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Dynamic model of rotavirus transmission and the impact of rotavirus vaccination in Kyrgyzstan☆

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ABSTRACT

New rotavirus vaccines show promise to reduce the burden of severe diarrhea among children in developing countries. We present an age-specific dynamic rotavirus model to assess the effect of rotavirus vaccination in Kyrgyzstan, a country in Central Asia that is eligible for funds from the GAVI Alliance. A routine rotavirus vaccination program at 95% coverage and 54% effectiveness against severe infection is estimated to lead to a 56% reduction in rotavirus-associated deaths and a 50% reduction in hospital admissions, while outpatient visits and homecare episodes would decrease by 52% compared to baseline levels after 5 years of intervention. A 10% reduction in vaccine efficacy due to incomplete 3-dose regimen is estimated to increase the numbers of severe cases by 6–8%. Herd immunity was found to account for 1% or less of averted cases of severe gastroenteritis, while an extra 7–8% of all rotavirus infections would be avoided due to reduced transmission. *Conclusion*: Rotavirus vaccines would reduce the burden of rotavirus disease substantially, but the results are sensitive to delay in age-appropriate vaccination.

1. Introduction

Rotavirus is a common cause of severe acute gastroenteritis among children <5 years of age, causing an estimated 570,000 deaths annually [1]. Currently two new vaccines, Rotarix® and Rotateq®, are recommended for routine immunization and both products has shown good efficacy in clinical trials conducted in high- and middle-income countries. Although vaccine trials in developing countries are ongoing, early post-licensure data from these settings demonstrated a lower reduction in severe disease than was found in industrialized countries [2,3]. Several questions on the vaccine impact remain open, including the role of indirect effects and potential herd immunity.

Mathematical modeling is increasingly used to inform policy decisions on the use of vaccines. Several models of rotavirus infection have been published [4–10], including two dynamic transmission models [11–13] that have been fitted to data from the United States. However, no reports of dynamic modeling of rotavirus infections in developing countries are currently available. In this paper, we present a dynamic transmission model that includes primary, secondary and later rotavirus infections in a developing country setting. We fitted the model to rotavirus surveillance data from Kyrgyzstan, a low-income country in Central Asia that is eligible for vaccine funding from the GAVI Alliance. Kyrgyzstan has 5.3 million inhabitants and an annual estimated birth cohort of 116,000. Rotavirus disease in Kyrgyzstan was recently estimated to cause 4200 (range 3895–4781) hospitalizations, 33,600 (range 21,000–42,000) outpatient visits, and 134,000 (range 100,800–168,000) home care episodes annually in children aged <5 years [14]. Between 174 and 285 annual deaths in children <5 years were estimated to occur, representing 3.7% of all deaths in that age group [15]. Childhood vaccines are free, immunization services are widely accessible, and mortality rates in children <5 years are lower than several low-income countries in Asia and Africa. The country has conducted active hospital-based rotavirus surveillance during 2005–2009.

The aims of this study were to estimate the age-specific reduction in rotavirus burden after the introduction of rotavirus vaccine in routine immunization and to explore the role of the indirect effects of vaccination. Kyrgyzstan is representative of GAVI-eligible countries in terms of economic, demographic, and mortality indicators and findings from this study could be useful for policy decisions in other developing countries.

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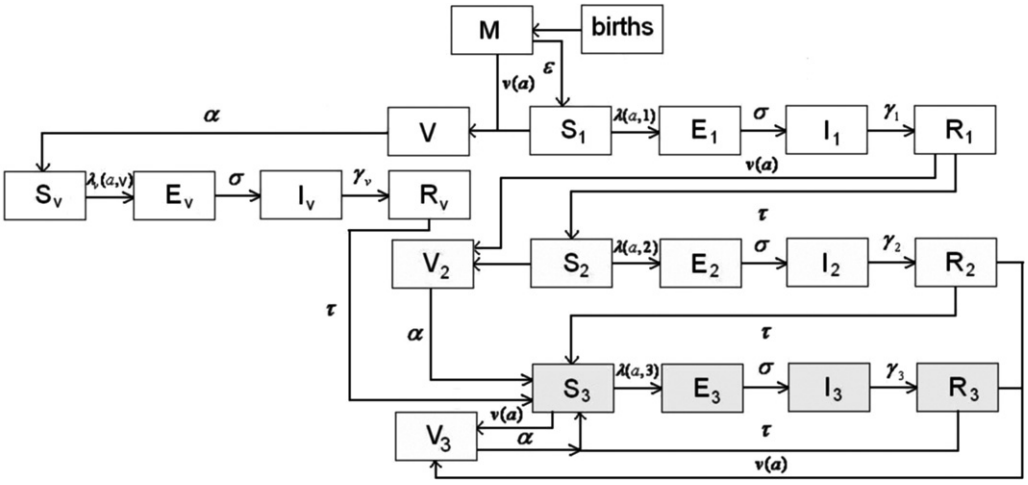

Fig. 1. Diagram illustrating dynamic rotavirus transmission model: newborns enter age group $a = 1$, and are assumed protected from maternal antibodies (M), and the protection is lost over time so the children become susceptible to the first infection. Upon primary infection, an individual moves to the exposed compartment (E) where no transmission occurs, before the person becomes infectious (I) with rate σ. An infected individual enters the recovered compartment (R) with rate γ, where protection is lost with rate τ, and then enters the compartment of susceptible to the second infection. The second and later infections follow the same structure. We apply a universal mortality rate μ to all age groups (not shown).
We model the effect of vaccination by transferring breast-fed, susceptible and recovered children to a vaccinated state where they are temporarily immune to infection. Vaccination is modeled as similar to a natural rotavirus infection. Children with no prior natural infection transfer from the vaccinated state (V) to become susceptible to the second rotavirus infection, and this infection is modeled separately with distinct epidemiological characteristics. After recovery from the second infection, the vaccinated children are not distinguished, and they enter a susceptible compartment to the third and later infections, which are shared with non-vaccinated children. Children who have already had their primary or secondary infection will move to vaccinated states (V_2, V_3) from where they become susceptible to the third and later infections, similar to the children not vaccinated.

2. Methods

Our modeling approach includes four steps: (i) development of a dynamic model of natural rotavirus infection that incorporates primary, secondary and subsequent rotavirus infections and grouping of infected children aged <5 years of age into asymptomatic, mild symptomatic and severe symptomatic cases, using data from the literature; (ii) fitting the model to the age-specific Kyrgyz data on rotavirus hospitalizations; (iii) calibration of rotavirus-associated events (deaths, hospitalizations, outpatient visits, and home care episodes) using national and international estimates; (iv) simulation of short- and long-term impact of vaccination on disease incidence and rates of rotavirus-associated events.

