Vaccine 39 (2021) 6671–6681

Contents lists available at ScienceDirect

Vaccine

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

Impact analysis of rotavirus vaccination in various geographic regions in Western Europe

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ARTICLE INFO

Article history:
Received 1 July 2021
Received in revised form 30 August 2021
Accepted 22 September 2021
Available online 9 October 2021

Keyword:
Gastroenteritis Rotavirus Vaccines Children Diarrhoea Europe Impact

ABSTRACT

Background: Universal mass vaccination (UMV) against rotavirus has been implemented in many but not all European countries. This study investigated the impact of UMV on rotavirus incidence trends by comparing European countries with UMV: Belgium, England/Wales and Germany versus countries without UMV: Denmark and the Netherlands.
Methods: For this observational retrospective cohort study, time series data (2001–2016) on rotavirus detections, meteorological factors and population demographics were collected. For each country, several meteorological and population factors were investigated as possible predictors of rotavirus incidence. The final set of predictors were incorporated in negative binomial models accounting for seasonality and serial autocorrelation, and time-varying incidence rate ratios (IRR) were calculated for each age group and country separately. The overall vaccination impact two years after vaccine implementation was estimated by pooling the results using a random effects meta-analyses. Independent t-tests were used to compare annual epidemics in the pre-vaccination and post-vaccination era to explore any changes in the timing of rotavirus epidemics.
Results: The population size and several meteorological factors were predictors for the rotavirus epidemiology. Overall, we estimated a 42% (95%-CI 23;56%) reduction in rotavirus incidence attributable to UMV. Strongest reductions were observed for age-groups 0-, 1- and 2-years (IRR 0.47, 0.48 and 0.63, respectively). No herd effect induced by UMV in neighbouring countries was observed. In all UMV countries, the start and/or stop and corresponding peak of the rotavirus season was delayed by 4–7 weeks.
Conclusions: The introduction of rotavirus UMV resulted in an overall reduction of 42% in rotavirus incidence in Western European countries two years after vaccine introduction and caused a change in seasonal pattern. No herd effect induced by UMV neighbouring countries was observed for Denmark and the Netherlands.

1. Background

Despite the availability of vaccination, rotavirus is still the leading cause of acute gastroenteritis (AGE) in children under the age of five worldwide [1–3]. In Europe, rotavirus-related childhood mortality is low, but the disease burden without rotavirus vaccination is still considerable. It is estimated that without vaccination

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https://doi.org/10.1016/j.vaccine.2021.09.059
0264-410X/

rotavirus accounted for one-third of primary care consultations for AGE [4,5], as well as two-thirds of AGE hospitalizations (more than 87,000 hospitalizations every year) [2]. Incidence rates are highest for children aged 6–23 months [5] and nearly every child is infected at least once before the age of five [6].

Over one hundred countries worldwide have implemented rotavirus vaccination as part of their national vaccination program, including 17 European countries [7–9]. Belgium was the first country starting with universal mass vaccination (UMV) in November 2006 [10], followed by Finland in 2009 [11]. Thereafter, Germany and England started in 2013 and Norway in 2014 [12,13]. Italy and Sweden introduced regional vaccination in 2013 and 2014, respectively. The vaccine has not been universally implemented in countries such as the Netherlands, Denmark, Spain, Portugal and France.

All UMV countries showed significant decreases in rotavirus hospitalizations after vaccination: Belgium reported an 87% reduction [14], Finland around 92% [11,15], Germany 27–70% [16–18], England 83–94% [19,20] and Norway 73% [21]. Since the introduction of rotavirus vaccines, some UMV countries have reported on altered rotavirus seasonal peaks and incidence [14,18]. Even in the Netherlands, a country without UMV, a reduction was observed in rotavirus incidence including a change in epidemiological pattern [22,23]. It was hypothesized that the decline in rotavirus incidence in the Netherlands may be a result of vaccine introduction in neighbouring countries [16,17]. However, research indicated that rotavirus epidemiology is driven by other factors as well, such as the size of the susceptible population and meteorological factors [22–30]. Effectiveness and impact studies should account for the natural variation in rotavirus epidemiology to adequately estimate vaccination benefit. Another observation from countries that started UMV is a shift in genotype distribution after rotavirus vaccination was implemented [31,32].

The aim of this study was to estimate the impact of rotavirus vaccination on rotavirus incidence in UMV European countries (Germany, England/Wales and Belgium) and non-UMV countries (the Netherlands and Denmark), considering meteorological and population factors. Secondary aims were to explore any changes in the timing and seasonal pattern of rotavirus incidence due to vaccination and to give an overview of genotype distributions over the years.

2. Methods

2.1. Study design

For this observational retrospective cohort study, time series data from 2001 to 2016 on rotavirus detections, meteorological factors and population size were collected for five countries: Belgium, England/Wales, Germany, Denmark and the Netherlands. Due to known differences in childcare attendance, economic status, health insurance and vaccination coverage among the sixteen federal states of Germany, especially between the Western and Eastern regions [16], the data collection and analyses for this country was divided into the Eastern region (Brandenburg, Sachsen, Mecklenburg-Vorpommern, Sachsen-Anhalt, and Thüringen) and Western region (Baden-Württemberg, Bremen, Niedersachsen, Schleswig-Holstein, Rheinland-Pfalz, Bayern, Hessen, Nordrhein-Westfalen, Berlin, Hamburg, and Saarland). This resulted in six European regions for this study: the Netherlands (NL), East Germany (East-DE), West Germany (West-DE), England/Wales (EW), Belgium (BE) and Denmark ((DK) excluding Greenland and Faroe Islands).

