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The cost-effectiveness of pentavalent rotavirus vaccination in England and Wales

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ABSTRACT

Rotavirus vaccines have shown great potential for reducing the disease burden of the major cause of severe childhood gastroenteritis. The decision regarding whether rotavirus vaccination will be introduced into the national immunization program is currently being reviewed. The conclusions of previous evaluations of rotavirus vaccination cost-effectiveness contradict each other. This is the first analysis to incorporate a dynamic transmission model to assess the cost-effectiveness of rotavirus vaccination in England and Wales. Most previously reported models do not include herd protection, and thus may underestimate the cost-effectiveness of vaccination against rotavirus. We incorporate a dynamic model of rotavirus transmission in England and Wales into a cost-effectiveness analysis to determine the probability that the pentavalent rotavirus vaccination will be cost-effective over a range of full-course vaccine prices. This novel approach allows the cost-effectiveness analysis to include a feasible level of herd protection provided by a vaccination program. Our base case model predicts that pentavalent rotavirus vaccination is likely to be cost-effective in England and Wales at £60 per course. In some scenarios the vaccination is predicted to be not only cost-effective but also cost-saving. These savings could be generated within ten years after vaccine introduction. Our budget impact analysis demonstrates that for the realistic base case scenarios, 58–96% of the cost outlay for vaccination will be recouped within the first four years of a program. Our results indicate that rotavirus vaccination would be beneficial to public health and could be economically sound. Since rotavirus vaccination is not presently on the immunization schedule for England and Wales but is currently under review, this study can inform policymakers of the cost-effectiveness and budget impact of implementing a mass rotavirus vaccine strategy.

1. Introduction

Rotavirus is the leading cause of severe diarrhea in young children and leads to half a million deaths each year [1]. Rotavirus vaccines have recently been licensed in 2006 to reduce the morbidity and mortality associated with rotavirus. In Europe, the introduction of mass rotavirus vaccination strategies have been limited to Austria, Belgium, and Luxembourg in 2006, Finland in 2009, and Greece in 2012 [2]. Early data from Austria, Belgium, Germany, Greece, France, Spain and the United States in which vaccination has been introduced either partially or fully show that rotavirus vaccination is effective in reducing the incidence of rotavirus gastroenteritis (RVGE) [3–11]. Therefore although vaccination policy decisions are made on a country by country basis according to the specifics of the respective healthcare system and population structure, there is evidence to support adoption of rotavirus vaccination by other European countries [12,13]. For countries in which rotavirus vaccination has been introduced, post-vaccine surveillance data also reveals a reduction in RVGE cases among individuals who have not been vaccinated [14,1,15]. Thus, indirect protection appears to be a greater benefit of mass vaccination than first anticipated.

The predicted long-term effects of indirect protection from vaccination range in size depending upon the model used and the country analyzed [16–18]. Cost-effectiveness analyses (CEAs) for rotavirus that used static models, which only consider direct effects, predict a conservative effect of vaccination. For example, CEAs for the Netherlands and Belgium predicted that introducing vaccination was not cost-effective using static models, but taking into account herd protection tipped rotavirus vaccination into the cost-effectiveness range [19,20,12,21]. These studies highlight the importance of incorporating indirect effects of vaccination into valuations of the cost-effectiveness of rotavirus vaccination [14,22].

England and Wales (E&W) are reviewing the decision to introduce a mass rotavirus vaccination program within the coming year. To inform this decision, we assessed the cost-effectiveness

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of a pentavalent rotavirus vaccination program, using a dynamic model for E&W parameterized with incidence data, contact data and clinical trial data. This is the first cost-effectiveness analysis of a rotavirus vaccination program for a European country that incorporates herd protection using a dynamic model. Our analysis uses clinical trial data for the pentavalent rotavirus vaccine to assess the cost-effectiveness of introducing a pentavalent rotavirus vaccine to E&W. To calculate the probability that a mass vaccination strategy is cost-effective, we conduct a probabilistic sensitivity analysis using Monte Carlo simulations. Our results indicate that pentavalent rotavirus vaccination is likely to be cost-effective, for reasonable vaccine course prices for E&W.

2. Methods

2.1. Dynamic model

A dynamic model estimating the incidence of severe and mild rotavirus gastroenteritis (RVGE) in E&W a dynamic model was used to estimate the cost-effectiveness of introducing rotavirus vaccination into the national immunization schedule [23,58]. Vaccination efficacy parameters are based on large clinical trials of RotaTeq®. A dynamic model implicitly captures the herd protection conferred by vaccination as onward transmission between individuals is taken into account. The dynamic model was fit to ten years of age-stratified E&W RVGE incidence data by estimating unknown epidemiological parameters including the reporting fraction of severe RVGE, and those determining the seasonal forcing of transmissibility (Table 1).

The vast majority of reported rotavirus cases occur in children under five years and past data collection and published economic analyses have focused on this group [24,25]. Thus, only individuals under five years of age were included in the CEA although the whole population was taken into account in the dynamic model. RotaTeq® is administered orally in a three dose course with the first dose at 6–12 weeks, the second four weeks later, and the third before 20–22 weeks (no later than 32 weeks). The DTap/IPV/Hib combination vaccine is administered as a three dose course at 8, 12 and 16 weeks. Since the combination vaccine (DTaP/IPV/Hib) already has a 95% full-course uptake, we also assumed a 95% coverage for the total rotavirus vaccination course [25]. We assumed that a vaccinated individual who becomes infected has the same chance of a clinical outcome (i.e., hospitalization, home-care etc.) as an unvaccinated individual. This was because similar two year vaccine efficacies were observed for hospitalizations as for emergency room visits [26], and one year vaccine efficacies were not available for all healthcare outcomes. Pentavalent vaccine efficacy was assumed to be on average 100% and 72% against severe and any severity rotavirus RVGE, respectively, consistent with the efficacy data from the clinical trial with over 30,000 infants conducted in Europe [26]. Vaccine efficacy against mild infection was estimated as 63% using these data [23].

We conducted a probabilistic sensitivity analysis via Monte Carlo sampling that gave us a distribution of realistic rotavirus incidence over the time horizon of the analysis. This distribution of rotavirus incidence was generated by repeatedly sampling from both birth rate and vaccine efficacy. These two parameters which have an important impact on rotavirus dynamics and their mean values are either subject to change, in the case of birth rate, or uncertain, in the case of vaccine efficacy. We used the 2008 England and Wales birth rate, with the standard deviation extracted from years 1988 to 2008 [27] (0.0008, giving a 95% range for the birth rate to be 0.0114–0.0146). Consequently, for a population of 54.5 million we assume an average birth cohort of 708,500 (621,300–795,700 individuals). Our probabilistic sensitivity analysis generated a range of feasible predictions of RVGE incidence under different scenarios of vaccine introduction over which cost-effectiveness could be calculated [23]. The remainder of the epidemiological parameters were fixed, and thus varying both birth rate and vaccine efficacy generated uncertainty in RVGE incidence.

