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Explaining the formation of a plateau in rotavirus vaccine impact on rotavirus hospitalisations in Belgium

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ABSTRACT

Background: Observational data on the reduction in hospitalisations after rotavirus vaccine introduction in Belgium suggest that vaccine impact plateaued at an unexpectedly high residual hospitalisation rate. The objective of this analysis was to identify factors that influence real-world vaccine impact.
Methods: Data were collected on hospitalisations in children aged ≤ 5 years with rotavirus disease from 11 hospitals since 2005 (the RotaBIS study). The universal rotavirus vaccination campaign started late in 2006. A mathematical model simulated rotavirus hospitalisations in different age groups using vaccine efficacy and herd effect, influenced by vaccine coverage, vaccine waning, and secondary infection sources. The model used optimisation analysis to fit the simulated curve to the observed data, applying Solver add-in software. It also simulated an 'ideal' vaccine introduction maximising hospitalisation reduction (maximum coverage, maximum herd effect, no waning), and compared this with the best-fit simulated curve. Modifying model input values identified factors with the largest impact on hospitalisations.
Results: Compared with the 'ideal' simulation, observed data showed a slower decline in hospitalisations and levelled off after three years at a higher residual hospitalisation rate. The slower initial decline was explained by the herd effect in unvaccinated children. The higher residual hospitalisation rate was explained by starting the vaccine programme in November, near the rotavirus seasonal peak. This resulted in low accumulated vaccine coverage during the first rotavirus disease peak season, with the consequential appearance of secondary infection sources. This in turn reduced the herd effect, resulting in a diminished net impact.
Conclusions: Our results indicate that countries wishing to maximise the impact of rotavirus vaccination should start vaccinating well ahead of the rotavirus seasonal disease peak. This maximises herd effect during the first year leading to rapid and high reduction in hospitalisations. Secondary infection sources explain the observed data in Belgium better than vaccine waning.

1. Introduction

Vaccines are established as effective preventive measures against infectious disease [1-4]. The design and implementation of vaccine programmes has an important influence on the overall impact of vaccination in infectious disease control. For some vaccines, such as zoster, the optimum implementation strategy is relatively simple; vaccination of all at-risk individuals is the most effective way to reduce the disease burden [5]. For others, such as vaccination against rotavirus, the situation may be more complex. Rotavirus is highly transmissible, and only part of the at-risk population group of children aged < 5 years can be vaccinated, because safety concerns mean that full vaccination must be completed before the age of 6–8 months [6].

The effectiveness of a vaccine programme can be assessed by collecting data on reductions in disease-specific mortality and/or hospitalisations during the first years of programme

Abbreviations: GRG, Generalised Reduced Gradient; HIC, high income countries; RCT, Randomised controlled trials; UK, United Kingdom.

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implementation. Effectiveness evaluations comparing different vaccination strategies could provide valuable insights into features of disease transmission and vaccine performance. However, such evaluations are not commonly conducted as they are not easy to perform. Randomised controlled trials (RCT) to compare different implementation strategies cannot be set up after a vaccine has already been introduced. A different approach is required, collecting and analysing detailed observational data during vaccine launch programmes over an observation period of several years [7-16]. This will need to use an outcome measure such as hospitalisation that is frequent, easily measured and verified, linked to vaccine effectiveness and with a clear benefit. We have undertaken such an assessment of rotavirus vaccine introduction in Belgium in the RotaBIS study, collecting and publishing field data and the effect on rotavirus hospitalisations over time [7,17,18]. This observational study provided real-world data on the impact of the rotavirus vaccination programme on rotavirus hospitalisations in children aged < 5 years . It was conducted in 11 hospitals across Belgium with an observational period starting in 2005, collecting annual data on the number of rotavirus-positive test results in hospitalised children [18]. The results showed a rapid fall in rotavirus hospitalisations in the first two years after vaccine introduction, after which the decrease levelled off to a plateau [18].

Models can build further on observational study data by providing a mechanism to test the influence of various potential explanatory variables. This helps to identify factors that could drive the observed results, and also to define vaccination implementation strategies that are most likely to maximise success. Parsimonious models are preferable as a starting point, using simple mathematical equations with time- and age-adjusted parameters. The model can be fitted to the observed data and the parameters varied to test the influence of critical factors on the overall outcome. The model can also identify additional observational data to be collected that would be useful to test model-generated hypotheses [19]. We have previously applied a modelling approach to the data from the RotaBIS study, and the results from that analysis indicated that the starting date of the vaccination programme and vaccine coverage rate in the population aged 3–12 months were important factors in overall vaccine impact on rotavirus hospitalisations [7].

In this paper we present a further modelling analysis of the RotaBIS data. The objective of this evaluation was to identify credible explanations for the pattern of rotavirus hospitalisations observed over time, particularly the plateau reached in the vaccine impact during the vaccine uptake period. For rotavirus vaccination the uptake period is at least 5 years, because the vaccination window for this vaccine is only 18–24 weeks starting from 6 weeks of age, due to a higher risk for intussusception with increasing vaccination age [20]. This plateau has often been attributed to vaccine waning in modelling exercises of the vaccine impact conducted at vaccine launch [21-24]. Our analysis aimed to test this possibility and explore other possible explanations.

2. Methods

2.1. Observed data

The outcome measure selected to assess the impact of rotavirus vaccination in high income countries (HIC) such as Belgium is rotavirus hospitalisations of children aged $\leq$ 5 years. We retrieved these data from our observational RotaBIS study (period 2005–2019). The data were split into six age-groups (0–2 months; 3–12 months; 13–24 months; 25–36 months; 37–48 months; 49–60 months), presented by year. The initial paper and subsequent reports have been published [7,17,18,25-27]. Supplemental material 1 provides brief details of the initiation of the RotaBIS study in 2007. The summary of the observational annual hospital data used relative instead of absolute numbers, with 100% being the level before introduction of the vaccine.

