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Modelling norovirus transmission and vaccination

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ABSTRACT

Background: Norovirus is thought to be responsible for a fifth of all acute gastroenteritis cases globally each year. The population level transmission dynamics of this very common virus are still poorly understood, in part because illness is under-reported. With vaccines undergoing clinical trials, there is a growing need for appropriate, empirically grounded models, to predict the likely impact of vaccination.
Methods: We developed a dynamic age-specific mathematical model of norovirus transmission and vaccination, informed by available data, particularly age-stratified time series case notification data. We introduce the use of a self-reporting Markov model to account for variation by age and over time in the statutory reporting of norovirus in Germany. We estimated the model using a sequential Monte Carlo particle filter. We then extended and applied our estimated model to investigate the potential impact of a range of immunisation strategies. We performed sensitivity analyses on the mode of vaccine action and other vaccine-related parameters.
Results: We find that routine immunisation could reduce the incidence of norovirus by up to 70.5% even when those vaccines do not provide complete protection from disease. Furthermore, we find that the relative efficiency of alternative strategies targeting different age groups are dependant on the outcome we consider and are sensitive to assumptions on the mode of vaccine action. Strategies that target infants and toddler are more efficient in preventing infection but targeting older adults is preferable for preventing severe outcomes.
Conclusions: Our model provides a robust estimate of a dynamic transmission model for norovirus at the population level. Vaccination may be an effective strategy in preventing disease but further work is required to ascertain norovirus vaccine efficacy, its mode of action and to estimate the cost-effectiveness of immunisation against norovirus.
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1. Introduction

Norovirus is the most common viral cause of gastroenteritis in humans, with one in five cases of acute gastroenteritis attributable to norovirus [1,2]. The virus has been estimated to cause approximately 700 million illnesses and 219,000 deaths globally each year, at a cost of around $60 billion, mostly attributable to losses in productivity [3]. However, estimates of the true burden of norovirus are uncertain because many individuals will not seek health care for what is usually a self-limiting illness. In the UK, only one in 218 cases of norovirus is thought to be notified [4].

Several vaccines that offer the potential to reduce the burden of illness due to norovirus are in development, with the most advanced product from Takeda Pharmaceuticals in the proof of concept stage [5]. To date only one modelling study, informed by US data, has explored the potential impact of such vaccines [6]. A wider range of modelling approaches and estimation techniques have been applied to norovirus at the outbreak level [7]. However, by their nature outbreak settings are highly diverse and context specific. As a consequence there is disparity between model structures and key parameter estimates at the outbreak level. In contrast, at the population level most studies have utilised the Infectious Intestinal Disease survey data from the UK [7]. The discrepancies between models are well illustrated by the variation in the basic reproduction number, R_0 between modelling studies. While population level models have tended to use similar data and approaches, with R_0 in the region of 1.6 [8], outbreak reproduction numbers have been found to be as high as 14 [9]. These differences may be real, if the outbreak represents an exceptional situation or subset of the population. However, the low mean age at first infection implied by serological data suggests that the population level R_0 may be greater than 10 [10–13]. Under-estimating R_0 has important

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implications for control strategies; with a higher R_0 resulting in a higher critical vaccination threshold for elimination.

In this paper, we leverage population level data sources, particularly case notification data from Germany to estimate a novel population level model of norovirus transmission. We use our robustly estimated model to investigate a spectrum of vaccine strategies and effects given the uncertainty in both the application of a vaccine in the population and the mode of action of a successful vaccine candidate.

2. Materials and methods

2.1. Demographic model

For convenience we assume the population size remains constant, ignoring migration and population growth. We assume that life-expectancy follows a Gompertz model, with death rates for each age group estimated from the United Nations population data for 2015 [14].

2.2. Epidemiological model

We adapt a deterministic Susceptible, Exposed, Infectious, Recovered (SEIR) model to include individuals protected by maternal antibodies, an approximately gamma-distributed latent period and asymptomatic individuals, as shown in Fig. 1.

The model tracks annual cohorts up to the age of 70 years, with a continuous ageing model. Model output and transmission rates are aggregated into seven age groups motivated by visual inspection of the case notification data and for younger ages key groups with the German school system; 0–8, 8–18, 18–26, 26–37, 37–50, 50–70 and 70+. Individuals protected by maternal antibodies are accounted for by a Maternal (M) antibody class which individuals leave at rate α, fixed at a value of 2.5×10^{-3}, as estimated in [10].