2.1. Model structure

We stratified the population by age into 20 groups: 2-month age groups from 0 to 23 months, and 6 months age groups from 1 to 4 years, 5–19 years, and ≥20 years. Based on age and the number of previous rotavirus infections, persons enter and exit the following mutually exclusive compartments in the model: Maternal antibody protected M, Susceptible S, Exposed E, Infected I, Recovered R and Vaccinated V (Fig. 1 and Appendix A.1). All children were considered to be protected by maternal antibodies at birth, and we assumed exclusive breastfeeding to protect against infection [16,17]. The maternal protection was modeled assuming an exponential decline with a mean duration of 158 days, in agreement with Kyrgyz data showing that approximately 31.5% of children are exclusively breast-fed up to the age of 6 months [18]. As the protective effect of maternal antibodies wanes over time, children become susceptible and transfer to the compartment S. Infected persons enter the exposed compartment E before they become infectious and move to compartment I. The incubation period of rotavirus infection is 1–3 days, and viral shedding may begin before symptoms develop. We used a latency period of 1 day, as the replication cycle of rotavirus in human cell lines is around 20–24 h [19], and in volunteer studies viral shedding have be found to start on the second day after oral administration [20]. Viral shedding is detectable by antigen enzyme immunoassays (EIA) up to 1 week after infection or for more than 30 days in immunodeficient persons [21]. The mean length of the primary infectious period was assumed to be 10 days [22–24], whereafter the persons recover and move to compartment R where they are temporarily immune to re-infection. The time when antibodies may protect against infection is short, and the minimal time between subsequent rotavirus infections has been estimated around 21 days [24]. However, antibody induced protection may protect against clinical re-infection for a longer period of 6 months in children <2 years [25], and in older children and adults protection may last longer and up to around 1 year [22]. The recovery period was set to 2 months based on model performance (Appendix A.3).

The secondary and later infections follow the same structure of natural history. Since subsequent infections are less likely to be symptomatic and severe, the duration of viral shedding is shorter [26], and the mean duration of infectiousness was assumed to be 7.5 and 5 days, respectively.

We grouped rotavirus infections by severity using results from the prospective study by Velázquez et al. [27] who found that symptomatic disease occurred in 47%, 25%, and 24–32% of infected children during primary, secondary, and subsequent infections, whereas 13.0%, 4.8%, and 0% of these infections were severe. The model demography was based on international estimates of birth and mortality rates (Appendix A.2) [28].

2.2. Transmission

We modeled a density-dependent transmission of rotavirus, implying that contact rates increase with the population size. Rotavirus transmission is affected by the susceptibility, the infectiousness and the social contact patterns in the population. We assumed a lower susceptibility to infection among re-infected individuals with factors of 0.65 and 0.4 for the second and later infections based on previous estimates [21].

Viral shedding data indicate that children with severe rotavirus diarrhea shed more virus than children with sub-clinical infections [29], and symptomatic adults [22], but further work is needed to quantify the relation between viral shedding and risk of transmission. The infectiousness of the second infection was assumed to be reduced to 1/2 relative to the primary infection, whereas infectivity of the later infections was assumed to be 1/8 compared to the first infection (Appendix A.3).

Social studies demonstrate that people in general tend to mix with people of the same age [30–32]. In Kyrgyzstan, it is common for several generations (grandparents, parents, and children) to live together in one household, and many pre-school children do not attend day care centers, which may favor random mixing. Rotavirus is mainly transmitted via the fecal-oral route, and possibly by contaminated objects and hands [33]. It is therefore plausible that young children who tend to put fingers and objects in the mouth may stand a higher risk of being infected compared to older children. We fitted the model assuming: (1) homogenous mixing, (2) assortative mixing, and (3) higher susceptibility in <3-year-old children. The best performing model was found with higher transmission to the youngest age groups (Appendix A.3).

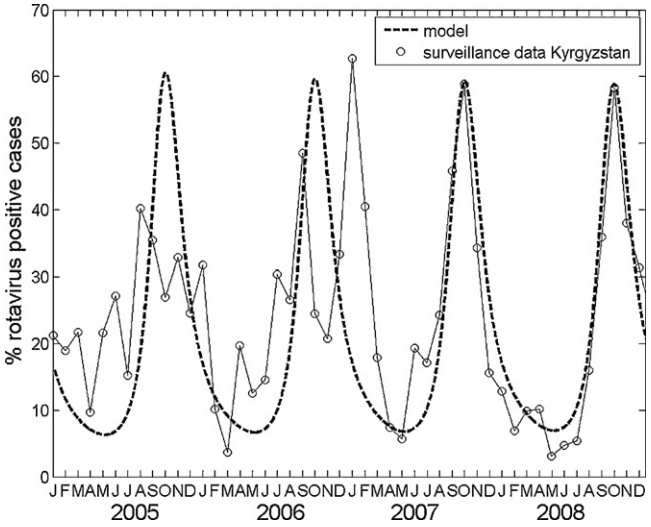

Fig. 2. The proportion of rotavirus-positive cases among children <5 years hospitalized with acute diarrhea in Kyrgyzstan, 2005–2008. We modeled rotavirus transmission with seasonality (Appendix A.3). The modeled incidence is drawn without scale to show the relative annual variation.

2.3. Vaccination

Current rotavirus vaccines protect against clinical disease rather than infection, similar to natural rotavirus infection. We modeled vaccination to be similar to the experience of primary infection (or a later infection for the minority of children who have already been infected when they are vaccinated) [12]. However, the vaccine efficacy against severe and symptomatic disease was allowed to differ from the corresponding efficacies of natural rotavirus infection (Fig. 1).

The mean duration of vaccine-duced protection was assumed to be 2 months following the end of the vaccination period (6 months), and set equal to the assumed recovery period of natural infection. We considered that 95% of the vaccinated children would be successfully immunized in accordance with data on antibody response after vaccination [34]. A study in Nicaragua demonstrated a vaccine effectiveness of 58% (95% CI 30–77) in preventing severe and 77% (95% CI 39–92%) in preventing very severe infection [2]. These results are in line with results from clinical trials in South Africa and Malawi showing a 61% (95% CI 44–73%) efficacy against severe gastroenteritis [3]. In the latter study, the susceptibility of the vaccinated children was estimated at 70% compared to non-vaccinated children. Accordingly, we assumed that 35% of the vaccinated children with no prior infection would experience a symptomatic secondary infection, with 19.75% of these infections being severe. This provides a vaccine efficacy against severe infection of $0.95(1–0.70(0.0691/0.1316)) \sim 0.60$, and a vaccine efficacy against symptomatic disease of $0.95(1–0.70(0.35/0.47)) \sim 0.38$ compared to the primary infection. When calculating rotavirus-induced deaths, an additional 25% reduction was added for vaccinated children to provide an efficacy of 75%. Because available molecular data indicate that mainly common rotavirus genotypes circulate in Kyrgyzstan [14], we did not include serotype-specific vaccine efficacy in the model.