2.2. Research questions

Three research questions were formulated. The first was to identify the differences in overall hospitalisation numbers over the study period between the RotaBIS observational data and two simulated vaccine programmes, presented through a model that integrates variables influencing the impact of vaccination on hospitalisations. The first simulated programme ('ideal') had an early vaccination start, maximum coverage, maximum herd effect, no waning, and no secondary sources of infection. The second ('direct vaccine effect only') included only the variables related to the direct impact of the vaccine on hospitalisations, excluding indirect effects, vaccine waning, and secondary sources of infection.

The second question was to identify potential deviations in the declining hospitalisation curve seen in the RotaBIS data compared with the curves from the two simulated programmes, related to the sharpness of the decline during the first two years after the vaccine introduction and the shape and level of reduction in hospitalisation thereafter during the vaccine uptake period [28].

The third question was to identify potential explanations for any deviations. This was investigated using the model, first fitting the model to replicate the observed data, then varying the critical parameters to identify those that had the most important effects on the vaccine impact.

2.3. The model

2.3.1. Model structure

The model was developed in MS Excel. The design is a static, population, intervention-impact model of the at-risk group, children aged 0–5 years. The model operates on an annual cycle. The population structure of the model is modified each year with an incoming birth cohort and an outgoing cohort aged 6 years. The group aged up to 1 year is divided into two age groups, those aged 0–2 months and those aged 3–12 months, reflecting the age at which children become eligible for rotavirus vaccination and using the herd or indirect vaccine effect observed in the RotaBIS data previously published [7]. Children aged > 1 year are categorised into four age groups: 13–24 months; 25–36 months; 37–48 months; 49–60 months. The annual population structure therefore remains stable over the investigation period, which is limited to eight years of vaccination follow-up relative to the baseline value (pre-vaccination). The outcome measure selected was the number of rotavirus hospitalisations.

The model focusses on rotavirus hospitalisations during the vaccine uptake period when the hospitalisations in Belgium were seen to plateau in the RotaBIS data. Once the vaccine uptake period ends (after 7–8 years), a new infection equilibrium is reached in the at-risk population with new forces operating in the post-vaccine uptake period, requiring a different type of model to evaluate long-term vaccine impact. The current model therefore contains only nine years of evaluation, 0 (=pre-vaccination) plus eight years of vaccine uptake), each of which has six age groups. This gives in total 48 vaccine uptake datasets or cells in a model grid (Fig. 1). The first six datasets of year 0 that define the annual hospital data pre-vaccination by age groups are the starting observational numbers.

2.3.2. Secondary infection sources

The accepted epidemiology of rotavirus disease spread in children indicates that the dominant transmission is from young children aged 3–15 months to the other age groups in the at-risk

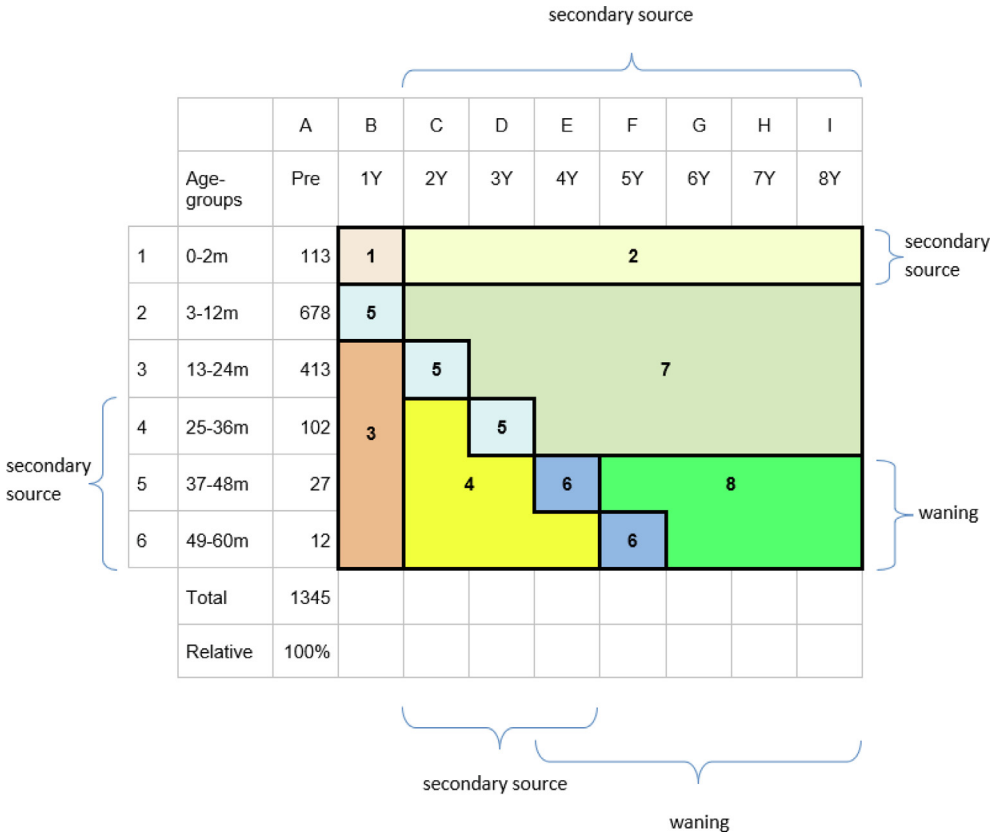


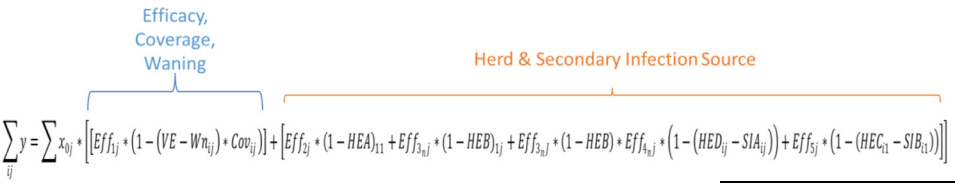
Fig. 1. Model grid structure. Area 1: no vaccination, limited herd effect of 1st year vaccine coverage; area 2: no vaccination, herd effect under vaccine coverage of subsequent years; area 3: no vaccination, herd effect under vaccine coverage 1st year; area 4: no vaccination, herd effect and secondary sources of infection appearing; area 5: vaccination 1st year with vaccine effect in the cohort over two additional years; area 6: vaccination 1st year with vaccine effect and vaccine waning starting in year 4 post-vaccine introduction; area 7: vaccination under vaccine coverage of subsequent years; area 8: vaccination at vaccine coverage of subsequent years with vaccine waning.