2.2. Data sources

Data from the nationwide national sentinel laboratory surveillance or notifiable disease reporting system on weekly rotavirus positive stool samples were obtained for each region [14,33–36]. These contained the number of individuals with a rotavirus positive stool test and are used within each country for their national surveillance and have shown to be representative for rotavirus infection over time [14,35,37,38]. In this study, the positive stool samples were used as proxy for the relative incidence of rotavirus per country. For all regions, data were divided into nine age strata: 0, 1, 2, 3, 4, 5–14, 15–44, 45–64 and 65+ years except for NL as information on age was not available for this country (Table 1). Data on the maximum, minimum and average daily temperature, relative humidity and rainfall were collected from the meteorological stations in De Bilt (NL), Berlin (East-DE), Frankfurt (West-DE), Birmingham (EW) and Uccle (BE), which are located in the middle of the regions and considered representative for the region (Table 1) [39–44]. For DK, the average values from the 60 weather stations over the region were used. The relative humidity was not available for West-DE and East-DE and rainfall was not available for DK. Data on the weekly live births and age-specific annual population numbers were retrieved from the National Statistics Offices and Eurostat (Table 1) as they represent the number of susceptibles for rotavirus infection within a country [45–49]. Rotavirus genotype information was retrieved from the European rotavirus surveillance network EuroRotaNet [50]. EuroRotaNet comprises genotype data from 16 laboratories in 15 European countries for the purpose of monitoring the molecular epidemiology of rotavirus infections, and to monitor the emergence of novel rotavirus strains and genetic drift and shift after rotavirus UMV implementation [51]. We obtained the number of detected strains per seasonal year (Sep-Aug) for each region from 2006 to 2015.

2.3. Statistical analyses

Our primary objective was to determine the effect of rotavirus vaccination in both UMV and non-UMV countries (for non-UMV countries through indirect effects). For each region separately, we first sought to determine which variables were possible factors driving rotavirus weekly incidence. To this end, using negative binomial regression we assessed the univariate association between weekly rotavirus incidence and time-varying meteorological and population factors that are described in supplementary file 1, thereby including the start of vaccination for UMV countries to filter out any effects induced by vaccination. The effect of weekly meteorological factors was modelled using natural cubic splines. The population data was smoothed and included as weekly data using the Loess regression [52]. For each region, correlations between factors demonstrating significant associations ($p < 0.1$) were tested using Pearson's correlation coefficients. In case of a correlation coefficient of greater than 0.3 between variables [53], we used the Akaike Information Criterion (AIC) to select the one that provided the better fit for inclusion in multivariable analysis [54]. Where the AIC values differed by less than 10, indicating a minor difference in model fit, the variable that we included in the multivariable model was selected on the basis of biological plausibility [55]. Next, using the variables selected for multivariable analysis above, we performed backward stepwise selection to arrive at the final multivariable model and the final set of predictors for each region. A threshold of $p < 0.1$ was used for variable selection. All univariate and multivariate models were additionally corrected for serial first order autocorrelation and annual and biannual seasonality using four Fourier terms.

Thereafter, for each region and each age group (where available) we sought to determine the impact of rotavirus UMV introduction, while controlling for the predictors obtained from the multivariable models as described above. Using negative binomial models with a log-link function, the weekly time series data were decomposed into a time-varying seasonality effect using time-varying Fourier terms, a

Table 1
Overview of data collected per region.

	Rotavirus laboratory detections	Meteorological data	Population data[c]	Genotype information
BE	01-Jan-2001–01-Jul-2002 and 01-Jul-2005–01-Jul-2016 (14)	01-Jan-2001–01-Jul-2016 (39)	01-Jan-2001–01-Jul-2016 (47)	2007–2015 (48)
EW	01-Jan-2001–01-Jul-2016 (35)	01-Jan-2001–01-Jul-2016 (41, 42, 63)	01-Jan-2001–01-Jul-2016 (47)	2005–2013, 2015 (48)
DE	01-Jan-2001–01-Jul-2016 (36, 64)	01-Jan-2001–01-Jul-2016 (40)[a]	01-Jan-2001–01-Jul-2016 (47)	2005–2014 (48)
DK	01-Jan-2010–01-Jul-2016	01-Jan-2001–01-Jul-2016 (38)[b]	01-Jan-2001–01-Jul-2016 (47)	2009–2014 (48)
NL	01-Jan-2001–01-Jul-2016 (31)	01-Jan-2001–01-Jul-2016 (37)	01-Jan-2001–01-Jul-2016 (47)	2002–2014 (48)

Abbreviations: BE = Belgium; EW = England and Wales; DE = Germany; DK = Denmark; NL = the Netherlands.
[a] Data on relative humidity not available for this country.
[b] Data on rainfall not available for this country.
[c] Live births were available monthly for The Netherlands, Belgium, Germany and England/Wales, and quarterly for Denmark.

maximum temperature effect using natural cubic splines, a vaccination effect, and a first order serial autocorrelation term. For countries that started UMV during follow-up, the effect of vaccination was constrained to zero for all weeks up to one year after vaccine introduction, and the impact thereafter was flexibly modelled using a natural cubic spline, with the degrees of freedom proportional to the length of the post-vaccination period. For countries without UMV (NL and DK), we investigated any possible vaccination effect by similarly incorporating the start of the UMV program in a neighbouring country (i.e. BE and West-DE, respectively). Meteorological predictors based on the multivariable models were included in the decomposition as offset terms, using a flexible natural cubic spline with two degrees of freedom. Log-population-size was included as offset term. Results were presented as time varying incidence rate ratios (IRRs), with 50% and 95% confidence intervals (CI). For all countries with UMV, IRRs two years after vaccine implementation were pooled using a random effects meta-analysis to determine the overall impact of vaccination. The percentage reduction was calculated as (1-IRR)*100.