Individuals are infected at a rate (λ_i), with the relative transmission rates between age-groups determined by a POLYMOD mixing matrix. The POLYMOD survey, conducted in eight European countries, provides social contact information stratified by age, gender, contact type and duration [15]. We use the POLYMOD data from Germany and methods employed by Eames et al., Baguelin et al. and Meyer et al. to arrive at a contact mixing matrix which is symmetrised and weighted for weekdays and weekends [16–18]. See the supplementary information for further details.

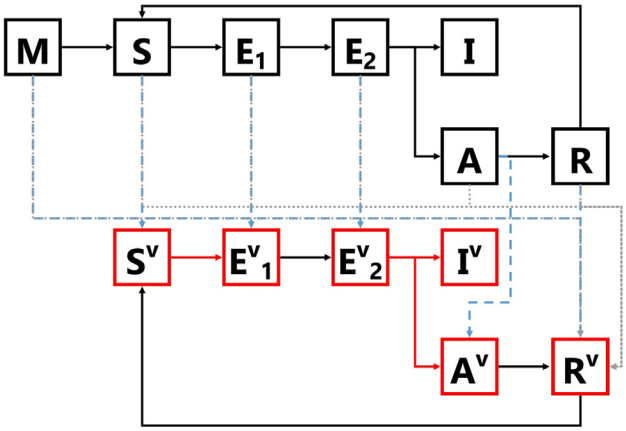

Fig. 1. Diagram of model transitions and classes for each age group. Classes are as follows: M, individuals protected by maternal antibodies; S, susceptible individuals; E_i, individuals in the approximately gamma distributed latent period; I, infected and symptomatic individuals; A, infected and asymptomatic individuals; and R, recovered individuals. A superscript V denotes vaccinated and red outlines denote a difference in state or rate to unvaccinated individuals. There are two routes to vaccination; either individuals clear any existing infection as shown in grey dots, or they remain in their current infection state, shown in blue dashes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

We assume that asymptomatic individuals contribute to the force of infection at a reduced level, ν, derived through the inference process. As such, the force of infection for age group i is as follows:

$$\lambda_i = qZ\sum_j c_{ij}(I_j + \nu A_j + \zeta(I_j^V + \nu A_j^V))$$

where q is a transmission rate, c_{ij} is the contact matrix and Z is a seasonal component depending on a seasonal amplitude, ω_1, and a seasonal offset term, $\omega_2 : Z = 1 + \omega_1 \cos\left(\frac{2\pi t}{364} + \omega_2\right)$. We fix the seasonal offset term, ω_2, for each age class according to where the mean seasonal peak occurs. The offset values can be found in the supplementary material and illustrate the staggered nature of the seasonality of norovirus where incidence in children peaks first, followed by the older age groups. We also include the vaccinated classes, denoted with superscript V, which contribute to the force of infection at reduced rate scaled by ζ. Once an individual is infected, they enter a gamma distributed latent period approximated by the inclusion of two 'E' classes. The rate individuals exit the latent classes is fixed at 1 leading to an average latent period of 2/1 days, consistent with [19]. Once individuals exit the latent class, only a proportion σ will be symptomatic. We also fix the value of σ to be 0.75, as estimated from challenge studies mentioned in [20], see supplementary material. Infected individuals lose their symptoms at rate ψ, fixed at 0.5 thus giving an expected duration of symptoms of two days. Asymptomatic individuals continue to shed virus and are therefore considered infectious. Once individuals recover, R, they are protected from infection for a period of time; this protection wanes at rate δ (which is estimated from the inference process) and individuals become fully susceptible to infection again.

2.3. Norovirus notification data

The Robert Koch Institute collects statutory notifiable disease data from across Germany in the database SurvStat [21]. We estimate our model from the reported case notifications of norovirus from 2008 to 2016. This anonymised data is freely available and stratified by age, gender and region. There are known biases and systematic changes in reporting of norovirus within the German notification system that need to be appropriately modelled [22]. Under-reporting of norovirus infections is expected to be substantial with healthcare seeking behaviour for individuals with symptoms likely to vary with age [17]. Finally, there was a change in case definition during our study period. Before 2011 an epidemiological diagnosis of norovirus was sufficient for a case to be reported in SurvStat, whereas after 2011 only laboratory confirmed cases are reported. We use a novel self-correcting markov process model to account for this change in notification. Full details of the observation model can be found in supplementary information.

When estimating our models, we simulate our deterministic epidemiological model over the study period (2008–2016) and calculate the expected incidence for each weekly period as the product of the accumulated new infections ($C(t)$) multiplied by the time, age and case dependant probability of reporting. If we treat each of our M reported case notifications, per week and age class, as an independent binomial trial we can construct an approximate likelihood for our model as the product of these M trials. To estimate potential over-dispersion of the data due to model misspecification and extra-demographic stochasticity, we use a

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