population [7,29]. This primary source of infection is tackled by vaccination of infants, resulting in a dramatic reduction of infection spread from this age group in the first and subsequent years. However, older children in the same at-risk population can act as a secondary source of infection. As these children are too old for vaccination, this secondary source of infection is not covered by the vaccination when first introduced. If vaccination coverage is low in the group forming the primary source of infection, this group may be a source of infection for other children who then become a secondary source of infection. In turn, this secondary infection source may infect unvaccinated susceptible individuals. As herd effects from the vaccination rely on reducing transmission from the primary infection source, the appearance of significant secondary infection sources will attenuate any herd effects. This is a particular issue with the rotavirus vaccine, because for safety reasons vaccination is limited only to children aged < 8 months. Therefore, in the first year of the vaccination programme, the maximum proportion of the total at-risk population that can be vaccinated and directly protected against the infection is 1/5. The rest of the at-risk population (4/5) cannot be vaccinated, and even if only a small proportion of this group is infectious it may still be an important source of infection.

The present model includes both primary and secondary infection sources. The herd effect in unvaccinated children may be reduced or removed by secondary sources of infection. This will appear as a plateau or levelling-off in the reduction in rotavirus hospitalisation data, which may look similar to vaccine waning causing a reduction in the effect of vaccination. However, by including primary and secondary sources of infection separately, it is possible to model simulated graphs showing the separate impacts of vaccine waning on the direct vaccine effect and secondary infection sources on the attenuation of the herd effect. Comparing the shapes of the simulated graphs to the observed data allows us to evaluate which factor is a better match (and therefore a more likely explanation) for the observations.

2.3.3. The model grid

The model grid is presented in Fig. 1. The first uncoloured column gives the starting numbers of hospitalisation pre-vaccination by age group. The remainder of the grid from cells B1 to I6 is split into eight coloured areas (described in detail in Supplemental material 2). Briefly, the first row represents the group too young to be vaccinated (Areas 1 and 2). Column 2 (Area 3) represents the group too old for vaccination in the first year, who are therefore subject only to herd effect and not direct vaccine effect. Area 4 represents this unvaccinated group in subsequent years when they are potentially subject to herd effect and secondary infection. Areas 5 and 6 represent the first birth cohort to be vaccinated, progressing through the subsequent years of the model, with vaccine waning appearing in year 4 after vaccine introduction. Areas 7 and 8 represent the normally vaccinated birth cohorts, with vaccine waning appearing in year 4 after vaccine introduction. The sum of hospitalisations by year and age group is calculated using the following equation:



$i = year$
$j = age - group$
$y = rotavirus\ \ hospitalisations\ post - vaccination$
$x_{0j} = rotavirus\ \ hospitalisations\ pre - vaccination$

Other codes are explained in Table 1.

The equation includes parameters related to direct vaccine effect (efficacy, coverage and waning), and parameters related to indirect vaccine effect (herd effect and secondary infection sources). The values for these parameters are defined by year and age group for the eight areas shown in Fig. 1. The sources and rationale for these values are described in the next section.

2.3.4. Input data

The data inputs for the model are shown in Table 1. Vaccine efficacy is based on clinical trial data [30], vaccine coverage is based on Belgian sales data [7,18,31], and first-year herd effect based on the observed RotaBIS data [7]. The first-year herd effect depends on the accumulated vaccine coverage during the peak season. The direct effect of the vaccine is also influenced by vaccination compliance/completion rates, which reduce the vaccine efficacy if fewer or no doses are given during the indicated time window. Because rotavirus vaccination is normally given together with other multidose vaccines in HICs, the effect of this is likely to be minimal and has not been considered in the model.

Values for vaccine waning and the impact of secondary sources of infection on the herd effect from the second year of vaccine introduction are assumptions, estimated by fitting the model to the observed data (Table 1). Cohort waning, which may start within a vaccinated cohort after vaccine exposure, is presumed to occur no earlier than 3 years (36 months) after the start of the vaccination and will appear as a reduction of vaccine efficacy. Other timescales for this vaccine waning are tested in scenario analysis. Population waning, which is the reduction in vaccine efficacy in new birth cohorts because of serotype shifts in the virus, has not yet been observed for this vaccine and this virus and therefore is not considered in the model.

For the group too young for vaccination, herd effect in the first year is influenced only by the accumulated vaccine coverage rate during the peak season. In subsequent years, and in the group too old for vaccination, the herd effect each year depends on vaccine coverage and the presence of secondary sources of infection. The net effect of herd protection minus the impact of secondary infection sources is simulated in the model and fitted to the observed data to obtain the Belgian values in Table 1.

For each parameter in the model minimum and maximum values were defined, representing realistic values for change in the local environment (Table 1), assessed through local expert review. The constrained optimisation model must comply with these minimum and maximum values. Supplemental material 2 and 3 provide greater detail of the model operation and constrained optimisation. In each of the eight areas in Fig. 1, the same regression equation is applied to calculate the hospitalisation numbers seen in that area. For four of the eight areas, the sum of hospitalisations should match the observed number of hospitalisations, because the parameter values were obtained from the RotaBIS database, and these matches are additional constraints in the optimisation process. For the four other areas, the optimisation process adjusts the variables within their minimum and maximum value range to obtain the values that provide the best match between the model result and the observed data in each area and across the whole model grid.

