Vaccine 30 (2012) 6766–6776

Contents lists available at SciVerse ScienceDirect

Vaccine

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

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

Katherine E. Atkins[a,*], Eunha Shim[b], Stuart Carroll[c], Sibilia Quilici[d], Alison P. Galvani[a]

[a] Yale School of Public Health, 135 College Street, New Haven, CT 06510, USA
[b] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, Pittsburgh, PA 15261, USA
[c] Sanofi Pasteur MSD, Mallards Reach, Bridge Avenue, Maidenhead SL6 1QP, UK
[d] Sanofi Pasteur MSD, 8 Rue Jonas Salk, 69 367 Lyon Cedex 07, France

ARTICLE INFO

Article history:
Received 1 February 2012
Received in revised form 4 September 2012
Accepted 10 September 2012
Available online 21 September 2012

Keywords:
Rotavirus gastroenteritis
Dynamic epidemiological model
Threshold analysis
Budget impact

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

* Corresponding author. Tel.: +1 2039038789.
E-mail addresses: katherine.atkins@yale.edu (K.E. Atkins), eshim@pitt.edu (E. Shim), scarroll@spmsd.com (S. Carroll), sibilia.quilici@gmail.com (S. Quilici), alison.galvani@yale.edu (A.P. Galvani).

0264-410X/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2012.09.025

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