As a secondary aim, we explored any changes in the timing and seasonal pattern of rotavirus incidence due to rotavirus UMV introduction. For each region, to facilitate within-country seasonal comparisons from year to year, we plotted weekly rotavirus incidence for all ages, and we reported the onset, peak, end and duration of the annual epidemics (definitions see supplementary file 1). A change in the timing and/or seasonal pattern after vaccination for each region was detected by comparing the mean start, mean duration and mean peak of the annual epidemics in the pre-vaccination era and the post-vaccination era using independent t-tests. For NL and DK, vaccination in BE and West-DE, respectively, was used as proxy to investigate whether vaccination in neighbouring countries was associated with changes in rotavirus epidemiology. For each region, we visualized changes in the rotavirus genotype distributions over time, and descriptively outlined these changes.

As DK changed their rotavirus testing practices in 2013, we added a testing term into all analyses of DK to prevent any artificial effect. For the other regions, there were no signs that the detections were subject to artificial effects. All analyses were performed using Stata (Stata Corporation, version 16.0; College Station, TX, USA) and R (R Foundation of Statistical Computing, version 3.2.3; Vienna, Austria).

3. Results

An overview of available data per country is presented in Table 1. Fig. 1 shows the observed rotavirus incidence collected from sentinel laboratory surveillance, accompanied by the vaccination coverage in UMV regions. Highest rotavirus numbers were reported in 0-, 1- and 2-year-olds. All regions showed similar annual seasonal patterns, with peak incidence generally occurring in February-March (data not shown).

The multivariate analyses (supplementary file 1) showed the drivers of weekly rotavirus incidence per region: the total population size was statistically significant for most regions (NL, BE, East-DE), but for West-DE the multivariable model ended up with the population under the age of two. To be able to compare the vaccination effect between regions, the total population was included in the subsequent analyses for all regions. Several meteorological factors were also significant, but the intercorrelation was high and varied per region. To avoid collinearity, we have included the average maximum temperature for each region in all subsequent analyses as this was available for all countries (See supplementary file 1 for detailed results).

In all vaccinating regions (East-DE, West-DE, EW and BE), a significant reduction of rotavirus incidence was observed in 0-, 1-, and 2-year-olds after UMV introduction. Fig. 2a-2c show these time-varying incidence rate ratios (i.e. vaccination effect), corrected for the total population size and the average maximum temperature. Effects in other age groups differed per region (Supplementary file 2). No significant reductions were observed in the oldest age group (65-year-old individuals), except for EW. In the analyses for all ages, an immediate reduction in rotavirus cases was seen in West-DE, EW, and BE. In East-DE a reduction was observed five years after UMV (Fig. 2d). In both NL and DK, there was no statistically significant reduction in rotavirus incidence caused by vaccine introduction in neighbouring countries. Pooling the IRRs of two years post vaccine implementation, the overall IRR in the UMV regions was 0.58 (95%-CI 0.44;0.77), resulting in a 42% (95%-CI 23;56%) overall reduction in rotavirus incidence. The largest effect was found for 0-, 1- and 2-year-olds (IRR: 0.47, 95%-CI 0.37;0.55; IRR: 0.48, 95%-CI 0.36;0.65 and IRR: 0.63, 95%-CI 0.52;0.76, respectively).

In most UMV countries, the start and end of the annual epidemics after vaccine implementation was on average a few weeks later in the season compared to the pre-vaccine period. This shift was not observed for NL and DK when surrounding countries started UMV (Table 2). Moreover, the peak of the annual epidemics occurred later in the post-vaccination period compared to the pre-vaccination period (EW: on average 7 weeks later, West-DE: 4 weeks, East-DE: 4 weeks and BE: 5 weeks).

In Fig. 3, rotavirus genotype distribution is depicted as the relative contribution of six common rotavirus strains in each seasonal year (Sep-Aug) and country. Overall, G1P8 and G9P8 were the most prevalent genotypes. In later years, a decrease in G1P8 is observed for UMV and non-UMV countries. In the UMV countries there was a slight increase in G2P4.

4. Discussion

Rotavirus vaccination in UMV countries resulted in a 42% overall reduction in rotavirus cases two years after vaccination. This reduction was continued throughout the study period. No herd