Three simulations were run: fitted to the RotaBIS observed data (Value BE); an 'ideal' simulation; and a 'direct effect only' simulation including only direct vaccine effects (Table 1). The 'ideal' simulation used values of 99% for vaccine efficacy, 85% for coverage in the first year and 98% in subsequent years, and herd effect of 50–87% depending on age group and year (Table 1), which we believe to be the best realistically achievable.

2.4. Statistical analysis

The best fitting curve of the model output with parameter values for all the variables selected minimises the accumulated difference in hospitalisations during the evaluation period compared with the observed dataset using the optimising process. This is based on the lowest total sum of the difference in square products per area between the modelled and observed data with the highest R^2-score on the regression line of the deviations measured in each

Table 1
Input values for the simulation fitted to the observed Belgian data (Value BE), for an 'ideal' simulation maximising the reduction in hospitalisations (Value Ideal) and for a simulation including only direct vaccine effect (Direct only).

			Uncertainty				
Variable/Force	Code	Value BE	Min	Max	Value Ideal	Direct only	Source
Vaccine efficacy	**VE**	**95%**		95%	99%	95%	[30]
Vaccine coverage 1st year	**Cov_{1j}**	**52%**	49%	54%	85%	52%	[7,18,31]
Vaccine coverage subsequent years	**Cov_{ij}**	**83%**	82%	85%	98%	83.4%	[7,18,31]
Herd effect (0–2 m 1st year)	**HEA**	**15%**	13%	17%	50%		[7]
Herd effect (older unvaccinated 1st year)	**HEB**	**31%**	29%	33%	83%		[7]
Herd effect (older unvaccinated subsequent years)	*HED*	*33%*	30%	45%	87%		Assumption
Herd effect (0–2 m subsequent years)	*HEC*	*75%*	60%	80%	80%		Assumption
Secondary infection source (2nd year older)	*SIA*	*35%*	30%	45%			Assumption
Secondary infection source (0–2 m subsequent years)	*SIB*	*27%*	25%	35%			Assumption
Waning cohort	*Wn*	*12%*	5%	20%			Assumption
Effect variables	Eff_{nj}	binary variables (0, 1) that activate or disactivate part of the equation					

BE, Belgium; m, month. Bold text indicates parameter values directly obtained from the RotaBIS data. Italic text indicates best estimates taking a conservative approach (see Supplemental material 2).

area. We used Solver, a MS Excel add-in software program, for performing the optimisation modelling with the GRG Nonlinear calculation method. Constraints were added for each parameter in the model, defined by the local operational minimum–maximum ranges for known values in the equations and much larger ranges for the parameters with unknown values (see Supplemental material 2). Some additional constraints requiring no difference between modelled and observed data in four areas of the model grid were added to force the model into simulating the best fit through the net differences of herd effect affected by secondary sources of infection and of vaccine effect affected by vaccine waning.

2.5. Scenarios

The analysis also modelled scenarios to test the effects of varying vaccine implementation. Scenarios included different vaccine coverages during the first peak season caused by different starting dates for the vaccination programme, vaccine waning with different ranges and start times, and the presence and absence of secondary sources of infection.

3. Results

3.1. Overall results

Table 2 presents the observed hospitalisation data of the RotaBIS study by age group and year, together with the simulation fitted to the observed data through the optimisation process, and the data from the modelled 'ideal' simulation. The 'direct effect only' simulation data are shown in Supplemental material 4.

In the 'ideal' simulation, the hospitalisation numbers in Area 4 as defined in Fig. 1 (C4-6, D5-6, E6) are lower compared with the year before (B4-6), whereas this decrease is absent from the observed data. This absence of reduction in the observed data requires an explanation, and this explanation cannot be vaccine waning because there is no direct effect of the vaccine in this age group, who are too old for vaccination.

The first research question can be answered by comparing the overall number of hospitalisations between the simulations. The accumulated number of hospitalisations in years 1–8 of the observed data was 3,314, compared with 741 in the 'ideal' scenario. Without vaccination, the expected number of hospitalisations would be approximately 10,760 (8 × 1,345) over 8 years. The observed Belgian vaccination programme therefore resulted in a substantial reduction in hospitalisations of 69% over the period, compared with the expected number without vaccination. However, the 'ideal' simulation suggests that the reduction could have been considerably larger, up to 93%.

Fig. 2 shows the data from the 'ideal' simulation, the simulation fitted to observed data, the direct vaccine effect only simulation and the observed data from the RotaBIS study. In general, the simulated observed data curve matched well with the observed data over the modelled period (Fig. 2), supporting confidence in the model. Comparing these curves answers the second research question. There were two places in the observed curve with substantial differences compared with the 'ideal' simulation. These are: a less sharp decline during the first two years after vaccine introduction

Table 2
Observed rotavirus hospitalisation data by age group and year post-vaccination in Belgium (RotaBIS data), simulation data fitted to the observational RotaBIS data, and 'ideal' simulation data.

Observed rotavirus hospitalisation data from the RotaBIS study in Belgium										
Age-groups	Pre	1Y	2Y	3Y	4Y	5Y	6Y	7Y	8Y	Accumulated 1-8Y
0–2 m	113	94	62	56	44	65	54	44	48	467
3–12 m	678	340	152	129	127	133	103	97	70	1151
13–24 m	413	311	208	100	139	134	114	107	74	1187
25–36 m	102	56	67	49	33	44	33	33	31	346
37–48 m	27	16	18	19	19	12	9	15	4	112
49–60 m	12	2	12	8	10	7	7	4	1	51
Total	**1345**	**819**	**519**	**361**	**372**	**395**	**320**	**300**	**228**	**3314**
Relative	**100%**	**61%**	**39%**	**27%**	**28%**	**29%**	**24%**	**22%**	**17%**	