The WHO estimates that the coverage of the third dose of diphtheria–tetanus–pertussis (DTP) vaccine in Kyrgyzstan was 95% in 2008 [35]. However, considering age restrictions for administration of rotavirus vaccines, potential delays in timely administration may reduce the coverage of these vaccines. Data from neighboring Kazakhstan with a similar immunization system reveal that fewer children are immunized on time with approximately 80% and 65% receiving their second and third dose of DTP vaccine with a delay of $\leq$1 month [36].

In the Nicaraguan study, vaccine effectiveness in preventing hospital admission or intravenous hydration with 2 or 3 doses did not differ significantly [2]. We modeled administration of a 3-dose vaccine at 2, 4 and 6 months by immunizing the children at the age of 4 months in the baseline case. We applied an effective coverage $cov_{eff} = eff \times cov$, where a proportion cov_{eff} of the vaccinated children were assumed to be successfully immunized. To account for reduced protection in children who do not receive a full 3-dose vaccination, we assumed that the relative effectiveness of the vaccine was 0.90, and multiplied this number with the seroconversion rate of 0.95 to obtain vaccine effectiveness $eff = 0.855$. In the baseline scenario we used the estimated DTP vaccine coverage of 0.95, resulting in an effective vaccine coverage $cov_{eff} = 0.812$.

The national roll-out of the vaccination program was implemented within 6 months with a linear increase in the coverage during this time period.

2.4. Validation procedure

We fitted the cumulative incidence of severe rotavirus infection in the model to Kyrgyz surveillance data on rotavirus hospitalizations collected in 2005–2008. Rotavirus surveillance was conducted in 3 hospitals and included children <5 years of age that was admitted for acute gastroenteritis within 7 days of onset. Collected stool samples were tested by a commercial enzyme immunoassay for rotavirus. Approximately 24% (95% CI 22.9–25.2) of children enrolled in the study tested positive for rotavirus. The data demonstrated a seasonal pattern of rotavirus infection with a peak from September to November, and we included this seasonality in the model (Fig. 2).

We calibrated the model assuming that all children with severe infection require medical treatment and applied a constant proportion of hospitalizations and deaths in each age group. Using the previous assessment of rotavirus burden in Kyrgyzstan [13], we found that about 1.09% and 19.9% of severe rotavirus infections in Kyrgyzstan may lead to death and hospitalization, respectively. Outpatient visits were estimated by assuming that on average each child with severe infection would require one outpatient visit, while 3.5% of all children with milder symptomatic infection will seek outpatient care. The remaining proportion of children with symptomatic infections was assumed to receive only home care.

Table 1
Model parameters.

Parameter	Value	Reference
Epidemiology		
β_0 mean transmission rate	1.62 per day	Fitted to sentinel data
β_t amplitude, transmission rate	0.079	Fitted to sentinel data
θ phase angle transmission	2.24	Fitted to sentinel data
$1/\varepsilon$ duration of breastfeeding	155 days	MICS survey [18]
$1/\sigma$ duration of latency period	1.0 days	[19,20]
$1/\gamma$ duration of infectious period	10, 7.5, 5 days	Varied[a]
$1/\tau$ duration of recovery period	60 days	Varied[a]
φ_2, φ_3 relative susceptibility second and later infections	0.65, 0.40	[27]
κ_2, κ_3 relative infectivity second and later infections	1/2, 1/8	Varied[a]
$p1_{symp}$, $p2_{symp}$, $p3_{symp}$ proportion symptomatic infections	0.47, 0.25, 0.24	[27]
$p1_{sev}$, $p2_{sev}$, $p3_{sev}$ proportion severe of symptomatic infections	0.28, 0.17, 0	[27]
$c1$, $c2$, $c3$ matrix coefficients ($W2$)	1.38, 3.38, 1.10	Fitted to sentinel data
Health sector and deaths		
p_{death} proportion dying from severe infection	1.09e−2	Calibrated
p_{hosp} proportion hospitalized with severe infection	0.199	Calibrated
p_{outp} proportion outpatient visits severe, mild infection	1.0; 0.035	Calibrated
Vaccination		
cov vaccine coverage	0.95	[35]
in eff incomplete vaccination protection effect	0.1 (0–0.1)	Author assumption [36]
t_{imp} period to implement vaccine program	0.5 year	Author assumption
$p1v_{symp}$ proportion symptomatic	0.35 (0.225; 0.425)	[2,3]
$p1v_{sev}$ proportion severe of symptomatic	0.1975 (0.15; 0.225)	[2,3]
$1/\alpha$ duration of vaccine immunity	60 days	Author assumption

[a] Parameters varied during model selection procedure (Appendix A.3).

2.5. Sensitivity analysis

Many aspects of natural rotavirus infection are unknown and uncertain. We therefore tested the model performance for various assumptions of the natural parameters, including the recovery period and the relative infectivity of later infections. The model performance of all candidate models were evaluated with use of Akaike's information criterion (AIC), balancing the number of model parameters against improvement of prediction quality [37] (Appendix A.3). The vaccine efficacy against severe infection was varied between 45 and 80% in accordance with data from Latin America [38] and Africa [2,3]. In addition, we varied the timing of vaccine protection between 2 and 6 months and estimated the impact of incomplete vaccination (Table 1).

3. Results

3.1. Model validation

The baseline model predicted an age-specific incidence of severe rotavirus infections resulting in hospitalizations that was similar to the Kyrgyz hospital surveillance data (Fig. 3). In 2009, the model predicted 288,000 asymptomatic and 129,100 symptomatic rotavirus cases among children <5 years of age in Kyrgyzstan, of which 20,800 were severe cases. By the age of 2 years, 94% and 72% of all children have had their primary and secondary infections, in line with the results from the prospective study by Velazquez et al. [27]; by the age of 5, every child has been infected at least once, in agreement with the current knowledge [26,39]. In 2009, rotavirus infections would result in 221 deaths, 4140 hospitalizations, and 24,500 outpatient visits in children <5 years of age. Additional 105,000 annual rotavirus-related homecare episodes are predicted in this age group (Table 2). These results are consistent with previous estimates [14] and serve as an indirect model validation because the total number of symptomatic infections is unaffected by the calibration.

The basic reproductive rate for the primary rotavirus infection was calculated to $R_0 \sim 21$–23 using the next generation method [40]. The results suggest that the numbers of rotavirus infections will increase by 1–3% annually between 2010 and 2020 due to population growth. Until 2015, the average annual increase in severe infections is around 1%, but later the birth cohort is expected to decline slightly.