In order to evaluate the impact of herd immunity on the cost-effectiveness of rotavirus vaccination, we also present a static model that does not take into account disease transmission. The static model calculates the reduction in RVGE incidence only accounting for the direct effects of vaccination. Therefore the expected reduction in RVGE incidence after vaccination is the reduction attributable to vaccinated individuals, as is calculated directly from the estimated vaccine uptake, vaccine efficacy, and assuming vaccine waning where appropriate. Details of this static model are given in Atkins et al. [23] Appendix D.

Two different assumptions of duration of vaccine immunity were considered: (1) the duration of immunity assumed to be elicited by the vaccine equals that elicited by natural infection, exponential waning of mean duration one year. This scenario (of *Immediate* waning) is consistent with reported levels of T-cell derived immunity following natural infection providing complete but temporary immunity of between 8 and 13 months of age [28,29] and (2) there is no waning of immunity in individuals under three years of age, so immunity lasts on average for one year thereafter (Fig. 2b). The second scenario (of *Delayed* waning) is consistent with a large European clinical trial follow up that reported a sustained vaccine efficacy for at least three years [30,31]. The vaccine efficacies used for RotaTeq® have been estimated from clinical trial data (Table 1). All epidemiological parameters were either estimated from previous studies or estimated via formal model fitting of the dynamic model to rotavirus incidence data [23] (Tables 1 and 2).

Because disease cases are predicted to be controlled quickly if vaccine efficacy is sustained for three years with a 95% vaccine coverage, extending the protection afforded by vaccination could not increase the effectiveness of the program further and the cost-effectiveness ratios would remain the same.

2.2. Clinical outcomes

Severe RVGE cases were assumed to seek medical care, whereas mild RVGE cases were assumed to require only home care. Five clinical outcomes were considered: (1) a telephone call to NHS (National Health Service) Direct (telephone advice line); (2) an appointment with a general practitioner (GP); (3) a visit to an Accident and Emergency department (A&E); (4) hospitalization (due to a community or nosocomial infection); and (5) death. The proportion of severe RVGE cases requiring each of the five outcomes is calculated from the reported incidences of these outcomes in previous studies divided by the total incidence of rotavirus-infected individuals seeking clinical care [32,25]. The total incidence is the sum of the incidences of GP consultations, A&E consultations, nosocomial infections, and NHS Direct calls advising patients not to seek further medical care given in these previous studies [32,25]. All these values have a base case or follow a normal distribution from which they were sampled in the sensitivity analysis (Table 1).

Because few people die from RVGE in developed countries, the probability of death due to rotavirus infection is not known with precision [33]. The base estimate was derived from the most recent data available and sampled from a uniform distribution with bounds of ±25% of this base case to reflect the underlying uncertainty [12,33].

The first rotavirus vaccine to be licensed in the US (Rotashield®) was withdrawn soon after its introduction in 1998 due to reports of increased risk of intussusception (IS) (bowel obstruction) following vaccination [34,35]. Subsequent clinical trials of rotavirus

Table 1
Parameter values and distributions used in the cost-effectiveness analysis. The parameter values are those used in the base case and the distributions were sampled during the probabilistic sensitivity analysis. If no distribution is given, the base case values were used. Vaccine immunity was analyzed using either immediate waning or delayed waning. Vaccine administration costs were either from separate administration (full price) of the vaccine or concomitant with the DTaP/IPV/Hib vaccine (a fraction of the price). Epidemic model parameters are used in the dynamic model [23]. RVGE is gastroenteritis caused by rotavirus infection. NHS is National Health Service, GP is General Practitioner, A&E is Accident and Emergency. Incidence/1000 children under 5 years is given to calculate the probability of healthcare outcome given severe RVGE. Actual incidence of severe RVGE is predicted by the dynamic model.

Parameter description	Value use in base case	Distribution used in probabilistic sensitivity analysis	Ref.
Epidemic model parameters			
Birth rate (annual per person), f	0.013	NORM(0.0130,0.0008)	[27]
Population size (million)	54.5		[27]
Maternal immunity waning rate (weeks), e	1/13		[54]
Natural immunity loss rate (per year), ϵ	1		[29,28,18]
Proportion severe RVGE cases (under 5 years), σ_0	0.24		[21,55]
Proportion severe RVGE cases (over 5 years), σ_5	0.015		[23]
Recovery rate (severe RVGE, per day), γ_I	1/7		[50,56]
Recovery rate (mild RVGE, per day), γ_H	1/3.5		[50,56]
Reduction in infectiousness for mild RVGE, ρ	0.5		[21]
Reporting fraction, δ	0.064		[23]
Seasonal amplitude, A	0.064		[23]
Seasonal offset, θ	4.622		[23]
Susceptibility, b_j			
<1	0.083		[23]
1–2	0.065		[23]
2–3	0.017		[23]
3–4	0.006		[23]
4–65	0.003		[23]
65+	0.025		[23]
Vaccine coverage, ϕ	0.95		[25]
Vaccine efficacy (severe), η_I	100%	BETA(30.7,1)	[26]
Vaccine efficacy (mild), η_H	64%	BETA(51.25,29.21)	[26]
Vaccine immunity loss rate (per year), τ Scenario 1:	1 (all ages)		[28,29]
Scenario 2:	0 (<3 years)		[30,31]
	1 (≥3 years)		[30,31]
Cost-effectiveness framework parameters			
Calls to NHS Direct (/1000 children under 5 years)	10.2	NORM(10.2,0.51)	[25]
GP consultations (/1000 children under 5 years)	28.4	NORM(28.4,1.38)	[25]
A&E consultations (/1000 children under 5 years)	9.3	NORM(9.3,1.02)	[25]
Hospital admissions (/1000 children under 5 years)	4.5	NORM(4.5,0.0958)	[25]
Nosocomial infections (/1000 children under 5 years)	1.43	NORM(1.43,0.094)	[25]
Deaths (/1000 children under 5 years)	0.00109	UNI(0.000872,0.0013)	[12]
Pr(calls to NHS Direct resulting in home care/other)	0.442	NORM(0.442,0.0089)	[32,25]
Vaccine cost per full course (£)	45, 60		[25,13]
Calls to NHS Direct (£)	27.42	UNI(24.68,30.16)	[46]
Cost of vaccine course admin. (£), concomitant:	15	UNI(10.5,19.5)	[47,25]
Separate:	36	UNI(33,39)	[47]
Cost of GP consultations (£)	36	UNI(32.4,39.60)	[47]
Cost of GP prescription (£)	2.33	UNI(2.10,2.56)	[25]
Cost of A&E consultations (£)	111	UNI(99.90,122.10)	[57]
Cost of hospitalization (£)	1047.96	UNI(943.16,1,152.76)	[45]
Discount rate	3.5%	UNI(0–6%)[a]	[44]
Quality of life lost (<5 years with severe RVGE)	0.0022	NORM(0.0022,0.000264)	[32,49]
Quality of life lost (<5 years with mild RVGE)	0.00055	NORM(0.00055,0.0000165)	[32,49,50]

[a] Not varied in probabilistic analysis in main text (for varying discount rate see Supplementary Material).

vaccines [36,37] and post-licensure surveillance in the US [38] have shown no increased risk of IS. Other clinical trials in Europe have too few cases of IS to make statistical inferences [39,31]. Very recently there have been reports of a small but significant increase in Mexico [1] and Australia [40]. In the US, the FDA advises that the benefits of vaccination outweigh any suggested risk. In line with previous cost-effectiveness studies, we assume no increased risk of intussusception [25,12,13,41–43].

