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# Cost-Effectiveness of Rotavirus Vaccination in France—Accounting for Indirect Protection

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ABSTRACT

**Background:** Vaccination against rotavirus has shown great potential for reducing the primary cause of severe childhood gastroenteritis. Previous economic evaluations of rotavirus vaccination in France have not modeled the potential impact of vaccines on disease burden via reduced transmission. **Objective:** To determine the cost-effectiveness of the introduction of pentavalent rotavirus vaccination into the French infant vaccination schedule. **Methods:** We developed an age-structured model of rotavirus transmission calibrated to 6 years of French gastroenteritis incidence and vaccine clinical trial data. We evaluated the cost-effectiveness of pentavalent rotavirus vaccination considering that 75% of infants would receive the three-dose vaccine course. **Results:** Our model predicts that rotavirus vaccination will decrease rotavirus gastroenteritis incidence and associated clinical outcomes in vaccinated and unvaccinated individuals, delay the seasonal peak of infection, and increase the age of infection. From the societal perspective, our base-case scenario predicts that vaccination coverage would be cost-effective at €115 or €135 per vaccine course at €28,500 and €39,500/quality-adjusted life-year (QALY) gained, respectively, and suggests that almost 95% of the financial benefits will be recouped within the first 5 years following vaccination implementation. From the third-party payer perspective, incremental cost-effectiveness ratios ranged from €12,500 to €20,000/QALY, respectively. Our uncertainty analysis suggests that findings were sensitive to various assumptions including the number of hospitalizations, outpatient visits, and the extent of QALY losses per rotavirus episode. **Conclusions:** Introducing pentavalent rotavirus vaccination into the French infant vaccination schedule would significantly reduce the burden of rotavirus disease in children, and could be cost-effective under plausible conditions.

*Keywords:* cost-effectiveness of rotavirus, herd immunity, rotavirus model, rotavirus vaccination.

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## Introduction

Rotavirus infection, the primary cause of gastroenteritis in children worldwide, carries a significant disease burden [1]. In the absence of oral rehydration therapy, rotavirus gastroenteritis (RVGE) can cause rapid dehydration, which may lead to death [2]. In developed countries, rotavirus infection is associated with low mortality, but is responsible for high morbidity. France faces a significant societal and economic burden due to rotavirus infection, with 19,200 hospitalizations and 131,200 ambulatory visits annually due to RVGE among children younger than 5 years [3].

Rotavirus vaccines have been introduced into infant vaccination schedules in several developed countries since their licensing in 2006, including the United Kingdom and Germany. In France, the Haut Conseil de Santé Publique recently published its recommendation for the implementation of national rotavirus vaccination for infants younger than 6 months [4]. Data from Australia [5], the United States [6–8], Belgium [9], and Israel [10] suggest that vaccination is highly effective in decreasing RVGE. Moreover, in countries where universal vaccination has been introduced, a 20% reduction in RVGE cases has been observed among unvaccinated children [11]. These reports indicate that there is a substantial RVGE case reduction due to both direct and indirect effects of vaccination. However, none of the previous studies assessing the cost-effectiveness of rotavirus vaccination in France [3,12–15] has modeled the effect of herd protection.

We developed a dynamic model of rotavirus transmission in France to evaluate the population-level impact of introducing universal pentavalent vaccination into the infant vaccination schedule in France. Using the predictions from the dynamic model, we evaluated the cost-effectiveness of pentavalent rotavirus vaccination from the third-party payer (TPP) and societal perspectives. This study could help to inform policy decisions in predicting the outcomes of a universal pentavalent rotavirus vaccination program in France.

## Methods

### Dynamic Model

We developed an epidemiological population-based model of rotavirus transmission in France (detailed in the supporting

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information). The dynamic model structure (Fig. 1) takes into account that the risk of infection depends on both the number of previous infections [16] and the age at exposure [17]. The model includes 19 age groups: 0 to 2, 2 to 4, 4 to 6, 6 to 12, … , 22 to 24 months and 2 to 3, 3 to 4, 4 to 5, 5 to 25, 25 to 45, 45 to 65, older than 65 years, and distinguishes between primary, secondary, and subsequent infections. Infection may be either asymptomatic or symptomatic with either mild or moderate-to-severe RVGE [16]. Following infection, we assume there is temporary complete immunity [18] that lasts for an average of 18 and 24 months following first and second infections, respectively [19,20]. The infectiousness of an infected individual is based on the viral shedding of the infected individual [21]. The extent of viral shedding depends on both the immunity of the infected individual that has been built up from previous exposures and on the severity of the disease. In our sensitivity analysis, we considered three additional waning scenarios (from 6 months to 3 years) (Table 1). Contact rates between age groups were parameterized using age-stratified European physical contact data [22]. We assumed that a vaccine dose is either effective or not effective, and that each effective vaccine dose confers the same protection as a single natural infection. We estimated the per-dose vaccine efficacy by calibrating the dynamic model to the pentavalent vaccine efficacy data from the 2-year clinical trial [23], assuming a given duration of temporary immunity following each dose. These trials showed that vaccinated individuals have their risk of any RVGE reduced by 68% and their risk of moderate-to-severe RVGE reduced by 86.7%.

