleinkindern in Deutschland. Monatsschrift fur Kinderh 2002;150:491–6.
[60] Raes M, Aerssens P, Alliet P, Gillis P, Verjans MP, Mewis A. Rotavirus gastroenteritis: epidemiological data from a regional hospital in Belgium. Eur J Pediatr 2008;167:71–3.
[61] Raes M, Strens D, Vergison A, Verghote M, Standaert B. Reduction in pediatric rotavirus-related hospitalizations after universal rotavirus vaccination in Belgium. Pediatr Inf Dis J 2011;30:e120–5.
[62] Albano F, Bruzzese E, Bella A, Cascio A, Titone L, Arista S, et al. Rotavirus and not age determines gastroenteritis severity in children: a hospital-based study. Eur J Pediatr 2007;166:241–7.
[63] Arientova S, Schramlova J, Ambrozova H, Maresova V, Holub M. Electron microscopy in the diagnosis of viral gastroenteritis in hospitalised children in the Czech Republic. Folia Microbiol 2012;57:177–82.
[64] Bucher B, Aebi C. Population-based epidemiology of rotavirus hospitalisations in Switzerland. Swiss Med Weekly. 2006;136:726–31.
[65] Buettcher M, Heininger U. Prospective surveillance of nosocomial viral infections during and after hospitalization at a university children's hospital. Pediatr Inf Dis J 2010;29:950–6.
[66] Castilla J, Beristain X, Martinez-Artola V, Navascues A, Garcia Cenoz M, Alvarez N, et al. Effectiveness of rotavirus vaccines in preventing cases and hospitalizations due to rotavirus gastroenteritis in Navarre. Spain Vaccine 2012;30:539–43.
[67] Cilla G, Gomariz M, Montes M, Mendiburu MI, Perez-Yarza EG, Perez-Trallero E. Incidence of hospitalization due to community-acquired rotavirus infection: a 12-year study (1996–2008). Epidemiol Infect 2010;138:1235–41.
[68] Cohen MB, Nataro JP, Bernstein DI, Hawkins J, Roberts N, Staat MA. Prevalence of diarrheagenic Escherichia coli in acute childhood enteritis: a prospective controlled study. J Pediatr 2005;146:54–61.
[69] Comeau JL, Gagneur A, Quach C. Impact of a publicly funded monovalent rotavirus vaccination program in the Province of Quebec (Canada). Vaccine 2016;34:893–8.
[70] Dalton RM, Roman ER, Negredo AA, Wilhelmi ID, Glass RI, Sanchez-Fauquier A. Astrovirus acute gastroenteritis among children in Madrid. Spain. Pediatr Inf Dis J 2002;21:1038–41.
[71] De Grazia S, Bonura F, Colomba C, Cascio A, Di Bernardo F, Collura A, et al. Data mining from a 27-years rotavirus surveillance in Palermo, Italy. Infect Genet Evolut 2014;28:377–84.
[72] De Grazia S, Ramirez S, Giammanco GM, Colomba C, Martella V, Lo Biundo C, et al. Diversity of human rotaviruses detected in Sicily, Italy, over a 5-year period (2001–2005). Arch Virol 2007;152:833–7.
[73] Diez-Domingo J, Baldo JM, Patrzalek M, Pazdiora P, Forster J, Cantarutti L, 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;170:213–22.
[74] Dona D, Mozzo E, Scamarcia A, Picelli G, Villa M, Cantarutti L, et al. Community-Acquired Rotavirus Gastroenteritis Compared with Adenovirus and Norovirus Gastroenteritis in Italian Children: A Pedianet Study. Int J Pediatr 2016;2016:5236243.
[75] Dudareva-Vizule S, Koch J, An der Heiden M, Oberle D, Keller-Stanislawski B, Wichmann O. Impact of rotavirus vaccination in regions with low and moderate vaccine uptake in Germany. Hum Vaccines Immunother 2012;8:1407–15.
[76] Ehlken B, Laubereau B, Karmaus W, Petersen G, Rohwedder A, Forster J, et al. Prospective population-based study on rotavirus disease in Germany. Acta Paediatr 2002;91:769–75.
[77] Fischer TK. Incidence of hospitalizations due to rotavirus gastroenteritis in Denmark. Acta Paediatr 2001;90:1073–5.
[78] Fischer TK, Rungoe C, Jensen CS, Breindahl M, Jorgensen TR, Nielsen JP, et al. The burden of rotavirus disease in Denmark 2009–2010. Pediatr Inf Dis J 2011;30:e126–9.
[79] 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: e393–400.
[80] Freedman SB, Williamson-Urquhart S, Farion KJ, Gouin S, Willan AR, Poonai N, et al. Multicenter Trial of a Combination Probiotic for Children with Gastroenteritis. N Engl J Med 2018;379:2015–26.
[81] Galdiero E, Marinelli A, Pisciotta MG, Pagliara I, Di Monteforte ES, Liguori G. Reverse transcriptase-PCR for the detection of Astrovirus in children with nosocomial acute diarrhoea in Naples Italy. Med et Mal Infect 2005;35:213–7.