3.2. Epidemiological impact of rotavirus vaccination

The model predicted that introduction of vaccination would reduce the incidence of rotavirus infections in children <5 years substantially, with the largest reduction occurring during the second year of intervention (Fig. 4B). During the first year of intervention (2010), new cases of severe infection and any infection were reduced by 25% and 22%, respectively, compared to the baseline scenario without vaccination. The numbers of severe infections decreased to 43% and 48% in 2011 and 2012, respectively. From 2014, the numbers of new severe infections was 50% and remained relatively stable afterwards.

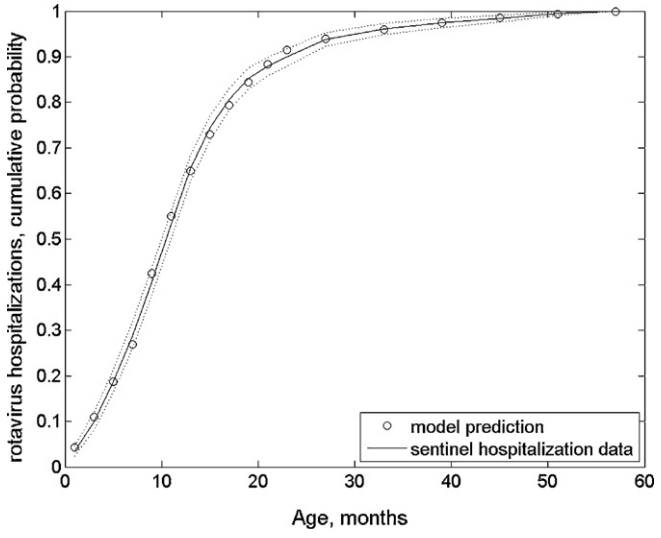

Fig. 3. Fit of the model to Kyrgyz rotavirus hospitalization data. Uncertainty in the data was estimated by bootstrap sampling ($N = 1000$); the full range of variation in the age-profile obtained in this way is indicated with error bars.

Table 2
Predicted annual incidence of rotavirus-associated events in Kyrgyz children <5 years at baseline (2009), and during the third (2012) and fifth (2014) years of intervention; vaccination initiated 1 January 2010.

Outcome	Baseline (2009)	Vaccination period			
	New cases	Third year (2012)		Fifth year (2014)	
		New cases[a]	Incremental avoided cases[b]	New cases[a]	Incremental avoided cases[b]
Deaths	221	99 [77,120]	329 [292,367]	104 [79,130]	595 [508,682]
Hospitalizations (1000×)	4.14	2.09 [1.56,2.60]	5.75 [4.83,6.67]	2.23 [1.61,2.85]	10.2 [8.07,12.3]
Outpatient visits (10,000×)	2.45	1.24 [0.96,1.51]	3.40 [2.92,3.90]	1.34 [0.99,1.66]	6.04 [4.93,7.20]
Homecare episodes (10,000×)	10.5	5.47 [4.83,5.82]	14.5 [13.9,15.6]	6.09 [5.33,6.51]	26.1 [24.7,28.7]

[a] 95% CI based on vaccine efficacy against severe infection ranging from 42% to 78% [2,3].
[b] 95% CI based on comparison with baseline scenario without vaccination.

We estimated the reduction in rotavirus-associated deaths, hospitalizations, outpatient visits and homecare episodes 3 and 5 years after vaccine introduction, and the incremental numbers of cases avoided during this time (Table 2). Our model suggested that in the 5th year of intervention (2014), the rotavirus-related deaths and hospitalizations among children <5 years would be 99 and 2230, respectively, corresponding to a 56% and a 50% reduction compared to baseline; the numbers of outpatient visits and homecare episodes were predicted at 13,400 and 60,900 equal to a reduction of 49% and 48%, respectively. Overall, vaccination was found to prevent 52% of all deaths and 47% of hospitalizations attributable to rotavirus infection in the first 5 years, compared to no intervention, whereas 46–47% of outpatient visits and homecare episodes would be avoided.

The model predicted a vaccine-induced delay in the seasonal peak of rotavirus infection by around 1–3 months; the peak incidence was shifted by around 3 weeks in 2010 and by 6 weeks in 2011. Thus, the seasonal rotavirus epidemics in Kyrgyzstan would be expected to occur in December, rather than in September–October as currently observed (Fig. 4).

3.3. Median age of infection and indirect effects

In the pre-vaccination era, the median age of the first infection was approximately 9 months (mean 13 months), and all children were infected at least once by the age of 5 years. We examined the expected impact of vaccination on the age-specific incidence of the primary infections (Fig. 5), using the incidence as a measure of the proportion susceptible as the two measures have a similar age-profile. The model predicted an increase in the median age of the primary infection to 11 months in 2012, before reaching a new equilibrium at approximately 14 months after 5 years. In the post-vaccination era, approximately 5% of children would escape rotavirus infection during their first 5 years of life.

We quantified the indirect protection of vaccination by comparing the incidence of rotavirus infection and severe infection with the values obtained from direct protection of vaccinated children (Fig. 6). In the pre-vaccination equilibrium, 85.4% of the children had not been infected with rotavirus before 4 months of age. The predicted reduction in severe infections from direct vaccine-derived protection is 49.3%, whereas the observed reduction is

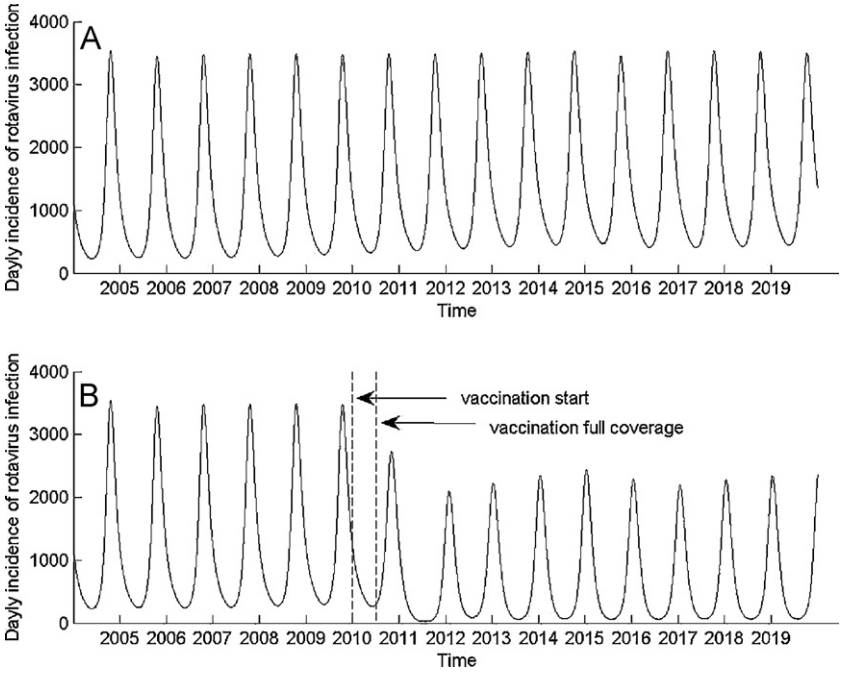

Fig. 4. Model-predicted daily incidence of rotavirus infections among children <5 years of age without vaccination (A) and with vaccination (B); the baseline scenario of 95% coverage and vaccine effectiveness of 60% is shown.