Table 2
Description of the scenarios used in scenario analysis used throughout our study. The cost of vaccine administration is either a fraction of the cost of the full consultation if the vaccine is administered at the same time as the DTaP/IPV/Hib vaccine (A and B, Concomitant); or, the full cost of a nurse consultation needed to administer all doses of the vaccine (C and D, Separate) [47]. The vaccine immunity duration is either the same as assumed for natural infection (A and C, Immediate)[28,29], or sustained for three years consistent with vaccine trial data (B and D, Delayed) [30,31]. All values of the parameters are given in Table 1.

Scenario	Vaccine immunity waning, τ	
	Immediate	Delayed
Cost of vaccine course admin.		
Concomitant	A	B
Separate	C	D

2.3. Costs

NHS-associated costs used are the most up-to-date available from 2010 to 2011, reflecting the re-estimation of costs four years after the price list used for previous cost-effectiveness analyses [25,12]. Consistent with National Institute for Health and Clinical Excellence (NICE) guidelines for E&W, the CEA was performed from the healthcare perspective, such that the mean costs associated with rotavirus infection were limited to those described in Section 2.2 (Table 1) [44]. The cost of hospitalization used was the weighted average cost of possible scenarios from the following references codes: FZ36D Intestinal Infectious Disorders with length of stay 2 days or more and major critical care (long stay

(£3305) and short stay (£441)), FZ36E Intestinal Infectious Disorders with length of stay 2 days or more without major CC (long stay (£1729) and short stay (£374)), FZ36F Intestinal Infectious Disorders with length of stay 1 day or less (long stay (£785) and short stay (£437.00)), PA21A (Infectious and Non-Infectious Gastroenteritis with critical care (long stay (£1598) and short stay (£533)), PA21B Infectious and Non-Infectious Gastroenteritis without critical care (long stay (£1031) and short stay (£472)) [45]. The cost of an NHS Direct call was estimated in 2008 [46], and inflated to 2011 prices using an increase of 107.39% [47].

Two scenarios for the cost of oral vaccine administration were used to reflect either separate vaccine administration or vaccine administration concomitant with the DTaP/IPV/Hib vaccine. The first scenario assumed a cost of £15 to account for the additional time for a nurse to administer the full rotavirus vaccine regimen along with the other childhood vaccines. This scenario reflects administering the vaccine concomitantly with the childhood vaccine DTaP/IPV/Hib (*Concomitant*). We estimated a cost for concomitant administration that reflected the oral rotavirus vaccine would be administered in less than 5 min as has been demonstrated for rotavirus vaccination in a recent randomized, nationwide survey conducted amongst 500 practice nurses from the UK [48]. The second scenario assumed a cost of £36 for the full nurse consultations required to administer the full-course regimen (*Separate*). This alternative scenario reflects administering the vaccine by itself. The administration costs reflect estimated prices for nurse consultations payable by the healthcare system. Both scenarios were sampled from non-overlapping uniform distributions (Tables 1 and 2).

It should be stressed that it is highly likely that a pentavalent rotavirus vaccine would only ever be administered concomitantly with DTaP/IPV/Hib as part of the existing UK vaccination schedule (Scenarios A and B) and this is consistent with the UK Department of Health's pronouncements. However, for full analytical completeness we include the possibility of separate administration as a sensitivity analysis (Scenarios C and D).

Because the market price of a full-course vaccine regimen greatly impacts the probability that vaccination will be cost-effective, this price was varied over a wide range in a threshold analysis (£0–180) [25,12,13]. The threshold analysis calculates the probability that pentavalent vaccination is cost-effectiveness as a function of vaccine course price. In the base case scenario, values of £45 and £60 per full-course regimen were used. The lower bound has been calculated approximately as the price at which the pentavalent rotavirus vaccine becomes cost-effective in previous economic evaluations for E&W without taking into account any indirect effects of vaccination [13]. Incorporating indirect protection in the analysis is thought to increase the cost-effectiveness of the vaccine. Therefore, we also use a higher bound, one third more than the lower bound, to consider the potential positive impact of including herd protection on the cost-effectiveness of the rotavirus vaccine.

2.4. Quality of life

The base case quality of life lost per severe RVGE episode was set as 0.0022 [49]. A mild case was defined as any infection ranking 0–10 on the Vesikari scale and a severe case was any infection ranking 11–20 [50]. This ranking takes into account not only the duration of infection with a mild infection lasting 3.5 days and a severe case lasting 7 days, but also the acuteness of the disease (including number of symptoms, rectal temperature and daily vomiting rate) [50]. Therefore, the base case quality of life lost per mild RVGE episode was assumed to be a quarter of that of a severe episode (0.00055). In accordance with the Joint Committee on Vaccination and Immunization (JCVI) recommendations, any reduction in the quality of life of caregivers was not taken into account in this analysis.

There has been found to be no statistically significant difference between the adverse events experienced by individuals who received the placebo and those who received RotaTeq®. Consequently, outcomes relating to adverse events were considered negligible and were not included in the analysis [26].

2.5. Calculations of cost-effectiveness

The basis of cost-effectiveness analysis of medical intervention is the balance between the cost of intervention and the incremental health effects that result from the intervention. For this analysis, these incremental effects were the differences between the incidence of RVGE with and without the vaccination program. To allow comparison with standard measures of cost-effectiveness in E&W, the results are presented in units of cost per quality adjusted life year (QALY) gained by vaccination (in comparison to no vaccination) to express the cost of purchasing a year of good health.

To calculate the incremental costs and health benefits, a procedure for determining the disutility (cost outlay) of vaccination and infection was developed from a dynamic model, in which the disutility of a vaccination decision depends on vaccine coverage and pricing. The discounted costs and benefits of a rotavirus vaccination program were summed over a time horizon of 50 years to ensure convergence. See Appendix A for additional details.

Consistent with NICE guidelines, an intervention producing a cost per QALY of less than £30,000 or £20,000 was considered cost-effective or very cost-effective, respectively, from the healthcare perspective. All effects were discounted at a base case rate of 3.5% or sampled uniformly from 0% to 6% in the sensitivity analysis [44].

3. Results

For all results, four scenarios are presented to account for different assumptions regarding the vaccine immunity duration and the vaccine administration costs (Tables 1 and 2). The scenarios are: A – Immediate vaccine waning and concomitant vaccine administration; B – Delayed vaccine waning and concomitant vaccine administration; C – Immediate vaccine waning and separate vaccine administration; and D – Delayed vaccine waning and separate vaccine administration. Both the base case and probability sensitivity analysis was conducted for the separate administration scenarios (C and D) for analytical completeness, but given that these scenarios are not congruous or applicable with the UK vaccination schedule, and the fact that a national rotavirus vaccination program would be administered concomitantly with other pediatric vaccines, emphasis is placed on Scenarios A and B.