To estimate empirically unknown epidemiological parameters (Table 1), we calibrated our model to weekly national acute gastroenteritis incidence from 2008 to 2013 in France. These data were collected from the French Sentinels network, detailing the incidence of acute diarrhea stratified by yearly age groups [24]. We converted these incidences to RVGE by considering the proportion of those with acute gastroenteritis who test positive for rotavirus each month [24–30] to capture the seasonal pattern of rotavirus in France. For individuals younger than 5 years, we scaled the age-specific incidences of RVGE with the following age groups: 0 to 6 months, 6 to 12 months, 1 to 2 years, 2 to 3 years, and 3 to 5 years to ensure that the age distribution among RVGE infected will match that in previous RVGE studies in France [26,27,29]. Given that not all cases are reported, we scaled the incidence by a fixed factor such that the overall mean annual number of RVGE in children younger than 5 years will be 296,500, as suggested by the High Council for Public Health in France [3].

To estimate the RVGE infection for individuals older than 5 years, we used prospective data from the Netherlands that estimate that the age-specific proportion of gastroenteritis cases attributable to rotavirus for individuals aged 5 years and older lies between 1.5% and 3.3% [31,32]. Given that the reported rates of RVGE in France are similar to the ones observed in the Netherlands (see, e.g., [29]), we assumed the same proportion of RVGE for those with gastroenteritis episode as the ones observed in those prospective studies [31,32]. This assumption leads to around 27.5% of all RVGE cases in France in individuals 5 years and older. Overall, our approach ensures that for our model calibration, the data used will capture the actual seasonal patterns, RVGE age distribution, and the total number of cases (both reported and unreported) in France.

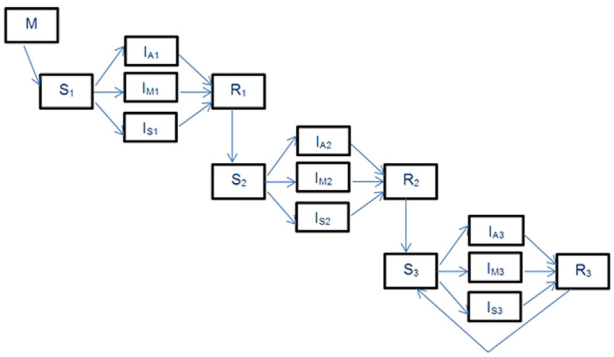


**Fig. 1 – State diagram of epidemiologic model, with arrows corresponding to possible transition between states as a result of infection, recovery, or immunity waning. Individuals are born with temporary maternal immunity (state *M*). This immunity wanes and individuals move to the susceptible state ($S_1$). Infections can be asymptomatic ($I_{A1}$), mild RVGE ($I_{M1}$), or severe RVGE ($I_{S1}$). Individuals recover from infection to become temporarily immune ($R_1$). This immunity wanes to allow repeat infections with either a secondary infection or a subsequent infection. Each effective vaccine dose confers protection equivalent to natural infection. RVGE, rotavirus gastroenteritis.**

### *Clinical Outcomes*

The epidemiological results generated by the dynamic model were integrated into an economic evaluation to estimate the cost-effectiveness of pentavalent rotavirus vaccination introduction into the French infant vaccination schedule. For the economic evaluation, we considered four clinical outcomes: 1) general practitioner (GP) visit, 2) hospitalization (due to a community or a nosocomial infection), 3) emergency department (ED) visit, and 4) death. A proportion of severe RVGE cases were assumed to be hospitalized, attend the ED, or die. A proportion of any (severe or mild) RVGE cases were assumed to require a GP visit. Specifically, in the absence of vaccination, we assumed that among individuals with severe RVGE infection, 19,200 will be hospitalized, 5,460 will attend the ED, and 13 will die annually [26,33]. Among individuals with any RVGE, 131,200 will visit the GP (Table 3) [26,33]. Clinical trials suggest that a full three-dose course of pentavalent vaccination prevents 95.6% of hospitalizations, 93.8% of ED visits, and 87.2% of GP visits in vaccinated individuals [34]. We combined both these clinical trial data with model predictions to estimate the proportion of clinical outcomes averted because of both direct and indirect effects (see Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.05.011).

In our univariate sensitivity analysis, we included the risk of intussusception consistent with a recent US study that found that within a birth cohort of 4.3 million infants vaccine-associated intussusception could cause an excess 0.2 (range 0.1–0.3) deaths, 45 (range 21–86) hospitalizations, and 13 (range 6–25) cases managed in short-stay or ED settings [35].

### *Quality of Life*

In the base-case analysis, we considered a loss of 0.003274 and 0.001715 quality-adjusted life- years (QALYs) per severe and mild RVGE episode for a child, respectively. This is based on the observation that each RVGE episode lasts for 5.4 and 6.5 days, with a daily utility of 0.816 and 0.884 for a mild case and a severe case, respectively [36,37], consistent with previous French economic analyses [13,36,37]. In the sensitivity analysis, we varied the QALY loss by ±20%. On the basis of previous studies that showed substantial parental QALY losses due to an RVGE infection of their child [38,39], and in line with previous cost-effective studies on rotavirus in France and elsewhere [14,40–42], we also considered the same QALY loss for one caregiver in our base-case scenario.

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