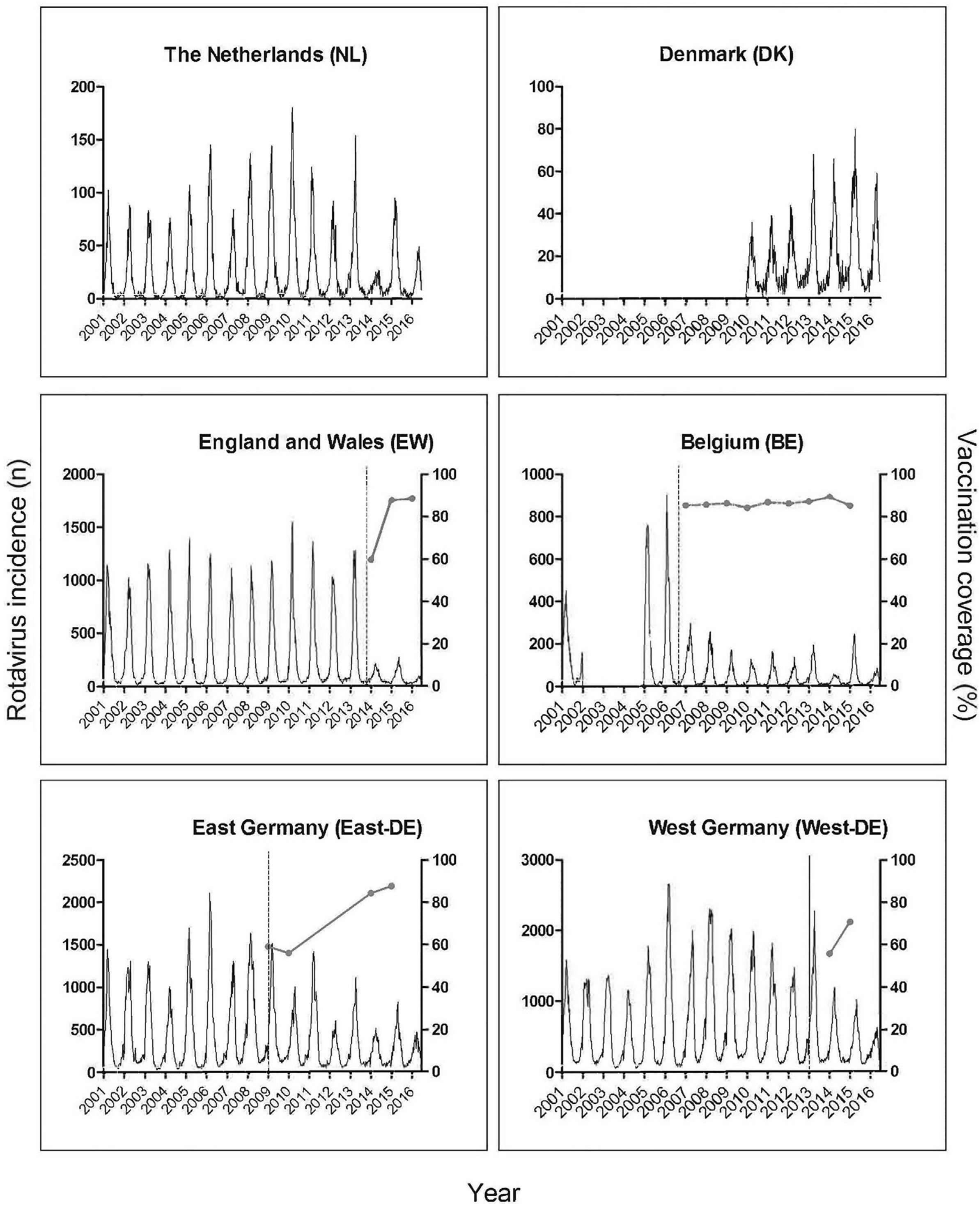


Fig. 1. Overview of absolute rotavirus numbers per country, as reported by their national sentinel laboratory surveillance. The dotted vertical line in the figures of England/Wales, Belgium, East-Germany and West-Germany represent the start of rotavirus universal mass vaccination. In Denmark and the Netherlands, universal rotavirus vaccination has not been introduced. The grey horizontal line shows the vaccination coverage (%) in the vaccinating countries.

effect induced by UMV surrounding countries was observed for non-vaccinating countries NL and DK. Vaccine introduction also affected rotavirus seasonality; the start, duration and peak of rotavirus season shifted towards later in the season in UMV regions. This study also confirmed that population size and meteorological factors affect the rotavirus epidemiology and should be accounted for in vaccination impact analyses.

The overall vaccination impact found in this study is lower compared to previous reports for high-income countries (65–98%) [37]. This is may be explained by the difference in study population, which was restricted to children under the age of five in most studies, and use of a stricter outcome (rotavirus-related hospitalisations instead of laboratory-confirmed rotavirus cases) [56–59]. The vaccination effect for the subgroup of 0–2-year-olds in our