3.1. Base case

Our transmission model predicts the annual incidence of RVGE in the community for children under five years, and the associated healthcare outcomes related to severe RVGE (Fig. 1). These annual incidences are shown for Scenarios A and C when the seasonal dynamics have settled to equilibrium. Scenarios B and D predict RVGE control within the first two years of a RotaTeq® vaccination program at 95% [23].

Our results show that pentavalent rotavirus vaccination would be cost-effective at both £45 and £60 per full vaccine course under the two realistic scenarios of concomitant vaccine administration (A and B) (Table 3). Furthermore, rotavirus vaccination is predicted to be cost-saving in Scenario D for a £45 full-course price.

The total quality of life lost due to rotavirus (measured in QALYs) is due to mild RVGE, severe non-lethal RVGE and lethal RVGE (Table 3). The relative QALY loss due to these three components

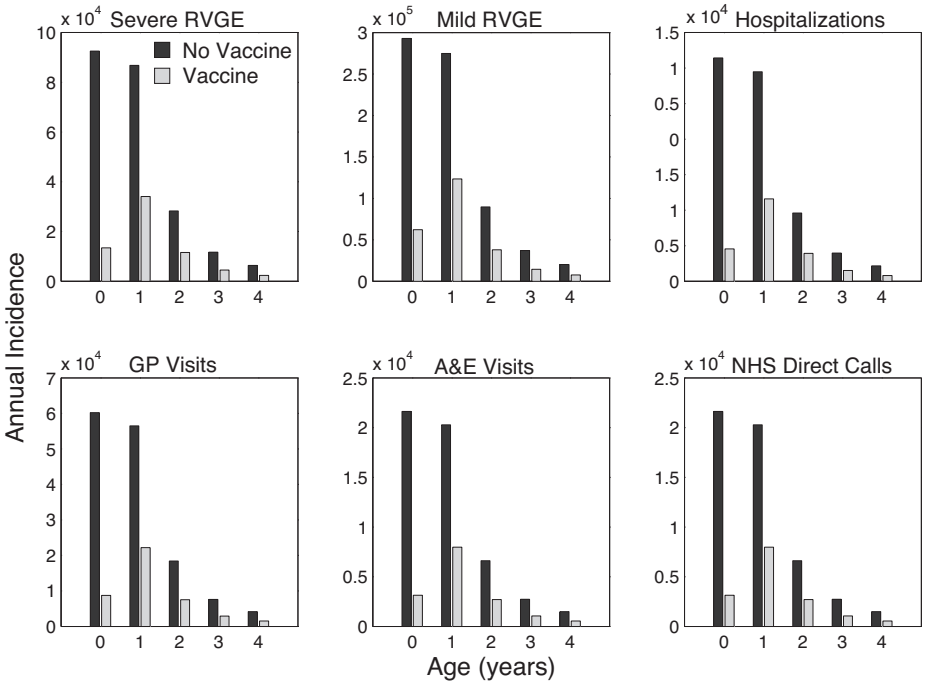

Fig. 1. Annual incidence predicted by the dynamic model both before and after RotaTeq® is introduced at 95% coverage into the infant population, and when the seasonal dynamics have settled to equilibrium. The dynamic model was fit to incomplete reported incidences from 1999 to 2009 [23]. These reported incidences were assumed to be a fraction of the severe RVGE in the population, with mild RVGE going unreported. Incidences are shown by year of age which are considered in the cost-effectiveness analysis. Only severe RVGE are assumed to seek healthcare, whereas both severe and mild RVGE incur loss of quality of life. Healthcare outcomes may be duplicated for each individual e.g., hospital admission occurs after an A&E visit or a GP visit. Note the different *y* axis scales. Cost breakdowns attributable to healthcare outcomes are given in Table 3.

is calculated directly in the analysis. Without vaccination, the discounted QALY loss attributable to mild infection, severe non-lethal infection and lethal infection was 38%, 48% and 14%, respectively. These relative severities of infection did not change significantly between Scenarios A, B, C and D (Table 3).

We found that herd protection significantly reduces the overall disease burden in E&W, as reflected by the prediction that rotavirus vaccination would be more cost-effective when indirect effects are considered in the CEA (Table 3). For example, using a full course price of £60 under Scenario A (immediate vaccine waning and concomitant vaccine administration), neglecting the indirect effects would lead to a conclusion that the vaccine was slightly over the cost-effectiveness threshold (at £35,000/QALY), contrary to the dynamic model which concludes the vaccine to be cost-effective (£27,000/QALY).

The percentage payback over time was dependent on the full course vaccine price. A vaccine price of £45 had a greater payback than if the vaccine was priced at £60 (Table 4). Scenario A produced a payback of 77% (for a £45 course price) and 62% payback (for a £60 course price). Scenario B enabled any vaccine costs to be recouped within ten years for a £45 course price, and over 80% of the costs within ten years for a £45 course price.

3.2. Probabilistic sensitivity analysis

Our study shows that at a price of £45–60 per full-course regimen, a pentavalent rotavirus vaccine is highly likely to be cost-effective in Scenarios A (concomitant vaccine administration and immediate vaccine waning) and B (concomitant vaccine administration and delayed vaccine waning) (Fig. 2). However, vaccine price can greatly influence the cost-effectiveness of vaccination in E&W (Fig. 3). The full-course vaccine price can dramatically increase the probability that vaccination will be cost-effective from 0% to 100%. In addition, cost-effectiveness is affected by the scenario of vaccine immunity waning and vaccine administration cost.

To achieve a 90% probability of being cost-effective, a full vaccine course should be priced between £53–72 according to a £30,000/QALY threshold using the dynamic model, depending on the scenario assumed. If a £20,000/QALY threshold is used, a 90% probability of being cost-effective is achieved with between £40 and 67.

If indirect effects of vaccination are neglected, the price per full-course regimen at which the vaccine becomes cost-effective should be lower (Fig. 3). For example, to gain a 50% probability that a vaccine will be cost-effective, the full-course regimen price dictated by the dynamic model must be reduced by approximately £10–20 in all scenarios if indirect effects are incorporated.

Our model predicts a percentage payback in Scenario A of 60% (46–71) and of 86% (54–116%) in Scenario B for a full-course regimen price of £60 (Fig. 4a and b). For some realizations of the model, a full-course regimen price of £60 generates a payback of greater than 100% when there is delayed vaccine immunity waning for three years (Scenario B, Fig. 4). In these outcomes, rotavirus is not just cost-effective, but also cost-saving.

4. Discussion

We used a dynamic model to parameterize a cost-effectiveness analysis of the economic impact for introduction of a rotavirus vaccine into the national immunization schedule of E&W. For this purpose, we performed a probabilistic and scenario sensitivity analysis to explore how key parameters impact the probability of cost-effectiveness. We found that rotavirus vaccination is likely to be cost-effective and possibly even cost-saving. However, cost-effectiveness is critically dependent on full-course price. The herd protection predicted in our dynamic model can significantly decrease the full-course price at which vaccination will become

Table 3
Results of cost-effectiveness analysis for the introduction of rotavirus vaccination in E&W, derived from base case value assumptions: costs and effects are given as discounted cumulative values after a period of 50 years after introduction of the vaccine unless otherwise stated. Annual costs are given undiscounted and show the annual cost at equilibrium. Incremental cost-effectiveness ratios (calculated over 50 years after introduction of the vaccine), and cost-effective prices are given both for the dynamic model that includes herd protection and for the static model that does not include herd protection. The cost-effective price is the highest course price at which RotaTeq® is cost-effective at £30,000/QALY. Scenarios refer to concomitant vaccine administration – per UK vaccination schedule and Department of Health Practice, and separate vaccine administration – hypothetical scenario not aligned with UK vaccination schedule.