Results of modelled simulation fitted to the observational data											
		A	B	C	D	E	F	G	H	I	Accumulated 1-8Y
	Age-groups	Pre	1Y	2Y	3Y	4Y	5Y	6Y	7Y	8Y	
1	0–2 m	113	94	54	54	54	54	54	54	54	471
2	3–12 m	678	339	145	145	145	145	145	145	145	1354
3	13–24 m	413	287	207	88	88	88	88	88	88	1023
4	25–36 m	102	71	70	51	22	22	22	22	22	301
5	37–48 m	27	19	18	19	16	10	10	10	10	111
6	49–60 m	12	8	8	8	9	7	4	4	4	54
	Total	**1345**	**818**	**502**	**365**	**333**	**326**	**323**	**323**	**323**	**3314**
	Relative	**100%**	**61%**	**38%**	**27%**	**25%**	**24%**	**24%**	**24%**	**24%**	

Results of modelled 'ideal' simulation											
		A	B	C	D	E	F	G	H	I	Accumulated 1-8Y
	Age-groups	Pre	1Y	2Y	3Y	4Y	5Y	6Y	7Y	8Y	
1	0–2 m	113	57	23	23	23	23	23	23	23	215
2	3–12 m	678	107	20	20	20	20	20	20	20	249
3	13–24 m	413	70	65	12	12	12	12	12	12	210
4	25–36 m	102	17	2	16	3	3	3	3	3	50
5	37–48 m	27	5	0	0	4	1	1	1	1	13
6	49–60 m	12	2	0	0	0	2	0	0	0	5
	Total	**1345**	**258**	**111**	**71**	**62**	**61**	**59**	**59**	**5**	**741**
	Relative	**100%**	**19%**	**8%**	**5%**	**5%**	**5%**	**4%**	**4%**	**4%**	

m, month; Pre, pre-vaccination; Y, year after vaccine introduction.

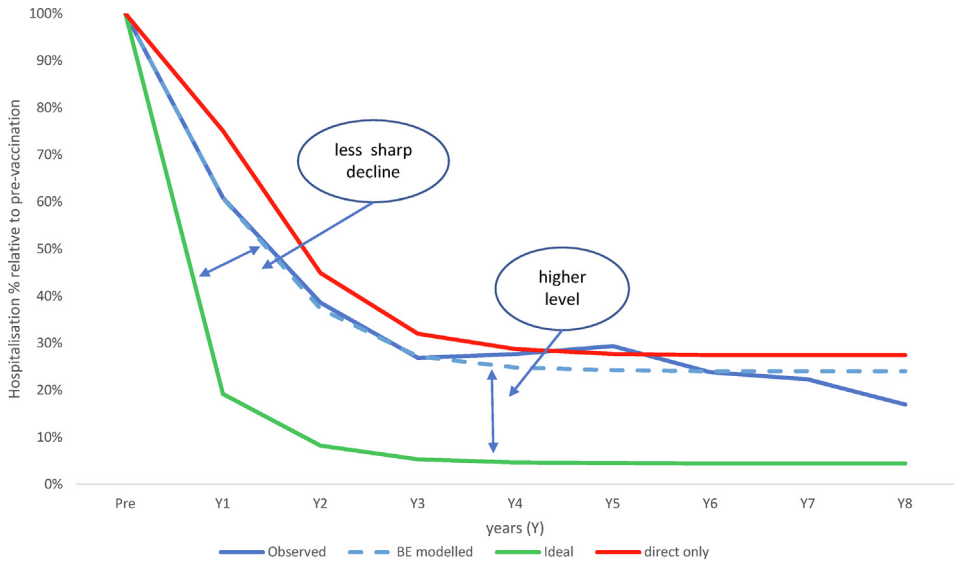


Fig. 2. Observed hospitalisation data compared with the simulation fitted to observed data (BE modelled), ideal and vaccine direct effect only simulations.

compared with the 'ideal' simulation; and a plateau in the observed curve at a much higher hospitalisation level compared with the 'ideal' simulation (24% of pre-vaccination level instead of 5%). The 'direct vaccine effect only' curve generally showed a slightly smaller reduction in hospitalisations than the observed RotaBIS data or the simulated observed data, because this simulation omits any indirect vaccine effects.

3.2. Explaining the deviations

3.2.1. Slower decrease in hospitalisations in the first year

The third research question was to seek potential explanations for observed differences between the simulations and observed data. The size of the herd effect in children too old to be vaccinated (HEB in Table 1) is the major factor underlying the slower decrease in hospitalisations in the simulated observed data compared with the 'ideal' simulation. In the 'ideal' simulation this herd effect was set at 83%, compared with 31% in the simulation fitted to the observed data (Table 1). Fig. 3 shows the effect of the starting date of the vaccination programme on the coverage achieved during the first year. Starting in June, nine months before the peak rotavirus disease season begins, the 'ideal' simulation reaches a high coverage by peak season. However, starting vaccination in November, as was the case in Belgium, means that only a limited maximum coverage rate can be reached by the peak disease season. The higher vaccine coverage achieved in the children who are the main transmitters of the virus (the primary source of infection), infants aged 3–15 months, by starting early, results in a larger herd effect and consequently a faster reduction in hospitalisations.

3.2.2. Levelling-off at higher residual hospitalisation rate

Herd effect and vaccine waning have opposite effects on the reduction in hospitalisations. The curve for the simulation fitted to observed data in Fig. 2 is modelled by adjusting the different forces using constrained optimisation (Supplemental material 2), and includes waning and herd effect with secondary infection forces. The secondary sources of infection potentially cannibalise the herd effect from the first year of vaccination in the subsequent years.