[82] Giaquinto C, Callegaro S, Andreola B, Bernuzzi M, Cantarutti L, D'Elia R, et al. Prospective study of the burden of acute gastroenteritis and rotavirus gastroenteritis in children less than 5 years of age, in Padova, Italy. Infection 2008;36:351–7.
[83] Giaquinto C, Van Damme P, Huet F, Gothefors L, Maxwell M, Todd P, et al. Clinical consequences of rotavirus acute gastroenteritis in Europe, 2004–2005: the REVEAL study. J Infect Dis 2007;195(Suppl 1):S26–35.
[84] Givon-Lavi N, Greenberg D, Dagan R. Comparison between two severity scoring scales commonly used in the evaluation of rotavirus gastroenteritis in children. Vaccine 2008;26:5798–801.
[85] Gonzalez-Galan V, Sanchez-Fauqier A, Obando I, Montero V, Fernandez M, Torres MJ, et al. High prevalence of community-acquired norovirus gastroenteritis among hospitalized children: a prospective study. Clin Microbiol Infect 2011;17:1895–9.
[86] Grimwood K, Huang QS, Cohet C, Gosling IA, Hook SM, Teele DW, et al. Rotavirus hospitalisation in New Zealand children under 3 years of age. J Paediatr Child Health 2006;42:196–203.
[87] Iturriza-Gomara M, Elliot AJ, Dockery C, Fleming DM, Gray JJ. Structured surveillance of infectious intestinal disease in pre-school children in the community: 'The Nappy Study'. Epidemiol Infect 2009;137:922–31.
[88] Jit M, Pebody R, Chen M, Andrews N, Edmunds WJ. Estimating the number of deaths with rotavirus as a cause in England and wales. Hum Vaccines 2007;3:23–6.
[89] Kaiser P, Borte M, Zimmer KP, Huppertz HI. Complications in hospitalized children with acute gastroenteritis caused by rotavirus: a retrospective analysis. Eur J Pediatr 2012;171:337–45.
[90] Kamiya H, Nakano T, Inoue M, Kamiya H, Abd TT, Patel M, et al. A retrospective evaluation of hospitalizations for acute gastroenteritis at 2 sentinel hospitals in central Japan to estimate the health burden of rotavirus. J Infect Dis 2009;200(Suppl 1):S140–6.
[91] Kelly MJ, Foley D, Blackmore TK. Hospitalised rotavirus gastroenteritis in New Zealand: The laboratory database is a valuable tool for assessing the impact of rotavirus vaccination. Vaccine 2017;35:4578–82.
[92] Kinoshita S, Noguchi A, Miura S, Nakagomi T, Nakagomi O, Takahashi T. A retrospective, hospital-based study to determine the incidence of rotavirus hospitalizations among children less than 5 years of age over a 10-year period (2001–2011) in Akita prefectureJapan. Jpn J Inf Dis 2014;67:464–8.
[93] Koch J, Wiese-Posselt M. Epidemiology of rotavirus infections in children less than 5 years of age: Germany, 2001–2008. Pediatr Inf Dis J 2011;30:112–7.
[94] Konstantopoulos A, Tragiannidis A, Fouzas S, Kavaliotis I, Tsiatsou O, Michailidou E, et al. Burden of rotavirus gastroenteritis in children <5 years of age in Greece: hospital-based prospective surveillance (2008–2010). BMJ Open. 2013;3:e003570.
[95] Koukou D, Chatzichristou P, Trimis G, Siahanidou T, Skiathitou AV, Koutouzis EI, et al. Rotavirus gastroenteritis in a neonatal unit of a greek tertiary hospital: clinical characteristics and genotypes. PLoS ONE [Electronic Resource]. 2015;10:e0133891.
[96] Campbell SJ, Nissen MD, Lambert SB. Rotavirus epidemiology in Queensland during the pre-vaccine era. Communicable Dis Intell Q Rep 2009;33:204–8.

[97] Galati JC, Harsley S, Richmond P, Carlin JB. The burden of rotavirus-related illness among young children on the Australian health care system. Aust N Z J Public Health 2006;30:416–21.

[98] Jayasinghe S, Macartney K. Estimating rotavirus gastroenteritis hospitalisations by using hospital episode statistics before and after the introduction of rotavirus vaccine in Australia. Vaccine 2013;31:967–72.

[99] Naing Z, Rayner B, Killikulangara A, Vunnam K, Leach S, McIver CJ, et al. Prevalence of viruses in stool of premature neonates at a neonatal intensive care unit. J Paediatr Child Health 2013;49:E221–6.

[100] Schnagl RD, Belfrage K, Farrington R, Hutchinson K, Lewis V, Erlich J, et al. Incidence of human astrovirus in central Australia (1995 to 1998) and comparison of deduced serotypes detected from 1981 to 1998. J Clin Microbiol 2002;40:4114–20.