Scenario	A	B	C	D
Vaccine waning scenario	Immediate	Delayed	Immediate	Delayed
Cost admin. scenario	Concomitant	Concomitant	Separate	Separate
Average cost per severe RVGE (£/case)	323	323	323	323
Incidence of severe RVGE (/1000 children per year)	43.6	43.6	43.6	43.6
No vaccination				
Costs of RVGE annually (undiscounted £million)	44.555	44.555	44.555	44.555
Costs of hospitalizations annually (undiscounted £million)	32.048	32.048	32.048	32.048
Costs of GP annually (undiscounted £million)	5.6318	5.6318	5.6318	5.6318
Costs of A&E annually (undiscounted £million)	5.3377	5.3377	5.3377	5.3377
Costs of NHS direct annually (undiscounted £million)	1.4480	1.4480	1.4480	1.4480
Costs of RVGE (£million)	1050	1050	1050	1050
Costs of vaccine (£million)	0	0	0	0
Total costs (£million)	1050	1050	1050	1050
QALYs lost – mild RVGE	9300	9300	9300	9300
QALYs lost – severe non-lethal RVGE	11,700	11,700	11,700	11,700
QALYs lost – severe lethal RVGE	3500	3500	3500	3500
Total QALYs lost	24,500	24,500	24,500	24,500
Incidence of severe RVGE (million)	279	279	279	279
Incidence of mild RVGE (million)	882	882	882	882
With vaccination				
Costs of RVGE annually (undiscounted £million)	13.02	0	13.02	0
Costs of hospitalizations annually (undiscounted £million)	9.3653	0	9.3653	0
Costs of GP annually (undiscounted £million)	1.6457	0	1.6457	0
Costs of A&E annually (undiscounted £million)	1.5598	0	1.5598	0
Costs of NHS Direct annually (undiscounted £million)	0.4232	0	0.4232	0
Costs of vaccine annually (undiscounted £45/course, £million)	40.274	40.274	54.37	54.37
Costs of vaccine annually (undiscounted £60/course, £million)	50.342	50.342	64.438	64.438
Costs of RVGE (£million)	316	21	316	21
Costs of vaccine (£45/course, £million)	949	949	1280	1280
Costs of vaccine (£60/course, £million)	1190	1190	1520	1520
Total costs (£45/course, £million)	1260	970	1600	1300
Total costs (£60/course, (£million)	1700	1220	2040	1550
QALYs lost – mild RVGE	3200	199	3200	199
QALYs lost – severe non-lethal RVGE	3500	232	3500	232
QALYs lost – severe lethal RVGE	1100	70	1100	70
Total QALYs lost	7800	501	7800	501
Incidence of severe RVGE (million)	83.4	8.24	83.4	8.24
Incidence of mild RVGE (million)	307	26.8	307	26.8
ICER – static model (£45/course, £/QALY)	20,497	−829	40,421	13,010
ICER – static model (£60/course, £/QALY)	34,728	9056	54,652	22,895
ICER – dynamic model (£45/course, £/QALY)	12,902	−3322	32,826	10,517
ICER – dynamic model (£60/course, £/QALY)	27,133	6563	47,057	20,402
Cost-effective price – static model (£)	54.99	91.77	33.99	70.77
Cost-effective price – dynamic model (£)	63.00	95.55	42.00	74.55

cost-effective. For example, accounting for herd protection reduces the threshold price of cost-effectiveness by between 4% and 13% for concomitant vaccine administration. Thus, herd protection affects model predictions and could influence the decision of if and at what price to introduce a vaccine [14].

The threshold price at which the vaccine becomes cost-effective (often termed the threshold price) is of critical importance in cost-effective analyses, especially when there is no current agreed price for mass vaccination of either of the rotavirus vaccines, which is the case in E&W [13]. Indeed, the threshold price will indicate the price at which vaccine companies can offer their products in order for them to be cost-effective. Therefore, while we present base case results for methodological transparency, we advocate a focus on the threshold analysis, rather than the consideration of an arbitrary price. A threshold analysis identifies the price at which rotavirus vaccination becomes cost-effective. This result provides fundamental information for health policy decisions. We present this threshold analysis (where the probability that the vaccine is cost-effective is calculated as a function of vaccine price) as an alternative method to the one currently used in rotavirus vaccination cost-effectiveness analyses that use a hypothetical fixed price in order to calculate whether the intervention is cost-effective [51].

We have evaluated pentavalent rotavirus vaccination cost-effectiveness in four scenarios to quantify the impact of vaccine waning and vaccine administration cost on the economic calculations. We include these four scenarios for reader interest and methodological transparency, however it may be argued that some scenarios are more realistic than others. For instance, because there already exists a current three-dose infant vaccine regimen implemented in E&W (DTaP/IPV/Hib), administered at the same time that RotaTeq® would be, the 'concomitant' administration scenarios (A and B) may be more realistic. Furthermore, there is evidence that vaccine efficacy is sustained for up to three years [30], and thus the 'delayed' waning scenario might be more realistic. With these considerations, Scenario B is likely the most realistic economic evaluation. However, our dynamic model predicts RVGE control if