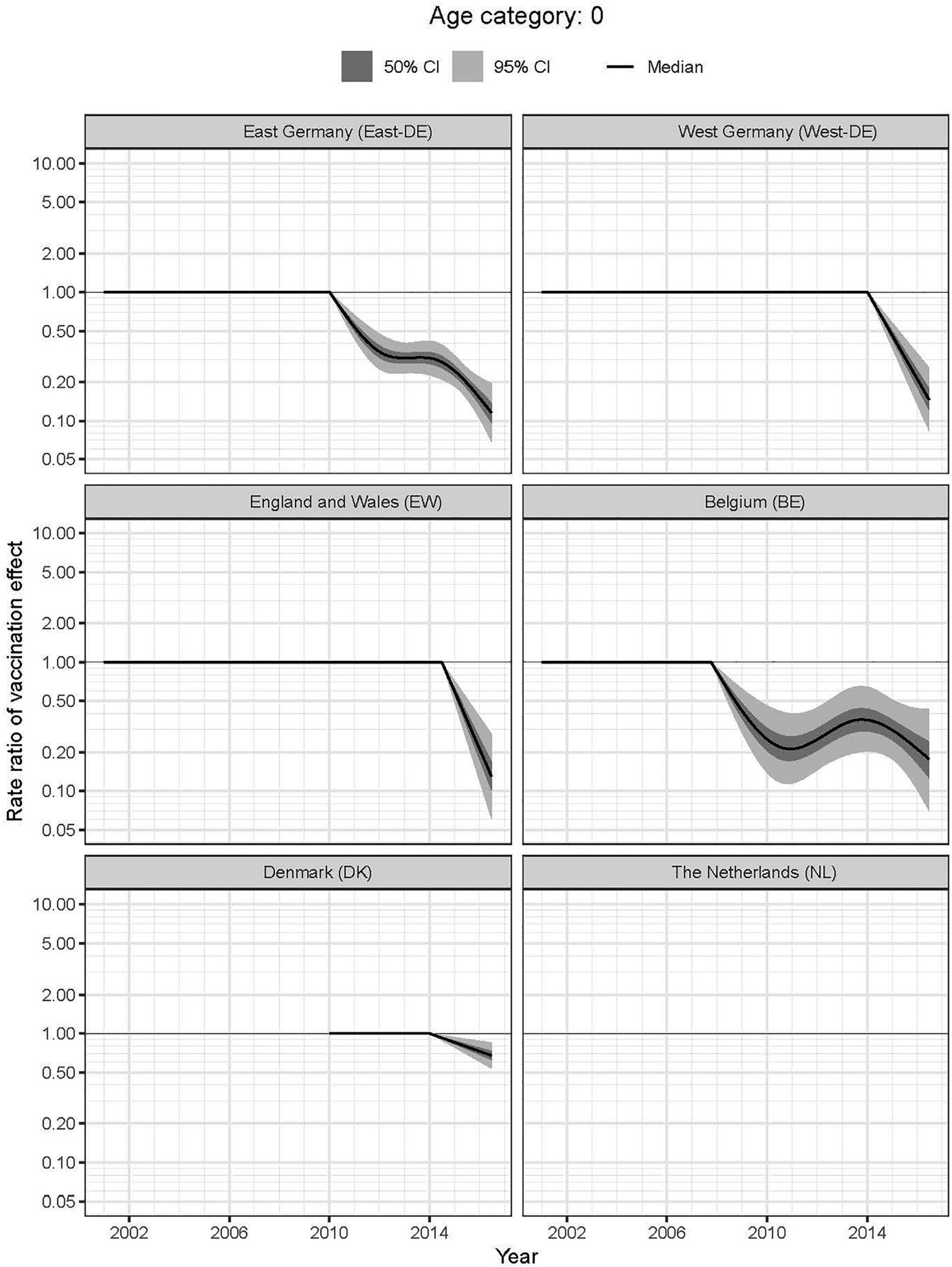


Fig. 2. Time-varying incidence rate ratios of reported rotavirus infection per region for age groups a) < 1-year-olds, b) 1-year-olds, c) 2-years-olds and d) all ages combined after the introduction of rotavirus vaccination. In Denmark and the Netherlands universal rotavirus vaccination has not been introduced, therefore the moment of implementing universal mass vaccination in neighbouring countries was used to observe any herd effect on the country level (the Netherlands: Belgium in 2006 and West Germany in 2013; for Denmark: West Germany in 2009). Note: for the Netherlands, no information on age groups was available.

study (IRR 0.47–0.63) was indeed closer to these previous estimates. More importantly, our analysis adjusted for other factors that are known to influence rotavirus epidemiology whereas previous studies did not. We first established the most influential population and meteorological parameters based on time series analyses and subsequently applied these in our final impact analysis [60–62]. Not all regions had the same set of predictors, and correlation between meteorological parameters was high. To be