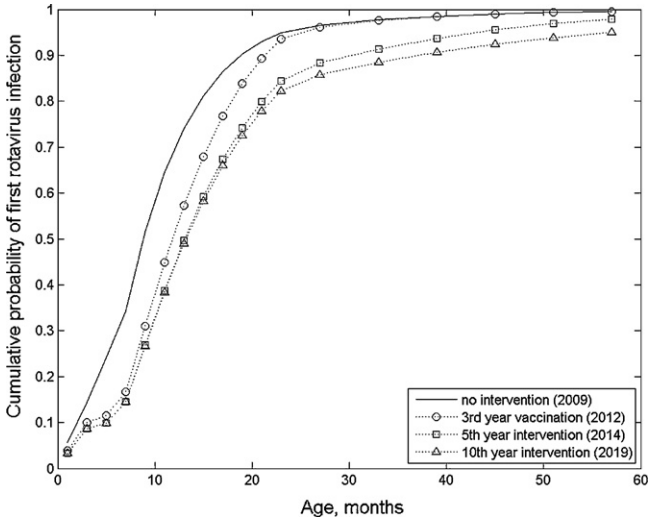

Fig. 5. Cumulative probability of first rotavirus infection.

50.3% after 5 years of intervention (100% coverage). Hence, the indirect effects account for around 1% of avoided severe infections; after 10 years, the indirect protection is even smaller. In conclusion, rotavirus vaccination does not appear to confer indirect protection against severe disease. However, vaccination seems to reduce rotavirus transmission sufficiently to reduce the overall long-term incidence of infection in the population. After 5 years of vaccination, the incidence of infection is reduced by 7–8% below the incidence expected from direct protection.

3.4. Sensitivity analyses

We quantified the effect of vaccination for various coverage levels (Fig. 6A and B). For examples, in the baseline scenario with a vaccine effectiveness of 85.5%, full (100%) coverage would reduce the numbers of severe infections in 2014 to between 36% (VE = 0.80) and 64% (VE = 0.45) of the level expected without vaccination. We found that the timing of the vaccine protection and the assumption of incomplete vaccination regimen affect the predicted reduction in deaths and health care resource utilization (Table 3). If full vaccine protection is achieved in all children, an extra 13–14% of deaths and hospital admissions would be averted in a 5-year period, assuming that vaccine protection is effective from 4 months of age. The results are most sensitive to a delay in vaccine protection until 6 months of age compared to vaccine protection starting from the age of 2 months. In the first case, additionally 5% extra hospitalizations and deaths are predicted to occur until 2015, while only 2–3% of cases are avoided assuming early vaccine protection.

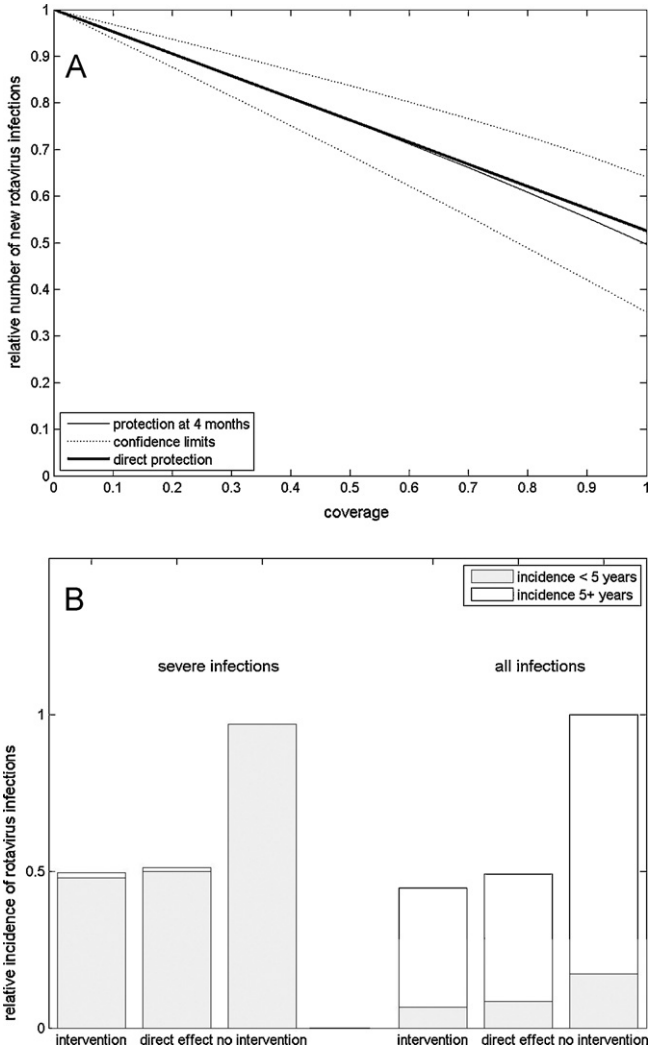

Fig. 6. (A) Direct and observed vaccine effect on incidence of severe infection after vaccination by coverage and vaccine effectiveness. The reduction is measured by comparing the incidence in the fifth year of intervention (2014) with the predicted incidence without vaccination in the same year. Lower and upper confidence limits correspond to vaccine efficacy of VE = 0.80 and VE = 0.45, based on results from clinical trials in low income countries. (B) Bar plots comparing the pre- and post-vaccination incidence of severe rotavirus infection and all rotavirus infections in the base scenario. The left bar displays the estimated cases of infection in the fifth years of intervention (2014), the middle bar displays the expected cases from direct protection alone, while the right panel shows the rotavirus cases expected without intervention in the same year. The herd immunity can be seen by comparing the levels of the first two bars. The relative contribution from children <5 years is also shown in grey.

Table 3
Effect of incomplete vaccination protection and timing of vaccine protection on deaths and hospitalizations in Kyrgyz children <5 years after 5 years of intervention (2014).