To evaluate which factors were most likely to explain the observed plateau in the hospitalisation data, we modelled four conditions. These were: absence of secondary sources of infections; no herd effect; adjusting the waning to compensate for the absence of secondary sources of infections; and absence of waning. The results are shown in Table 3, and plotted as summary curves in Fig. 4. When no secondary infection is present, the model predicts a reduction in hospitalisations of 264, compared with the observed data. To obtain the same result in the absence of secondary infection, waning needs to be increased to above 200% to arrive at the same summary result of 3,314 hospitalisations, which is quite impossible. With vaccine waning adjusted to 100% instead of the

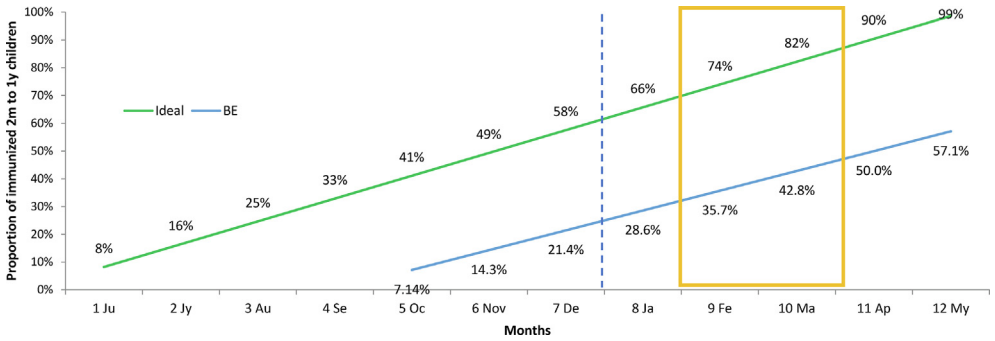


Fig. 3. Vaccine coverage as a function of the starting date of the vaccination programme. Yellow box: annual peak season of the disease; dotted blue line: year delimitation.

Table 3
Number of hospitalisations predicted by the model under different conditions: no secondary infections; no herd effect; vaccine waning adjusted to compensate for the absence of secondary sources of infection; and no vaccine waning.

	Reference value					
Area	Observed	Modelled	No secondary infection	No herd effect	Adjusted waning to 100%	No Waning
1	94	94	94	**113**	94	94
2	373	378	**168**	**790**	136	383
3	385	385	385	**554**	383	383
4	134	132	**83**	**192**	**83**	134
5	597	597	606	606	606	606
6	26	23	22	22	**40**	20
7	1653	1653	1648	1648	1648	1648
8	52	52	52	52	**150**	**31**
Total	3314	3314	3050	3976	3164	3289
Difference		0	264	−661	150	25

Area indicates the age group/year categories defined in Table 1. Area 1, Cell C1; Area 2, Cells D1–J1; Area 3, Cells C3–C6; Area 4, Cells D4–D6, E5–E6, F6; Area 5, Cells C2, D3, E4; Area 6, Cells F5, G6; Area 7, Cells D2–J2, E3–J3, F4–J4; Area 8, Cells G5–J5, H6–J6. Bold indicates important deviations.

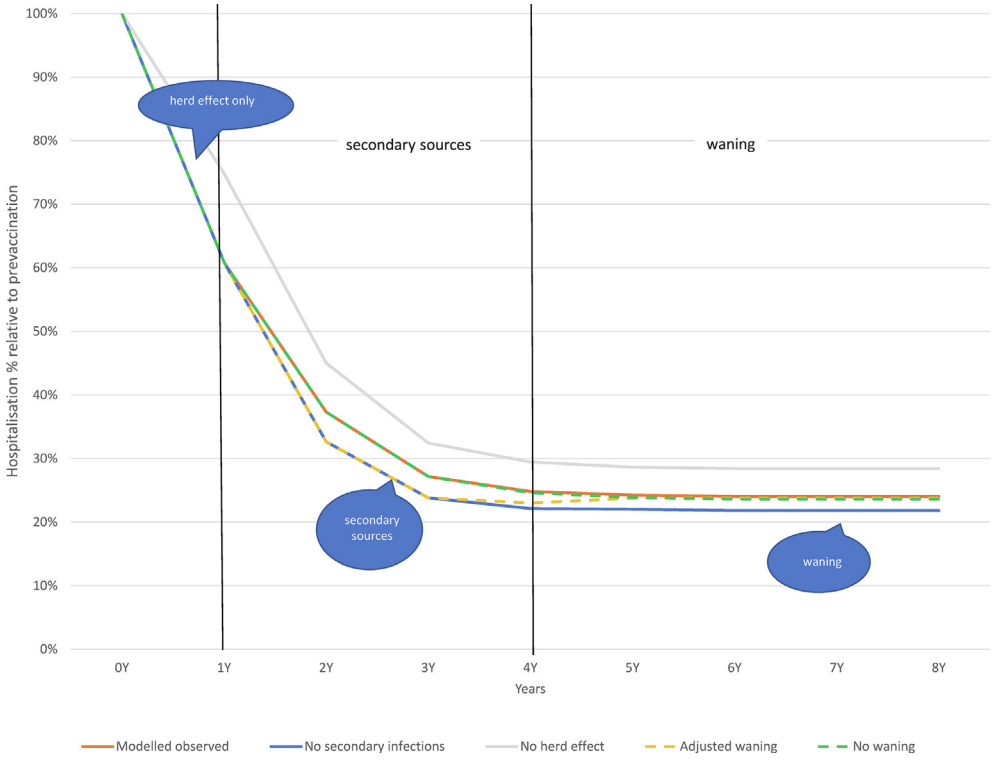


Fig. 4. Hospitalisations over time predicted by the four modelled conditions compared with the simulation fitted to the observed data.

modelled 10%, the reduction in hospitalisations is 150. As Fig. 4 shows, the curve with vaccine waning is not close to the observed modelled curve, while secondary sources of infection are operational during a short time-window (after 1Y to 4Y) to adjust the herd effect to the observed level. The curve with waning integrating into the other forces is active after year 4, as indicated by the vertical lines in Fig. 4. It should be noted that the model imposes a waning factor because of the additional decrease during the last year (Y8) in the observed data. In the absence of that decrease, no waning factor had to be included (Fig. 2).