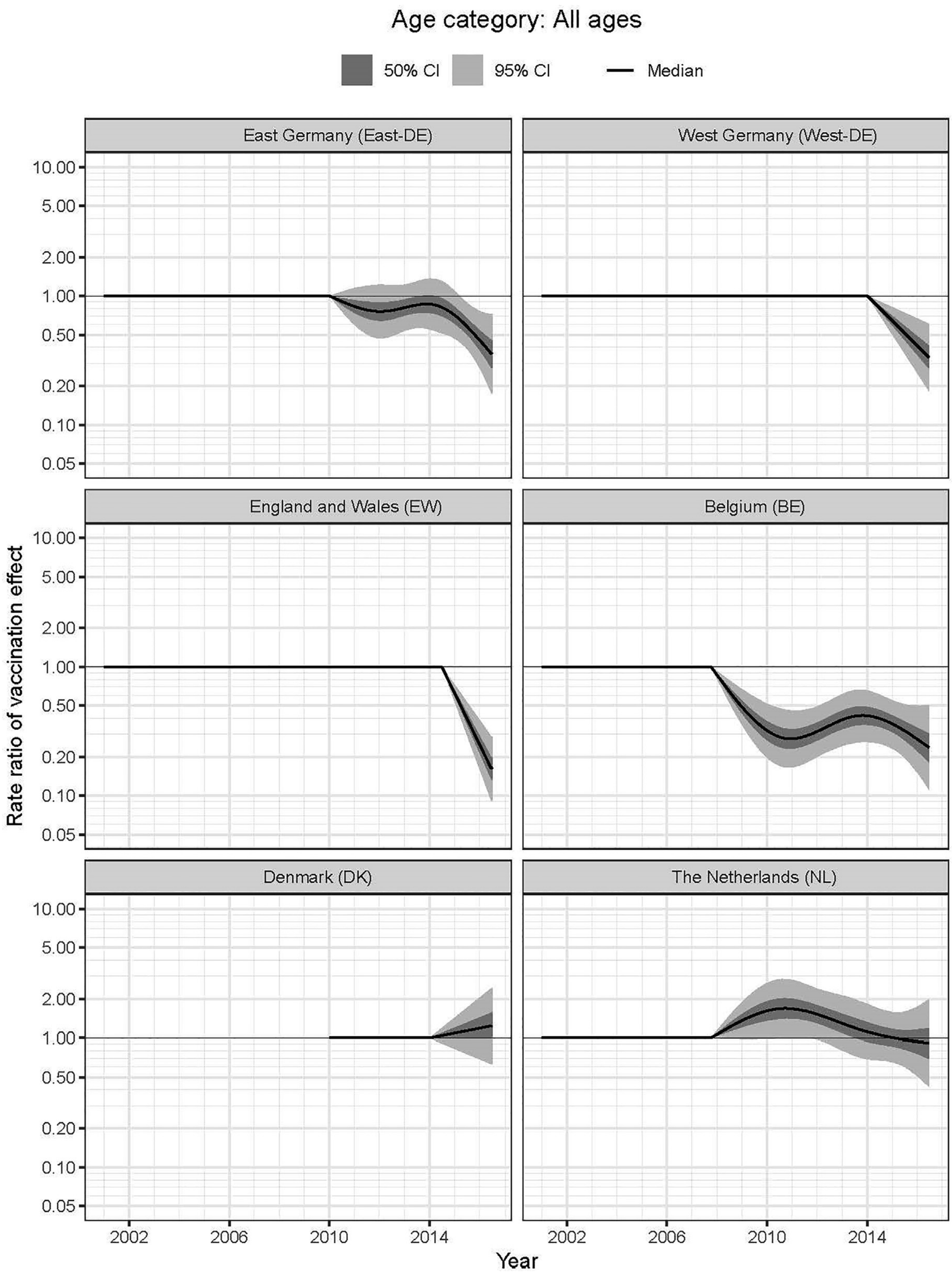
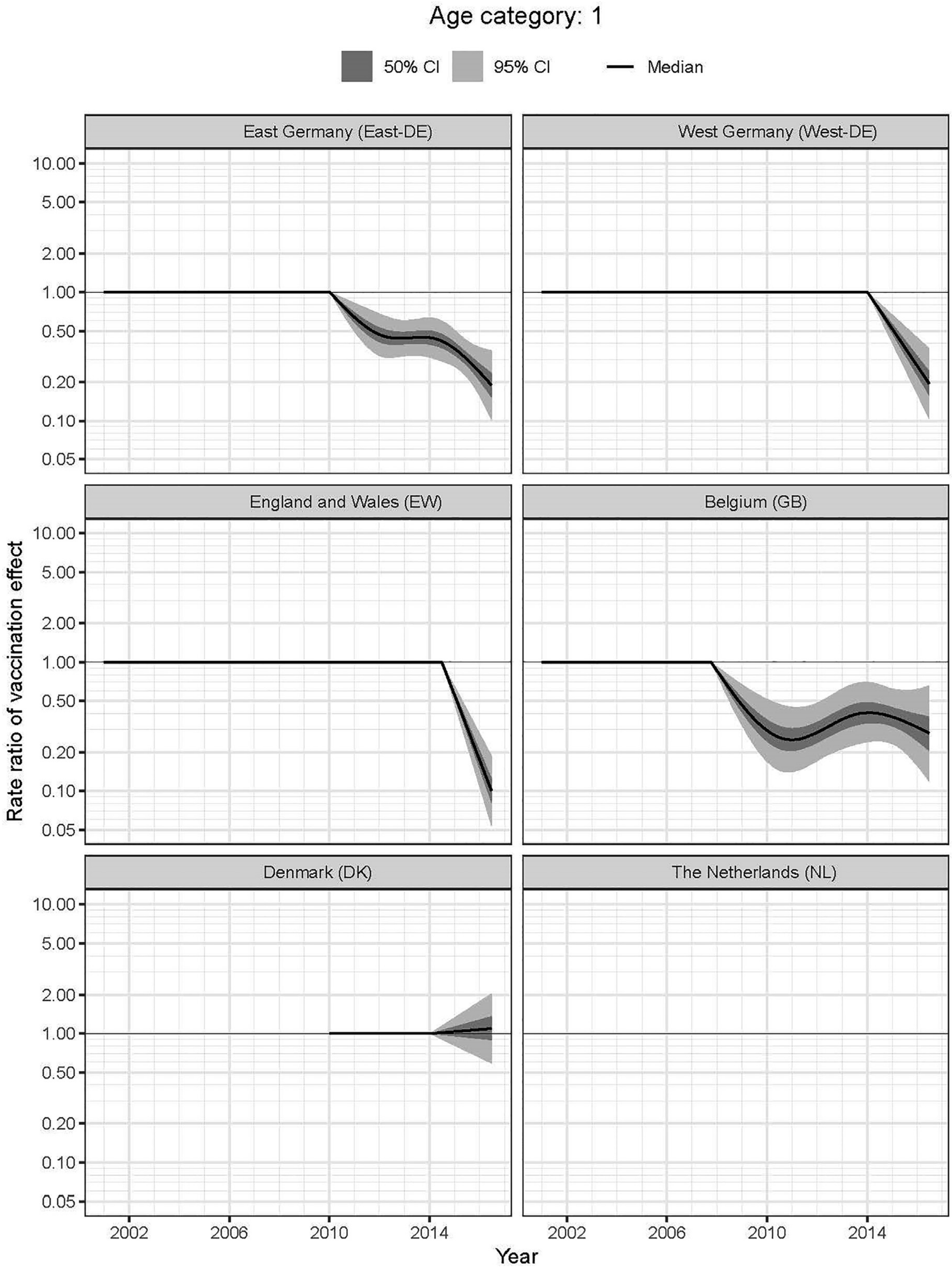


Fig. 2 (*continued*)

able to compare vaccine impact for all regions we have chosen to incorporate the same parameters for all regions (total population and maximum average temperature) in the final models estimating vaccine impact. Further, our analysis suggests that the seasonal change in rotavirus epidemiology observed during our study period was induced by UMV, as the start, end and peak of rotavirus seasons occurred later compared to pre-vaccine years. There was no observed change in the duration of the season.

Another potential driver of epidemic patterns is shift in genotype diversity due to natural changes or vaccine introduction