Timing/effect of incomplete vaccination protection	Deaths		Hospitalizations	
	New cases	Incremental avoided cases	New cases (1000×)	Incremental avoided cases (1000×)
Incomplete vacc. 10%				
2 months	94 (−5%)	610 (+3)	2.05 (−8%)	10.4 (+2%)
6 months	107 (+ 8%)	568 (−5%)	2.27 (+2%)	9.68 (−5%)
Incomplete vacc. 0%				
2 months	77 (−22%)	689 (+16%)	1.76 (−21%)	12.0 (+18%)
4 months	84 (−15%)	674 (+13%)	1.86 (−17%)	11.6 (+14%)
6 months	92 (−7%)	646 (+9%)	2.00 (−10%)	11.1 (+9%)

4. Discussion

We have developed an age-structured dynamic model of rotavirus transmission to evaluate the effects of routine rotavirus vaccination in a developing country setting. Key features of our model include a differentiation between primary and secondary infections, stratification of disease severity by age and numbers of previous infections, seasonality of rotavirus infection, and inclusion of population demographic changes. We validated the model using Kyrgyz surveillance data to create a more realistic picture of rotavirus infection in the local context. The presented framework could be adapted to other developing countries to maximize the use of existing data.

Our analyses suggest that vaccination would reduce the burden of rotavirus disease significantly, and the full effect of the program would be achieved after approximately 3–4 years. We estimated a 56% and 50% reduction in the incidence of severe rotavirus gastroenteritis leading to deaths and hospitalizations, respectively, after 5 years of intervention. During this period, 53% and 47% of the deaths and hospital admission would be avoided, when compared to no intervention. The predicted reduction in the incidence of outpatient visits was 49% after 5 years, whereas 48% of all outpatient visits would be avoided. When compared to other published studies in low-income country settings, the present Kyrgyz study provides a conservative estimate of the vaccine effect, which likely relates to the low vaccine efficacy employed and the inclusion of incomplete vaccine coverage in this study. We also did not consider the possibility of incremental vaccine protection (where each dose of vaccine is treated equal to a natural infection) [13,41], as we believe the current vaccine data from developing countries does not support this effect.

In general, dynamic models are advantageous compared to static models because they allow the force of infection to vary over time, and hence, they can be used to assess the indirect effects of vaccination. It is currently unclear how much herd immunity may be achieved with rotavirus vaccination. Available post-licensure data from the US demonstrate that rotavirus incidence also decreased among non-vaccinated children [42], suggesting that indirect protection may be present. In the current study, vaccination was found to diminish the transmission in the population sufficiently to reduce the incidence of mild or asymptomatic by an additional 6–8% compared to direct protection alone. However, herd immunity was not found to induce significant protection against severe disease. Our estimates are lower than results from a recent rotavirus modeling study for European countries showing that 13–19% of moderate-severe infections could be avoided for vaccine coverage levels of 70–95% [43].

We estimated the basic reproductive rate of the primary infection to $R_0 \sim 21$–22, which is consistent with a value $R_0 \sim 24$, estimated in a dynamic modeling study based on US data [13], although the mean age of hospitalized cases in the US data was 18 months, whereas the mean age of rotavirus hospitalizations in the Kyrgyzstan was only 12.7 months.

We found that the overall public health effect of rotavirus vaccination is sensitive to changes in the timelines of vaccination. We modeled rotavirus immunization to be administered between 2 and 6 months of age as per current WHO recommendations. Despite the high DTP coverage in Kyrgyzstan, many children in developing countries receive vaccines later than recommended, thus leading to a decreased overall impact of the program. It has been suggested to remove the age restriction on the rotavirus vaccine in countries with high rotavirus mortality because the potential risk of intussusception is low [40]. This approach may not be suitable in Kyrgyzstan, however, where rotavirus mortality rate is lower than in some other developing countries and therefore, any risk of intussusception may be unacceptable.

The present modeling approach has several limitations. First, the model includes a number of uncertain epidemiological parameters. More prospective epidemiological studies are needed to clarify the relationship between severe gastroenteritis, age and previous infections, and the importance of asymptomatically infected adults for rotavirus transmission [39]. For example, it is plausible that a shift towards older age in children who experience their first rotavirus infections will provide additional benefits, since older children are less likely to experience life-threatening dehydration. In our model, we used data from a single study on natural rotavirus infection conducted in Mexico, and we are unable to assess how country-specific differences would affect the course of infection. Second, the model fit is based on data from children <5 years of age, while data on the disease burden in adolescents and adults were not used in the model fitting. It is likely that some parameter assumptions are biased for that reason. We found that higher mixing rates among children 1–3 years of age provided the best model fit to the Kyrgyz hospitalization data. However, lack of data precludes any assessment of the validity of the mixing assumptions and parameter settings made. Third, the long-term predictions should be interpreted with caution given the uncertainty of vaccine efficacy and because rotavirus epidemiology may change following vaccination.

In conclusion, our dynamic model predicted that new rotavirus vaccines are likely to reduce disease incidence and associated hospitalizations and deaths substantially. This reduction in disease burden is predominantly due to direct vaccine-derived protection, while herd immunity may reduce the prevalence of infection in the population. Further modeling work should be done to incorporate serotype-specific efficacy estimates, and to adapt the model to other developing settings.

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Appendix A.

A.1. Model equations

The rotavirus transmission model consists of a set of coupled differential equation where the age variable is discretised into j age groups. The epidemiological groups are: $M_j(t), S_j^k(t), E_j^k(t), I_j^k(t), R_j^k(t)$ Maternal antibody protected, Susceptible-Exposed-Infected-Recovered individuals in age group j and infection number $k = 1, 2, 3$ with the following model equations for age groups $j \geq 2$:

$$\frac{dM_j(t)}{dt} = -\varepsilon M_j(t) - \mu M_j(t) + n_{j-1}M_{j-1}(t) - n_j M_j(t)$$

$$\frac{dS_j^1(t)}{dt} = \varepsilon M_j(t) - \lambda_j(t)S_j^1(t) - \mu S_j^1(t) + n_{j-1}S_{j-1}^1(t) - n_j S_j^1(t)$$

$$\frac{dE_j^1(t)}{dt} = \lambda_j(t)S_j^1(t) - \sigma E_j^1(t) - \mu E_j^1(t) + n_{j-1}E_{j-1}^1(t) - n_j E_j^1(t)$$

$$\frac{dI_j^1(t)}{dt} = \sigma E_j^1(t) - \gamma I_j^1(t) - \mu I_j^1(t) + n_{j-1}I_{j-1}^1(t) - n_j I_j^1(t)$$