3.3. Scenarios with worst-case conditions

Fig. 5 presents the results of two simulations exploring worst-case conditions for vaccine impact. In the first, vaccine waning starts in the second year after vaccine introduction, and in the second there is no herd effect because the vaccine coverage in the first year is too low (<35%). Fig. 5 shows that waning starting in the second year after vaccine introduction results in hospitalisations levelling out at around 30% of pre-vaccination levels, higher than the observed residual level. This indicates that early vaccine waning is not consistent with the observed data. Low vaccine coverage (VCA = 18%; VCB = 35%) and the resulting absence of herd protection shows a large effect, with the curve levelling off at around 70% of pre-vaccination levels, much higher than the observed data.

4. Discussion

This analysis of the RotaBIS data, using a simulation model to test the influence of different factors, helps to clarify issues in the optimum initiation of rotavirus vaccination in a HIC. Our 'ideal' simulation results indicate that the maximum reduction in rotavirus hospitalisations that can be achieved during the first years of vaccination could be over 90%, maintained throughout the

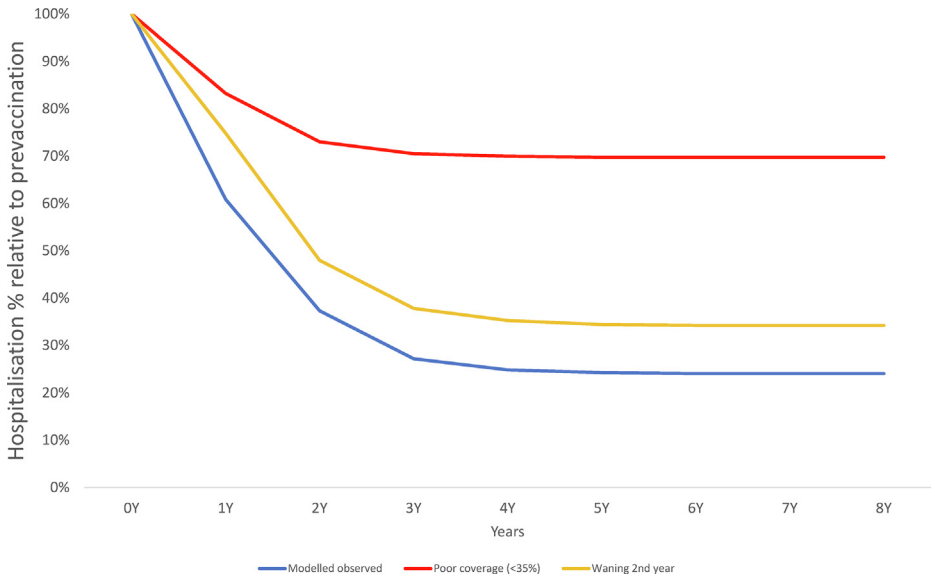


Fig. 5. Scenarios simulating different worst case conditions of vaccine introduction.

eight-year modelled period. This is substantially more than the reduction observed in Belgium. Our results also indicate that secondary sources of infection and their consequent influence on herd effects are more consistent than vaccine waning with the observed results in Belgium.

A decisive time point in a rotavirus vaccination programme is the inflection point when the decrease in hospitalisations levels off. Our modelled results indicate that the level of residual hospitalisations at this inflection point depends on the starting date of the vaccination programme in relation to the peak rotavirus season in the first year. An early start date maximises accumulated coverage during the first disease peak season, and this in turn maximises the herd effect. This model is the first to include secondary sources of infection that manifest themselves under conditions of partial attenuation of the primary source of infection by the vaccine. It builds on our previous model, which was unable to consider different sources of infection and acknowledged this as a limitation [7].

The model findings are supported by RotaBIS data indicating that herd effect was absent in years where it should be clearly observed. Table 2 shows that hospitalisations were higher in children too old for vaccination in years 2–4 after vaccination than in the first year of vaccine introduction, indicating that herd effect had been lost in these years. This could not be due to vaccine waning, because this group of children were too old for vaccination and therefore could experience no direct vaccine effect. The importance of secondary sources may be a feature of rotavirus vaccination, as vaccination is limited to only a part of the at-risk population for safety reasons. The vaccine uptake period therefore lasts at least five years before the whole at-risk population is covered, during which time the unvaccinated part of the at-risk population can act as a secondary infection source. The lower the vaccination coverage in the vaccine target group in the first disease season, the larger the pool of infectious children who may infect susceptible individuals, reducing or eliminating the herd effect. Secondary sources of infection are the best explanation for this reduction in vaccine effect seen in the early years of the vaccine introduction in Belgium. Although vaccine waning has most often been considered in the literature as the main cause [21-23,32], the results of our simulations are not consistent with vaccine waning as an explanation. Simulating an early waning scenario in our model, with waning beginning in the second year after vaccine introduction, produced results that differed from the simulation fitted to observed data. Furthermore, if vaccine waning occurs early, after the second year of vaccination, it would have been noticed in other countries, especially those where the effect of secondary sources of infection is absent. Early vaccine waning should manifest as hospitalisations of vaccinated children between one and two years old, which has not been reported in the literature.

This raises the question of whether these findings are unique to the RotaBIS study, or are consistent with other findings [21,32,33]. Fig. 6 shows rotavirus hospitalisations over time in four countries (Ireland, Belgium, Finland and the United Kingdom (UK)) that have implemented universal mass rotavirus vaccination, with our 'ideal' simulation for comparison. Finland and the UK achieved faster decreases than Belgium, and plateaued at a residual hospitalisation rate similar to our 'ideal' simulation. Both Finland and the UK started their vaccination programme early in the year (September/July) and obtained high vaccine coverage above 95% [10,34]. In contrast, in Ireland the decrease was slower than Belgium and no herd effect was apparent in the first year. In Ireland, rotavirus vaccination was initiated in December [13]. These results from countries with different start dates for the vaccination programme are consistent with our model results suggesting that start date, with its consequences for the accumulated coverage in the first peak season and for herd effect, is a major factor determining the impact of rotavirus vaccination.

