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Modelling the epidemiological impact of rotavirus vaccination in Germany – A Bayesian approach

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ABSTRACT

Background: Rotavirus (RV) infection is the primary cause of severe gastroenteritis in children aged <5 years in Germany and worldwide. In 2013 the German Standing Committee on Vaccination (STIKO) developed a national recommendation for routine RV-immunization of infants. To support informed decision-making we predicted the epidemiological impact of routine RV-vaccination in Germany using statistical modelling.

Methods: We developed a population-based model for the dynamic transmission of RV-infection in a vaccination setting. Using data from the communicable disease reporting system and survey records on the vaccination coverage from the eastern federal states, where the vaccine was widely used before recommended at national level, we first estimated RV vaccine effectiveness (VE) within a Bayesian framework utilizing adaptive Markov Chain Monte Carlo inference. The calibrated model was then used to compute the predictive distribution of RV-incidence after achieving high vaccination coverage with the introduction of routine vaccination.

Results: Our model estimated that RV-vaccination provides high protection against symptomatic RV-infection (VE = 96%; 95% credibility interval (CI): 91–99%) that remains at its maximum level for three years (95% CI: 1.43–5.80 years) and is fully waned after twelve years. At population level, routine vaccination at 90% coverage is predicted to reduce symptomatic RV-incidence among children aged <5 years by 84% (95% prediction interval (PI): 71–90%) including a 2.5% decrease due to herd protection. Ten years after vaccine introduction an increase in RV incidences of 12% (95% PI: −16 to 85%) among persons aged 5–59 years and 14% (95% PI: −6 to 109%) within the age-group >60 years was predicted.

Conclusion: Routine infant RV-vaccination is predicted to considerably reduce RV-incidence in Germany among children <5 years. Our work generated estimates of RV VE in the field and predicted the population-level impact, while adequately addressing the role of model and prediction uncertainty when making statements about the future.

1. Introduction

Rotavirus (RV) infection is a major cause of acute gastroenteritis among young children aged <5 years. It is estimated that RV leads worldwide to annually more than 110 million episodes of diarrhoea causing 25 million clinic visits, 2 million hospitalizations, and 453,000 deaths [1]. Although the number of RV-associated deaths is very low in Germany, RV-infection frequently leads to vomiting, diarrhoea, and severe dehydration requiring hospital admission. The resulting clinical and financial burden for the German health care system is substantial [2–4].

Two live RV vaccines, RotaTeq® (Merck & Co) and Rotarix® (GlaxoSmithKline), were licensed for use in Europe in 2006. Both vaccines are orally administered as a two or three-dose series within the period from 6 to 32 weeks of age. In clinical trials both vaccines demonstrated a good safety profile and high efficacy to protect against severe RV-infection [5–8]. In July 2013, the German Standing Committee on Vaccination (STIKO) decided to adopt RV-vaccination into the national vaccination schedule for children [9]. In Europe, routine RV-vaccination has been introduced in Austria, Belgium, the United Kingdom, Finland, and Luxembourg as of today [10].

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Before adoption into the national vaccination schedule, RV-vaccination was already recommended in some German federal states but not reimbursed by all insurance companies [11]. Still, especially in the five eastern federal states (EFS) both RV-vaccines have been widely used since 2008 with approximately equal share [11]. As a consequence, a significant RV-incidence decrease in vaccinated age-groups was already observed in the communicable disease reporting system when comparing seasons before and after RV-vaccine introduction [11]. In Germany, laboratory-confirmed rotavirus-infections are notifiable since 2001. By applying a Bayesian framework these notification data enable the estimation of the direct RV-vaccine effectiveness (VE) via a transmission model. Such a model-induced VE estimate can yield additional information for later incidence predictions, since efficacy estimates from clinical trials do not necessarily apply under field conditions.

To support informed policy-making with respect to vaccine introductions, dynamic epidemic models for RV-transmission and vaccination impact were developed for the United States [12], England and Wales [13,14], Mexico [15], and Kyrgyzstan [16], while in Germany the cost-effectiveness of RV-vaccination was assessed only based on a static cohort-model [2]. The aim of our work was therefore to provide further health policy support by (i) modelling the dynamic transmission of RV-infections and estimating RV VE based on notification data, and (ii) predicting the epidemiological impact of routine RV-vaccination in Germany, with a special focus on addressing uncertainty arising from the stochastic modelling and parameter estimation.