$$\frac{dR_j^1(t)}{dt} = \gamma I_j^1(t) - \tau R_j^1(t) - \mu R_j^1(t) + n_{j-1}R_{j-1}^1(t) - n_j R_j^1(t)$$

$$\begin{aligned}
\frac{dS_j^2(t)}{dt} &= \tau R_j^1(t) - \lambda_j(t)\varphi_2 S_j^2(t) - \mu S_j^2(t) + n_{j-1}S_{j-1}^2(t) - n_j S_j^2(t)\\
\frac{dE_j^1(t)}{dt} &= \lambda_j(t)\varphi_2 S_j^2(t) - \sigma E_j^2(t) - \mu E_j^2(t) + n_{j-1}E_{j-1}^2(t) - n_j E_j^2(t)\\
\frac{dI_j^2(t)}{dt} &= \sigma E_j^2(t) - 1.5\gamma I_j^2(t) - \mu I_j^2(t) + n_{j-1}I_{j-1}^2(t) - n_j I_j^2(t)\\
\frac{dR_j^2(t)}{dt} &= 1.5\gamma I_j^2(t) - \tau R_j^2(t) - \mu R_j^2(t) + n_{j-1}R_{j-1}^2(t) - n_j R_j^2(t)
\end{aligned} \tag{1.1}$$

$$\begin{aligned}
\frac{dS_j^3(t)}{dt} &= \tau(R_j^2(t) + R_j^3(t)) - \lambda_j(t)\varphi_3 S_j^3(t) - \mu S_j^3(t)\\
&\quad + n_{j-1}S_{j-1}^3(t) - n_j S_j^3(t)\\
\frac{dE_j^3(t)}{dt} &= \lambda_j(t)\varphi_3 S_j^3(t) - \sigma E_j^3(t) - \mu E_j^3(t) + n_{j-1}E_{j-1}^3(t) - n_j E_j^3(t)\\
\frac{dI_j^3(t)}{dt} &= \sigma E_j^3(t) - 2\gamma I_j^3(t) - \mu I_j^3(t) + n_{j-1}I_{j-1}^3(t) - n_j I_j^3(t)\\
\frac{dR_j^3(t)}{dt} &= 2\gamma I_j^3(t) - \tau R_j^3(t) - \mu R_j^3(t) + n_{j-1}R_{j-1}^3(t) - n_j R_j^3(t)
\end{aligned}$$

where j is the age group, 2 months age group from 0 to 23 months; 6 months age group 24–59 months, 5–19 years, 20+ years, ε the rate of loss of maternal antibody protection, $n_j(t)$ the rate of aging in age group $j = 1/(a_j - a^{j-1})$, $\mu(t)$ the mortality rate, σ the progression rate of exposed state, γ the recovery rate of infection, τ the rate of loss of immunity, $\varphi_{2,3}$ the relative susceptibility of the second and later infection compared to the primary infection, and $\lambda_j(t)$ is the force of infection in age group j.

For the first age group, $j = 1$, the inflow into the M-compartment equals the births into the population birth(t), while the inflow into all other compartments in that age group is zeros, i.e. $n_0 S_0^1 = n_0 S_0^2 = n_0 S_0^3 = 0$, etc. We used continuous aging in the model with 18 age groups representing children <5 years. This approach allows the execution of a fourth order Runge–Kutta method with adaptable step size, which is known for high numerical precision. However, in this procedure children do not take exactly the same length of time to reach a given age, which may bias the model results. The variability in the length of time decreases as the number of age groups increases. We decided on the number of age groups by comparing the model output with the epidemic profile in a model with (realistic) discontinuous time to make sure that the age structure did not influence the model output.

A.2. Population

The model population at start of the simulation was set equal to the Kyrgyz population in 1990 of 4.40 million people. The model was run for 20 years before the intervention was initiated at January 1, 2010. We used piecewise linear regression of the UN estimate of 5-yearly crude birth and death rates for 1990–2020 to simulate previous and projected population developments. The annual estimated growth rate during the study period ranged between 0.9 and 1.5% with a population size of 5.5 and 6.2 million people in 2010 and 2020. No immigration or emigration was considered.

A.3. Model fitting and model selection

We estimated the average transmission rate $\hat{\beta}_0$ and coefficients of the WAIFW-matrix numerically using *fmincon* in Matlab (Optimization Toolbox Version 5.0). The estimates were obtained by maximizing the likelihood under the assumption that the count of rotavirus positive hospitalization events N_j in each age group <5 years $j = 1, \ldots, 18$ is multinomial distributed. In this case the log-likelihood function has the form:

$$\ln L(\theta) = \sum_{j=1}^{18} N_j \ln\left(\frac{p_j(\theta)}{N_j/N}\right) \tag{1.2}$$

where θ is a vector of the parameters to be fitted, N_j is the number of hospitalized children with rotavirus in age group j in the Kyrgyz sentinel data, $p_j(\theta)$ is the inferred probability of severe infection in age group j, and $N = 1446$ is the total number of children that tested positive for rotavirus during the surveillance period.

The model fit was repeated for various assumptions on the value of the recovery rate τ, and the infectivity of the later infections κ_3 that could not be estimated with precision from the literature.

The alternative values of these parameters were chosen based on the range of values adopted in a previously published model; in this US study [13] the average recovery period was varied between 9 and 12 months, and the relative infectiousness of later infections was assumed at $\kappa_3 = 1/10$ of the primary infection. We found the relative infectivity of the later infections κ_3 influential in changing the model outcome in sensitivity analyses. This is expected because the κ_3 parameter characterizes the importance of adult/asymptomatic transmission in the model dynamics. In contrast, the corresponding parameter for the secondary infection κ_2 did not affect the model predictions significantly. For this reason, we kept κ_2 at its base case value in all models tested (Table A.1).