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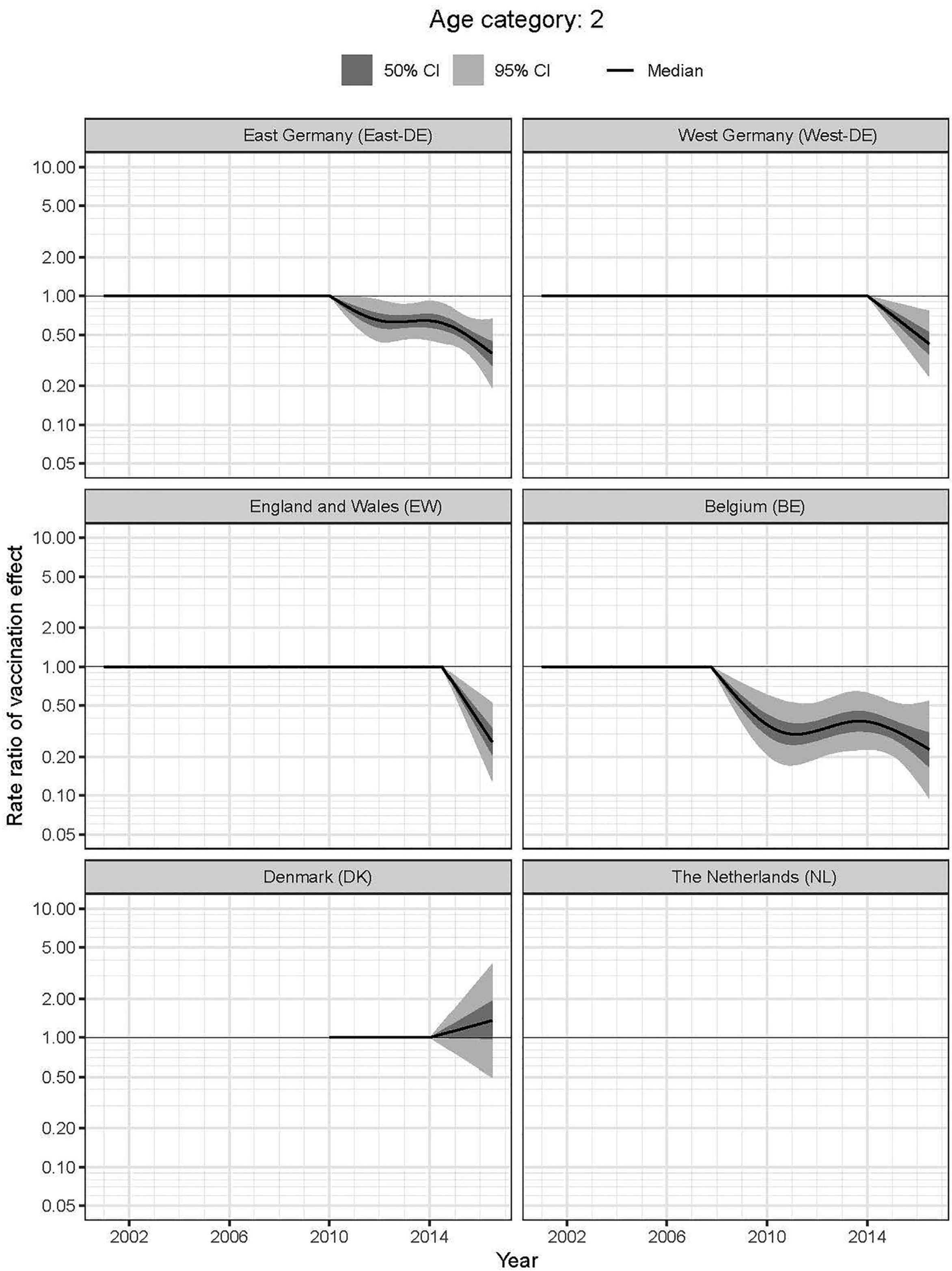
[30]. Across the countries studied, G1P8 dominance was replaced by a variety of strains including G2P4, which is in line with observations in several other countries [31,32,63]. Our model was not designed to incorporate strain distribution data. Other future research should address how strain diversity is driven by UMV and how this translates into overall rotavirus epidemiology.

In our study, a herd effect in individuals ineligible for vaccination was only observed in EW, but not in BE or DE. This is partly in contrast with evidence from a study in the US, where long-term time series analysis indicated herd effects of rotavirus vaccination in all age-groups [64]. Most evidence on herd effect of rotavirus vaccination is derived from observational studies and can



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therefore be biased by unmeasured confounding, such as a change in natural fluctuations in rotavirus epidemiology, effects of population size dynamics or meteorological factors possibly influencing rotavirus transmission. So far, no evidence is reported on herd immunity extending to non-vaccinating countries, even though this was hypothesized for the unexplained change in rotavirus epidemiology in the Netherlands [33,36]. This study did not support the hypothesis of herd effect on the country-level and from 2018 on, the biennial pattern is no longer observed in the Netherlands [63]. The cause of the low epidemics in 2014 and 2016 is still

Table 2
Shifts in rotavirus annual seasonality comparing pre- and post-rotavirus UMV introduction by region.

Mean number of weeks difference	EW	West-DE	East-DE	BE	DK after West-DE started vaccination	NL after BE started vaccination (2006)	NL after EW and West-DE started vaccination (2013)
Season start	**5.41**	**3.87**	1.87	0.23	3.50	−0.93	3.79
(95%-CI)	(2.01;8.81)	(0.47;7.27)	(-1.34;5.09)	(-4.54;5.01)	(-5.06;12.06)	(-4.97;3.10)	(-0.75;8.34)
Season end	**3.39**	1.85	**2.84**	**5.73**	1.41	−0.10	2.12
(95%-CI)	(0.56;6.21)	(-0.28;3.98)	(0.97;4.70)	(2.67;8.79)	(-0.97;3.81)	(-3.10;2.90)	(-1.39;5.64)
Season duration	−1.72	0.95	1.11	**5.43**	−1.58	−0.53	−1.84
(95%-CI)	(-5.38;1.95)	(-3.48;5.38)	(-1.79;4.01)	(1.89;8.97)	(-10.59;7.43)	(-3.12;2.06)	(-4.91;1.21)
Season peak	**6.77**	**3.89**	**4.00**	**4.90**	3.58	1.06	**5.33**
(95%-CI)	(3.87;9.67)	(0.31;7.47)	(1.11;6.88)	(1.38;8.42)	(-1.79;8.95)	(-3.34;5.47)	(0.73;9.92)

Statistical significant differences are highlighted in bold.
Abbreviations: BE = Belgium; EW = England/Wales; DE = Germany; DK = Denmark; NL = the Netherlands.