2. Methods

We developed a mathematical model governing the population-based RV-immunity in the German eastern federal states (EFS) over time. This model is an extension of a previously constructed dynamic transmission model, which is based on ordinary differential equations and stochastic case reporting and captures the German RV-epidemiology [17]. In this present work the model is now extended with mechanisms of vaccination. An overview of the main structure is displayed in Fig. 1. Key model characteristics include maternal antibody-mediated protection after birth, three distinct levels of immunity due to previous infections, differentiation between symptomatic and asymptomatic infection as well as potential waning immunity due to the absence of wild virus contacts.

Within our model vaccination is administered as a two-dose series at two and four months of age. After vaccine administration, individuals move to a secondary model arm consisting of four vaccine groups representing different levels of vaccine protection against RV-infection and developing symptoms. As immunity after incomplete vaccination was found to be already high for both vaccines [18], individuals move to the second highest vaccine group after the first dose administration and to the highest level after complete vaccination. Vaccine-induced immunity wanes over time such that individuals return to lower vaccine groups. After recovering from breakthrough infection, vaccinated individuals return to the highest immunity level within the primary model arm. Further details on the model and statistical methods, which were implemented using the statistical software environment *R*, can be found in the supplementary appendix.

2.1. Data on incidence, demographics, and vaccination coverage

For model calibration and VE estimation we used national case-based surveillance data of laboratory-confirmed RV-infections reported from January 2001 until July 2013 [19]. Case-reports contained information on age, region, symptoms onset, hospitalization, and fatal outcome. We stratified the data by five age-groups for children aged <5 years and five age-groups for individuals ≥5 years (i.e. 5–19, 20–39, 40–59, 60–79 and >80 years).

Vaccination coverage data was obtained from a retrospective survey performed in 2010 [11]. In our previous work, case-reports were stratified by the two regions of EFS and western federal states (WFS) to account for a potentially higher case reporting rate in the EFS while assuming that the true underlying incidences were equal until 2008 [17,20]. Due to the regional differences in RV-vaccination coverage thereafter (in 2009/10: WFS 22–28%; EFS 56–59%) we now focussed exclusively on the EFS case data since equal incidences in both regions can no longer be assumed [11]. The model population was defined by acquiring monthly birth rates and age-specific death rates from 1990 until 2013 for the EFS [21]. Year and age-specific migration rates where recalculated from the yearly population count changes.

2.2. Parameter estimation

Model parameters were estimated within a Bayesian framework using the weekly RV reporting data. Prior distributions for epidemiological model quantities governing transmission characteristics, e.g. duration of natural infection, seasonality, and contact behaviour, were based on published clinical data and expert opinion (supplement section 2.2.1).

Prior distributions for parameters defining VE were based on a meta-analysis examining the protection of both vaccines against severe rotavirus gastroenteritis (RVGE) and RVGE of any severity [9,22]. Within our model we defined a symptomatic infection to cause RVGE of any severity. According to the meta-analysis, the combined efficacy against acquiring infection (η_I) and developing symptoms in case of infection (η_S) was estimated at 74% (95% confidence interval (CoI): 61–83%). Our prior estimate for the waning rate (η_W) was a loss of one vaccine immunity level per year. Prior distributions for the annual vaccination coverage rates from 2006 until 2013 were constructed according to the survey data [11] (see Fig. 2).

Posterior distribution containing the final parameter estimates were computed by assuming the reported case numbers to be negative binomially distributed with the time-depending and age-stratified expectation given by the transmission model. A sample from the posterior was generated using an adaptive Markov Chain Monte Carlo scheme (supplement section 2.2.2).

For model validation we simulated a prediction of RV incidences in the WFS from 2001 until 2013 using corresponding data on demographics and vaccination coverage and finally compared the model prediction against the true WFS notification data (supplement section 2.4).

2.3. Impact analysis

Based on the calibrated model we calculated the age-stratified predictive distribution for future RV-incidence in the EFS. Different vaccination coverage levels in the range from 0% up to 100% were investigated. In the base case we assumed 90% coverage to be reached within two years after initiation of routine vaccination in 2013.

To assess uncertainty in the prediction originating from the estimation of input parameters we conducted multiple model runs using different samples from the parameters posterior distribution within each run. This includes both uncertainty regarding single transmission aspects but also VE. Considering demographic developments we assumed that births, migration and death rates remain at their current level (supplement section 3.1).

To evaluate the effect of herd protection, the expected population direct effect of vaccination was calculated from the decreased