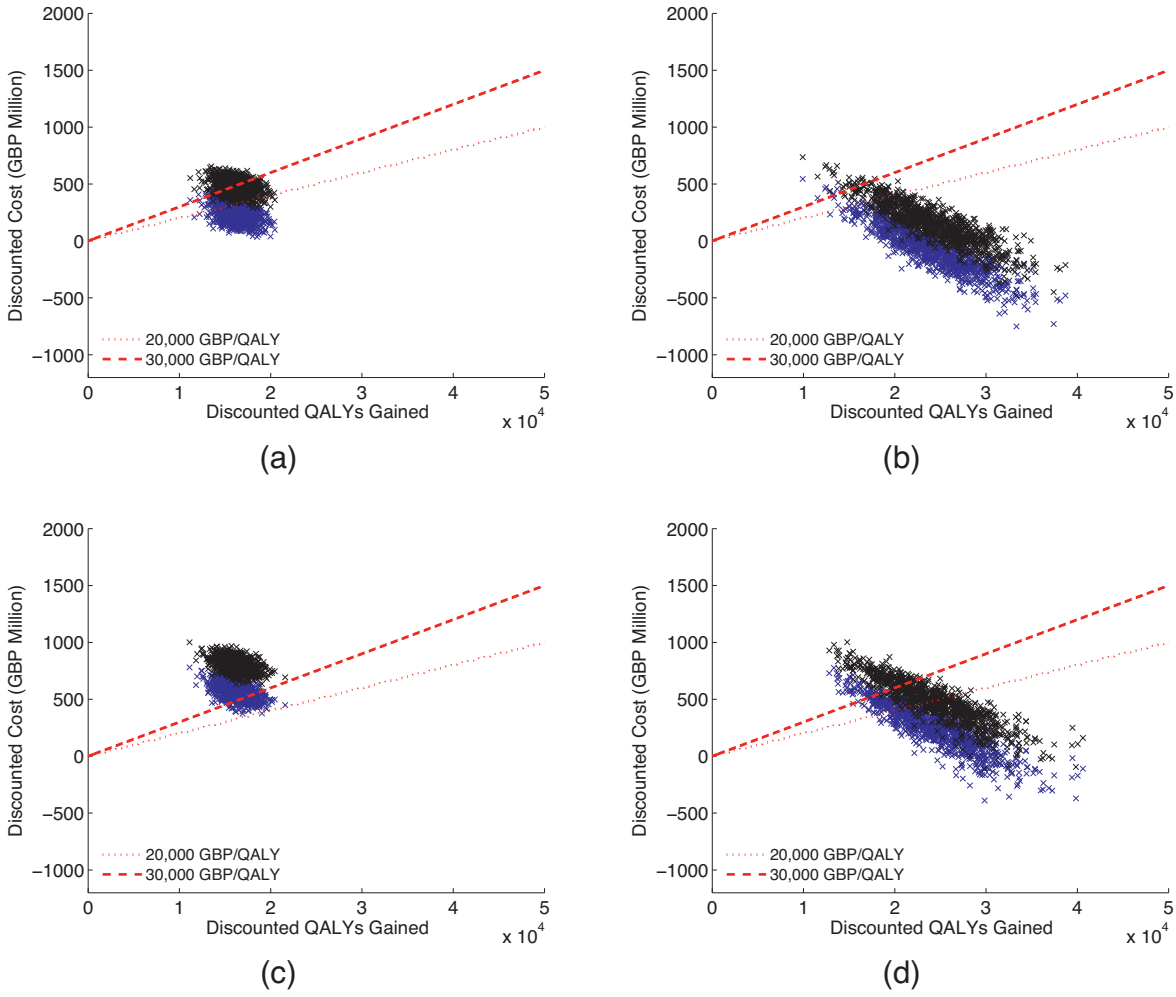

Fig. 2. Association between discounted QALYs gained and discounted costs of vaccination. The blue crosses are when the vaccine is priced £45 per full course and the black crosses when it is price £60 per full course. The different panels constitute different vaccine waning rates and administration cost scenarios: (A) when there is immediate vaccine immunity waning after vaccination and vaccine is administered concomitantly; (B) when there is delayed vaccine immunity waning after vaccination and vaccine is administered concomitantly; (C) when there is immediate vaccine immunity waning after vaccination and vaccine is administered separately; and (D) when there is delayed vaccine immunity waning after vaccination and vaccine is administered separately. Points below the dashed lines indicate cost-effective (£<30,000/QALY) and points below the dotted lines indicate very cost-effective strategies (£<20,000/QALY). Discount rate is fixed at 3.5%.

RotaTeq® efficacy is assumed to be sustained for two years or longer at 95% coverage. Therefore, Scenario B (and Scenario D) assume ongoing RVGE control for the duration of the time horizon. This prediction may be unrealistic due to epidemiological considerations such as rotavirus genotype replacement leading to lower vaccine efficacy, about which there is currently scarce information.

We have presented both a static model that does not take into account any reduction of transmission in the population by vaccination and dynamic transmission model. We have previously shown that using both these models, we can predict the reduction in RVGE incidence attributable to both the direct and indirect effects of vaccination [23]. In particular, our models predict that, after transient dynamics have subsided, indirect effects for children under five years alone account for an average 29% (vaccine waning) or 35% (no vaccine waning) reduction of any RVGE incidence at 95% vaccine coverage. This large contribution of indirect effects, consistent with recent data, is the reason for the difference in cost-effectiveness predictions between the static and dynamic models, a result that is consistent with our previous finding for the importance of herd immunity to the cost-effectiveness of influenza vaccination [52]. The size of these reductions due to indirect effects are consistent with the predictions of other dynamic model studies [16,53], and early data from countries which have already introduced rotavirus vaccination. For example, in the US, where vaccination coverage rose to 57% for eligible individuals at the start of 2008, there are been a significant reduction in rotavirus-related hospital admissions for all age groups less than 25 years. For example, the rate reduction in rotavirus-related admissions for the 5–14 year age group was between 55% and 81%, even though these individuals had never been eligible for vaccination. This trend has been reported in both El Salvador and Australia [1].

Our analysis indicates that mass vaccination is more cost-effective than previously thought [25,12,13]. A number of factors contribute to the difference in our findings. Firstly, our analysis uses a dynamic transmission model that implicitly calculates the level of herd protection afforded by mass vaccination of infants. This model predicts a lower incidence of not only vaccinated infants, but those individuals not vaccinated. This prediction leads to a larger overall reduction in RVGE incidence and therefore a more favorable prediction for the cost-effectiveness of pentavalent rotavirus vaccination. Secondly, our epidemic model used reported data of RVGE incidence, which allowed us to implicitly calculate the incidence of mild RVGE that are either underreported or unreported because medical treatment is not sought. This calibrated model indicates

Table 4
Budget impact of introducing rotavirus vaccination in E&W. The budget impact calculates the percentage payback over time after introducing a mass vaccination program. Percentage payback is a measure of how quickly cost outlay is recouped by cost savings as a result of vaccination. The cost outlays are the ongoing costs of buying and administering the vaccination. The cost reductions are due to a smaller incidence of RVGE treatment as a result of vaccination. The percentage of mean annual payback was calculated from both discounted cost outlays and cost savings using base case values for two prices of the vaccine (Table 1).

Scenario	A	B	C	D
Vaccine waning	Immediate	Delayed	Immediate	Delayed
Cost of vaccine admin.	Concomitant	Concomitant	Separate	Separate
£45/full course price				
Cumulative % payback by:				
1st year	44	52	33	38
2nd year	64	76	47	56
3rd year	70	90	52	67
4th year	73	96	54	71
5th year	74	99	55	73
10th year	76	104	56	77
20th year	77	107	57	79
50th year	77	108	57	80
£60/full course price				
Cumulative % payback by:				
1st year	35	42	27	32
2nd year	51	61	40	48
3rd year	56	72	44	56
4th year	58	77	45	60
5th year	59	79	46	62
10th year	61	84	47	65
20th year	61	86	48	67
50th year	62	87	48	68