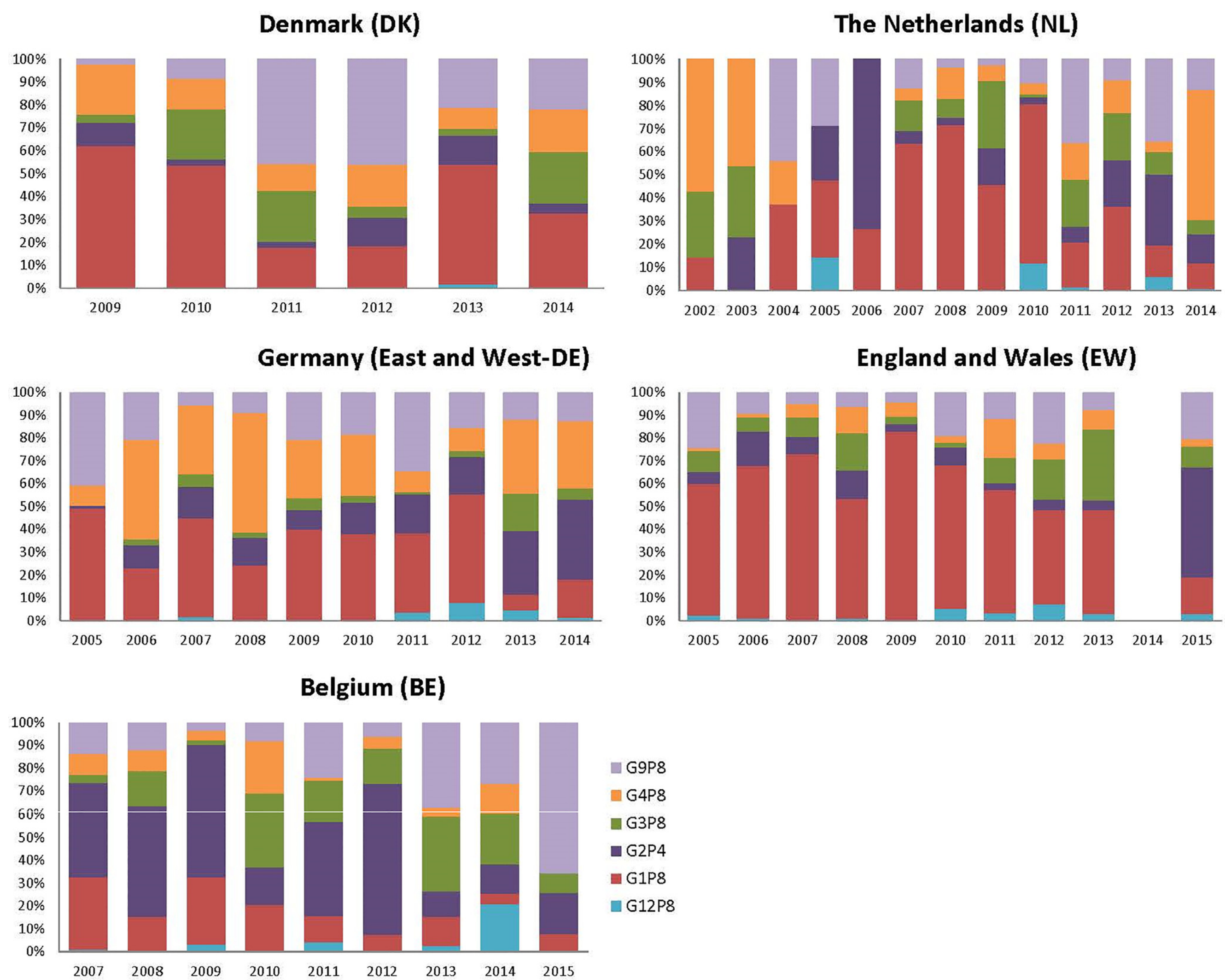

Fig. 3. Overview of the relative contribution of the six most common rotavirus genotypes per season (sep-aug), by region.

unknown, potentially this was due to a smaller susceptible population combined with altered genotype distribution. No increase in rotavirus vaccination uptake in the private sector was observed.

There are some limitations of this study. First, as each country has different national sources and registrations the available data varied somewhat per country. For instance, limited time series data was available for the pre-UMV period in BE, and the complete time series for DK covered only six years. Moreover, DK changed its rotavirus testing policy during the study period. While we controlled for this change in our analysis we cannot exclude it influenced our parameter estimates to some extent as we did not had any denominator data. To be able to compare the vaccination effect between regions, we arbitrary choose the parameters which proved to be a predictor in the majority of the regions (i.e.

population size) and was available for all regions (i.e. average maximum temperature). In addition, potential pre-vaccination trends in rotavirus epidemiology were not considered in the final models. The results should be interpreted with caution, however, they allow for comparison between regions and time-periods with UMV. Second, rotavirus vaccine introduction was not uniform across countries: in EW and BE, there was a clear time point of national vaccine introduction reaching high stable vaccination coverages in short time (Fig. 1). However, in East- and West-DE, the implementation was individually regulated by federal states, resulting in a slow uptake, and a gradual and moderate increase in vaccination coverage [17]. This gradual vaccine uptake and the modest overall vaccination coverage is reflected in lower effect estimates for West- and East-DE compared to the results for EW and BE. Vaccination coverage data were available on an annual basis, whereas for our time series analyses on weekly level, coverage data for smaller time units would be needed.

In summary, a reduction of 42% in rotavirus laboratory detections was observed for UMV countries (Germany, England/Wales and Belgium) two years after rotavirus vaccine implementation. A herd effect in older age groups ineligible for vaccination was only observed in EW, and there was no effect in non-UMV countries (NL and DK) on rotavirus epidemiology induced by UMV neighbouring countries. The implementation of rotavirus vaccination changed the annual epidemics with a 4–7 weeks delayed start and corresponding peak compared to pre-vaccination seasons.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.09.059.

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