The high variability in reported reduction in hospitalisations after vaccination by age group and year, seen in the RotaBIS data, is also more consistent with secondary sources of infection than with vaccine waning. Waning would be more likely to induce a constant reduction over time. The variability is also highest among children who were too young for vaccination (aged 0–2 months). Our results also show that for the impact of vaccine waning to be equivalent to that of secondary sources of infection, the waning would have to be unrealistically high.

One potential research question is whether the observed plateau in rotavirus hospitalisations forms due to an irreducible minimum level of rotavirus hospitalisations that cannot be further reduced regardless of vaccine coverage or efficacy. Published data from several countries and our 'ideal' simulation representing our interpretation of the best realistically achievable vaccine programme all result in the development of a plateau at some level (Fig. 6), which would be consistent with this hypothesis. However, the level of the plateau observed appears to vary between coun-

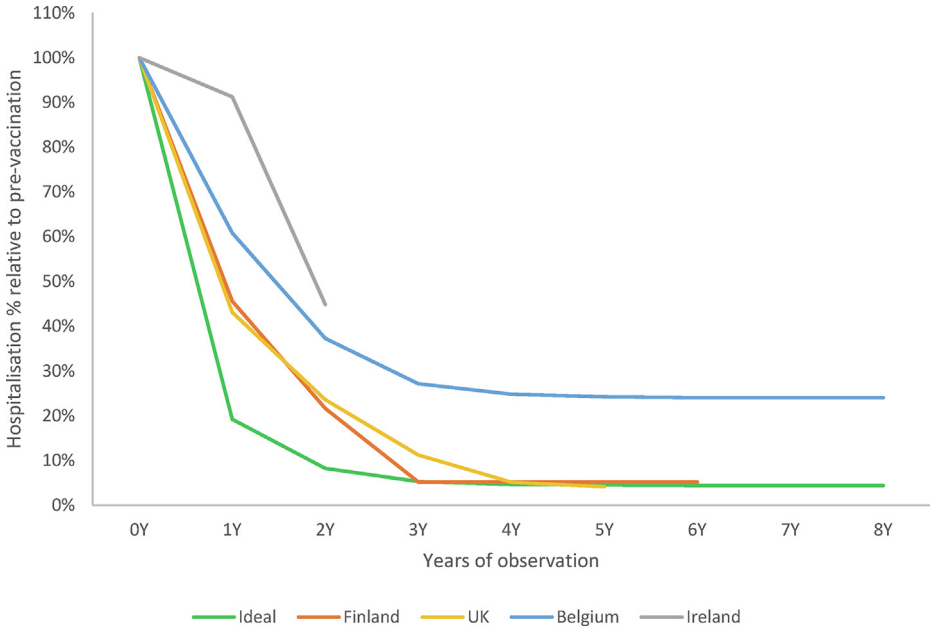


Fig. 6. The reported pattern of rotavirus hospitalisation in children aged ≤ 5 years in four countries in Europe that implemented universal mass rotavirus vaccination, compared with our 'ideal' simulation.

tries, being higher in Belgium than in the UK or Finland (Fig. 6). This suggests that the plateau is not entirely due to an irreducible minimum, but is influenced by factors that vary between countries. Our results suggest that the timing of vaccine introduction and the early coverage rate achieved may be key factors in the level of the plateau. It would be interesting to see whether a lower level of rotavirus hospitalisations is observed in the future, as this could help to indicate whether there is indeed a minimum level, or whether local disease elimination could be possible. This is a potentially valuable area for future research.

Confirmation of the real benefit of an early start date and high initial coverage in rotavirus vaccine introduction, as suggested by our model results, could be obtained if countries that are still to introduce rotavirus vaccination select an early start date and monitor the effect using a protocol similar to RotaBIS. Experimental comparisons of different launch processes cannot be initiated because of the substantial differences in outcome results over time.

This analysis has a number of limitations. The analysis and evaluation was conducted without having developed a prospective study protocol to compare two different vaccine launch scenarios. It was based on a single detailed dataset obtained in one country, and there could be other factors influencing the outcome in addition to those evaluated in the model. However, the comparison with results from other countries that followed a slightly different vaccine launch process helps to support the model findings.

5. Conclusion

When a new vaccine is introduced, close monitoring of its impact should be initiated at launch and maintained over a sufficient period to understand important factors in the implementation process. In the case of rotavirus, our analysis indicates that a key component of an optimum vaccine launch is to start well ahead of the next expected seasonal rotavirus disease peak, and aim for very high coverage of vaccine-eligible children. High vaccine coverage in the children who are the primary source of infection will maximise the herd effect achieved in the first year. This in turn helps to reduce the development of secondary sources of infection, leading to rapid and sustained control of the infection. Our results indicate that vaccine waning is not a satisfactory explanation for the plateau in hospitalisations observed in Belgium, and therefore that using a different vaccine or administering a booster dose is unlikely to improve the results. Conversely, our results and observations from other countries indicate that choosing an early start date for the vaccination programme can maximise real-world vaccine impact.

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BS was an employee of GSK until retirement in September 2020. The current research was conducted after he left GSK. He recently joined the Faculty of Medicine and Life Sciences, Research Group Care and Ethics, at the University of Hasselt, Hasselt, Belgium, as guest professor.

DS is a consultant and has not been paid for her contribution to this work.

MR is a paediatric professor and clinician. He has not been paid for his contribution to this work.

BB is an employee of GSK and holds shares of the GSK group of companies.

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Author contributions

All named authors for this manuscript meet the criteria of authorship according to the international Committee of Medical Journal Editors (ICMJE), have taken responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Proprietary Data Statement

All the data used have been retrieved from published papers or documents available on official websites. The models and methodology used in the research have been developed by BS and are available on request.

Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.02.053.

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