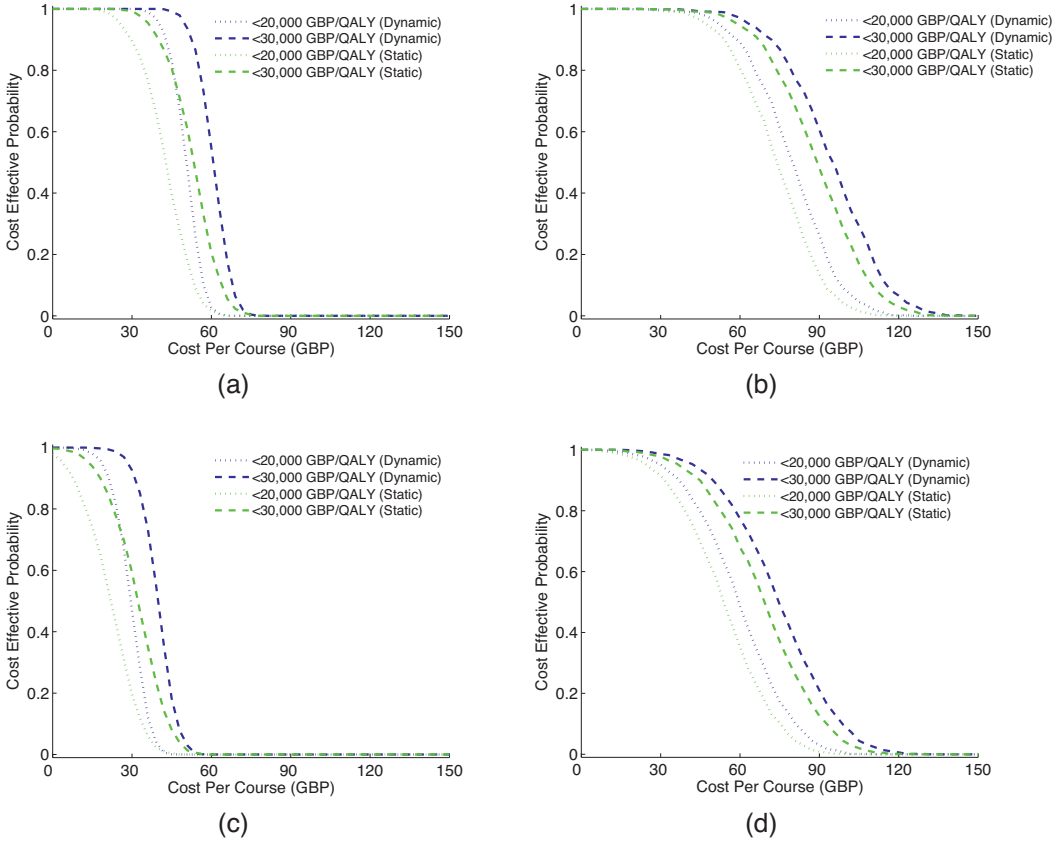

Fig. 3. Threshold curves showing the effect of vaccine cost on the probability that vaccination will be cost-effective (blue) or very cost-effective (green) in E&W. The different panels constitute different vaccine waning rates and administration cost scenarios: (A) when there is immediate vaccine immunity waning after vaccination and vaccine is administered concomitantly; (B) when there is delayed vaccine immunity waning after vaccination and vaccine is administered concomitantly; (C) when there is immediate vaccine immunity waning after vaccination and vaccine is administered separately; and (D) when there is delayed vaccine immunity waning after vaccination and vaccine is administered separately. Discount rate is fixed at 3.5%.

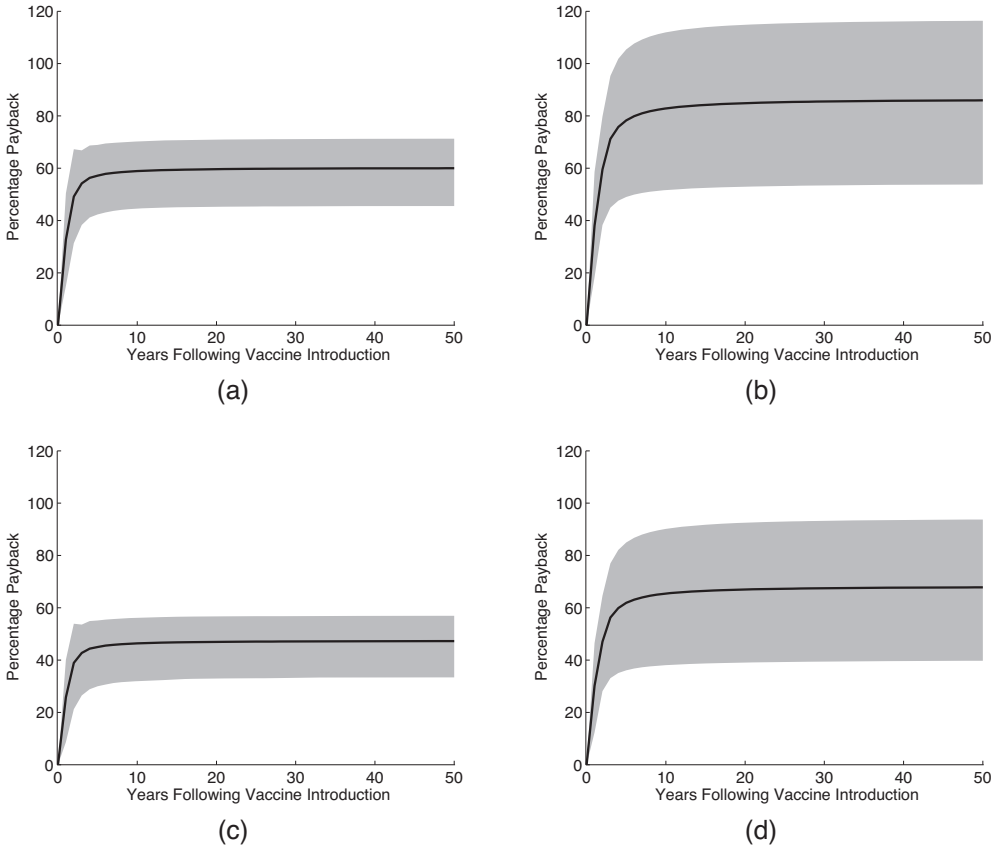

Fig. 4. Budget impact analysis showing the cumulative mean annual percentage payback predicted for introduction of a rotavirus vaccine in E&W over the complete time horizon of the analysis. The different panels constitute different vaccine waning rates and administration cost scenarios: (A) when there is immediate vaccine immunity waning after vaccination and vaccine is administered concomitantly; (B) when there is delayed vaccine immunity waning after vaccination and vaccine is administered concomitantly; (C) when there is immediate vaccine immunity waning after vaccination and vaccine is administered separately; and (D) when there is delayed vaccine immunity waning after vaccination and vaccine is administered separately. The black line is the median. The gray area represents the 95% predictive range. The price for a full-course regimen is taken to be £60. Discount rate is fixed at 3.5%.

that these mild infections account for a significant fraction of the disease burden (38% of the total QALY loss was attributable to mild RVGE). Consequently, these cases of mild RVGE contribute as much to the overall QALY loss as non-lethal cases of severe RVGE. Another effect of calibrating our dynamic model is that our incidence predictions are higher than in previous static models [25,13]. Data from the US show the cause-unspecific hospital discharges were significantly reduced by 29–48% for children under five years after rotavirus vaccination had been introduced. These data suggest significant underreporting of rotavirus-related disease. Thirdly, the base case assumption uses the full-course threshold cost-effective price published in previous CEAs using static models (£45 instead of £75 or equivalent in Euros) [41,12,25]. Lastly, the costs associated with healthcare outcomes of hospitalization, A&E visits, GP visits, and NHS Direct calls are more expensive in our model than those used in other published cost-effectiveness analyses because we have used more recent or inflated cost data [13,12,25]. In particular, we have used two different vaccine administration scenarios: concomitant (less expensive) and separate (more expensive). For comparison, previously studies have given the cost-effective threshold price of RotaTeq® as €68 per course, assuming no vaccine waning, concomitant administration and a €30,000 cost-effectiveness willingness to pay threshold [13]. With similar assumptions, our Scenario B is the most comparable. For Scenario B, our static model predicts a 76% probability of cost-effectiveness at £68 per course with a £30,000 cost-effectiveness willingness to pay threshold. In our base case scenario, we predict a cost-effective price of £91.77 using our static model. This difference in the static model predictions between our study and the most recent cost-effectiveness analysis for E&W can be accounted for by three reasons: firstly, the incidence predictions from the pre-vaccination model are higher than [13]; second, our analysis takes into account loss of QALYs from mild cases; and lastly, we have conducted our analysis using £ rather than €, which may alter the results.

Our budget impact analysis allows policy-makers to assess how quickly any cost outlay of vaccination can be recouped by cost savings from vaccination. These cost savings would be due to a reduced disease burden as a result of vaccination. For Scenarios A and B, our model predicts that on average at least 70% of the costs of purchasing and administering the vaccine would be recouped within three years of a vaccination program for full-course regimen price of £45 (or at least 56% with a full-course regimen price of £60). This analysis is vital for assessing the economic feasibility of introducing rotavirus vaccination. Indeed, because it is critical for the transfer of cost-effectiveness results to health policy, we would advocate this analysis be included in future cost-effectiveness studies.

This is the first analysis to include a dynamic model to assess the cost-effectiveness of introducing a rotavirus vaccination into E&W. Our findings support the use of dynamic models to inform the cost-effectiveness of introducing vaccination into E&W in general. This work can inform policymakers of the vaccine price at which mass vaccination becomes cost-effectiveness for the control of rotavirus infection – something critical when accounting for UK-wide tender

prices – and predict how quickly the cost outlay for implementing a vaccine policy is mitigated by reducing the healthcare costs associated with RVGE treatment.

5. Conclusions

We conducted a cost-effectiveness analysis for mass rotavirus vaccination in England and Wales. A mass rotavirus vaccination strategy was found to be cost-effective for England and Wales for a wide range of vaccine course prices. In some scenarios mass rotavirus vaccination was even found to be cost-saving. We found threshold vaccine course prices for which rotavirus vaccines would provide a cost-effective strategy. We compared our predictions with those from a static model in which herd protection is neglected. Threshold prices were found to be higher using the dynamic model than the static model. This work can inform the current decision whether to introduce mass rotavirus vaccination into England and Wales and the epidemiological and economic value of vaccinating against rotavirus disease.

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Appendix A.

The costs associated with RVGE infection depend on the rate at which individuals become infected and on disease fatality. The expected discounted disutility of infections from a healthcare perspective can be calculated as

$$U_{\mathrm{INF}} = \int_0^T \left(\sum_{j=1}^{m} I_j(t) \sum_{k=1}^{5} \mathbb{P}(k) C(k) \right) e^{-rt}\, \mathrm{d}t,$$

where each k corresponds to a different clinical outcome: hospitalization due to community or nosocomial infection, A&E consultation, NHS Direct call, GP consultation, and death. The reported severe cases of RVGE at time t in age class j is given by $I_j(t)$. $C(k)$ is the cost associated with each clinical outcome, and $\mathbb{P}(k)$ refers to the probability of each outcome. Finally, the cost associated with a vaccination program was calculated as

$$U_{\mathrm{VAC}} = \int_0^T \left(\phi(t) \sum_{j=vt_1}^{vt_3} C_{\mathrm{VAC}} P_j(t) \right) e^{-rt}\, \mathrm{d}t,$$

where C_{VAC} is the cost associated with each vaccine dose per capita, $\phi(t)$ is the vaccine coverage at time t and $P_j(t)$ is the number of individuals in the jth age group who receive a vaccine dose. This expectation is a summation over all potential futures from time 0 to T.

The total discounted QALY loss, Ψ_{INF}, can be written as

$$\Psi_{\mathrm{INF}} = \int_0^T e^{-rt} \left\{ \left[\frac{Q_{\mathrm{No\,Disease}}}{r} p_{\mathrm{Death}} \sum_{j=0}^{m} (1 - e^{rL(i,\mathrm{No\,Disease})}) I_j(t) \right] + [\Delta Q_{\mathrm{Severe\,Disease}} I(t) + \Delta Q_{\mathrm{Mild\,Disease}} H(t)] \right\} \mathrm{d}t,$$

where $Q_{\mathrm{No\,Disease}}$ is the quality of life in the absence of RVGE (assumed to be one), p_{Death} is the probability of death given severe RVGE, $L(i, \mathrm{No\,Disease})$ is the residual expected lifespan of an individual age i in the absence of RVGE, $\Delta Q_{\mathrm{Severe\,Disease}}$ and $\Delta Q_{\mathrm{Mild\,Disease}}$ is the quality of life lost per week per episode of severe or mild RVGE, and $I(t)$ and $H(t)$ are the total incidences of severe and mild RVGE, respectively, at time t. To calculate the health effects, the quality adjusted life expectancy (QALE) was first calculated in the case of a lethal rotavirus infection as

$$\text{Discounted QALE, at age } a \text{ with disease status, } D = Q_D \frac{1 - e^{rL(a,D)}}{r},$$

where Q_D is the quality of life associated with a disease state, D and L is the residual life expectancy for an individual. Therefore, the discounted QALY loss, at age a with disease status, D, Ψ, can be calculated as

$$\begin{aligned} \Psi(a, \mathrm{Lethal}) &= \Delta Q_D \frac{1 - e^{rL(a,D)}}{r} \\ &= Q_{\mathrm{No\,Disease}} \frac{1 - e^{rL(a,\mathrm{No\,Disease})}}{r} - Q_{\mathrm{Death}} \frac{1 - e^{rL(a,\mathrm{Death})}}{r} \\ &= Q_{\mathrm{No\,Disease}} \frac{1 - e^{rL(a,\mathrm{No\,Disease})}}{r}, \end{aligned}$$

For the associated non-lethal infections, the QALY loss for severe and mild RVGE is $\Delta Q_{\mathrm{Severe\,Disease}}$ and $\Delta Q_{\mathrm{Mild\,Disease}}$, respectively.

Consequently, the total discounted QALYs gained as a result of vaccination intervention can be written as $\Delta\Psi_{\mathrm{INF}}$. The incremental cost-effectiveness ratio (ICER), can be calculated thus

$$\mathrm{ICER} = \frac{U_{\mathrm{VAC}} + \Delta U_{\mathrm{INF}}}{\Delta \Psi_{\mathrm{INF}}}$$

where ΔU_{INF} is the cost saved because of outcomes averted by vaccination, i.e. the difference between U_{INF} in the presence and absence of a vaccination program. Ψ_{INF} is the QALYs gained due to a reduced incidence resulting from vaccination, i.e. the difference between Ψ_{INF} in the presence and absence of a vaccination program.

All calculations are performed in Matlab R2011a.

Appendix B. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2012.09.025.

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