For model simplicity, we collapsed the 20 age groups into 7 groups in the transmission matrix Eq. (1.3): (≤8 months, 9–23 months, 24–35 months, 36–47months, 48–59 months, 5–19 years, 20+ years). We assumed a prior structure of the WAIFW-matrix in terms of: homogenous mixing ($W1$), assortative mixing ($W2$), and unique transmission rates to the younger age groups <3 years ($W3$).

$$W1 = \begin{pmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1\\ 1 & 1 & 1 & 1 & 1 & 1 & 1\\ 1 & 1 & 1 & 1 & 1 & 1 & 1\\ 1 & 1 & 1 & 1 & 1 & 1 & 1\\ 1 & 1 & 1 & 1 & 1 & 1 & 1\\ 1 & 1 & 1 & 1 & 1 & 1 & 1\\ 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{pmatrix},$$

$$W2 = \begin{pmatrix} c1 & 1 & 1 & 1 & 1 & 1 & 1\\ 1 & c2 & 1 & 1 & 1 & 1 & 1\\ 1 & 1 & c3 & 1 & 1 & 1 & 1\\ 1 & 1 & 1 & c4 & 1 & 1 & 1\\ 1 & 1 & 1 & 1 & c4 & 1 & 1\\ 1 & 1 & 1 & 1 & 1 & c4 & 1\\ 1 & 1 & 1 & 1 & 1 & 1 & c4 \end{pmatrix},$$

$$W3 = \begin{pmatrix} c1 & c1 & c1 & c1 & c1 & c1 & c1\\ c2 & c2 & c2 & c2 & c2 & c2 & c2\\ c3 & c3 & c3 & c3 & c3 & c3 & c3\\ 1 & 1 & 1 & 1 & 1 & 1 & 1\\ 1 & 1 & 1 & 1 & 1 & 1 & 1\\ 1 & 1 & 1 & 1 & 1 & 1 & 1\\ 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{pmatrix} \tag{1.3}$$

The age-specific transmission $\beta_{ij}(t)$ from individuals in age group j to individuals in age group i was modeled by multiplying β_0 with the matrix elements W_{ij}, and incorporating seasonal forcing

$$\beta_{ij}(t) = \beta_0 W_{ij}(1 + \beta_t \sin(2\pi t + \theta)) \tag{1.4}$$

where β_0 is the mean transmission rate, β_t the amplitude of oscillation and θ is the shifted phase angle defining the timing of the maximum. The data quality of the weekly sentinel observations was not sufficient to allow the model to be fitted to the time series.

Table A.1
Estimated parameter values from nonlinear least squares fitting of the age-specific incidence of severe infection to Kyrgyz sentinel data and corresponding AIC values.

Mixing	$\hat{\beta}_0$	Additional fitted parameters	Varied parameters[a]	R_0	ΔAIC[b]	Rel. inc[c]
Homogenous						
*W*1	2.57			31.32	42.8	+6.1%
*W*1	2.23		$\kappa_3 = 1/7$	27.85	41.6	+5.1%
*W*1	2.61		$1/\tau = 6$ m; $\kappa_3 = 1/7$	35.50	51.3	+4.6%
*W*1	3.63		$1/\tau = 10$ m; $\kappa_3 = 1/7$	41.59	63.4	+8.0%
Assortative						
*W*2	1.78	$\hat{c}_1 = 1.02$; $\hat{c}_2 = 6.02$; $\hat{c}_3 = 1.50$; $\hat{c}_4 = 1.06$	$\kappa_3 = 1/7$	22.43	5.03	+1.3%
*W*2	1.87	$\hat{c}_1 = 1.52$; $\hat{c}_2 = 7.85$; $\hat{c}_3 = 9.73$; $\hat{c}_4 = 1.06$	$1/\tau = 6$ m; $\kappa_3 = 1/7$	23.79	13.8	+2.1%
*W*2	1.53	$\hat{c}_1 = 1.37$; $\hat{c}_2 = 3.38$; $\hat{c}_3 = 4.99$; $\hat{c}_4 = 1.83$	$1/\tau = 10$ m; $\kappa_3 = 1/7$	21.31	19.9	+1.2%
*W*2	1.79	$\hat{c}_1 = 2.45$; $\hat{c}_2 = 6.74$; $\hat{c}_3 = 1.19$; $\hat{c}_4 = \hat{c}_3$	$\kappa_3 = 1/7$	23.32	0.28	+1.4%
*W*2	1.69	$\hat{c}_1 = 2.85$; $\hat{c}_2 = 6.90$; $\hat{c}_3 = 1.11$; $\hat{c}_4 = 1.20$		22.89	3.28	−0.3%
*W*2	1.70	$\hat{c}_1 = 3.04$; $\hat{c}_2 = 6.94$; $\hat{c}_3 = 1.00$; $\hat{c}_4 = \hat{c}_3$		20.84	2.03	−1.2%
Unique rates						
*W*3	1.63	$\hat{c}_1 = 1.21$; $\hat{c}_2 = 2.99$; $\hat{c}_3 = 1.04$	$\kappa_3 = 1/7$	21.03	0.03	+1.1%
*W*3	1.40	$\hat{c}_1 = 1.25$; $\hat{c}_2 = 3.06$; $\hat{c}_3 = 1.03$	$1/\tau = 6$ m	19.34	6.68	−2.5%
*W*3	1.53	$\hat{c}_1 = 1.57$; $\hat{c}_2 = 4.99$; $\hat{c}_3 = 1.82$	$1/\tau = 10$ m	21.29	15.7	+3.4%
*W*3	1.62	$\hat{c}_1 = 1.38$; $\hat{c}_2 = 3.38$; $\hat{c}_3 = 1.10$		21.60	0.00	0.0%

[a] Only values different from base case values are listed.
[b] $\Delta\text{AIC} = \text{AIC}_i - \text{AIC}_{\min}$, difference between model *i* and the model with lowest AIC value.
[c] Percentage deviation in the incidence of severe infection following 5-year of vaccination (2014) compared to the incidence of severe infection in best-fitting model; baseline vaccination scenario assumed.

Consequently, we fitted the seasonal parameters to monthly data separately and after the primary model selection.

The force of infection was calculated as:

$$\lambda_i(t) = \sum_j \beta_{ij}(t)(I_j^1(t) + \kappa_2 I_j^2(t) + \kappa_3 I_j^3(t)) \quad (1.5)$$

where κ_2, κ_3 are the relative infectivity of the later infections compared to the primary infection.

In each case, the model performance was evaluated using Akaike's information criterion (AIC) [37]:

$$\text{AIC} = -2\ln L(\hat{\theta}) + 2p \quad (1.6)$$

where $\ln L(\hat{\theta})$ is the maximized log-likelihood for the candidate models tested. The model selection led to the following conclusions (Table A.1): (1) models consistently performed better with a short protective period of $\tau = 2$ months, as compared to 6 or 12 months. (2) Assuming homogenous mixing (*W*1) did not provide good model fit to the age-specific incidence of hospital admissions. These models overestimated the incidence in the youngest age groups, while underestimating the incidence among the children >9 months. (3) The best model fit were obtained with the relative infectivity of later infections at $\kappa_3 = (1/7)$–$(1/8)$. Models with $\kappa_3 = 1/10$ had ΔAIC scores > 5 and are not shown. The Kyrgyz sentinel data is limited and includes only young children and is not suitable to study the relative contribution of adults and asymptomatic transmission. Pitzer et al. [13] has found a correlation between high birth rates and early temporal timing of rotavirus epidemics, and the importance of adult transmission could potentially be identified by analyzing data in areas with extended surveillance of all age groups where the birth rates change substantially over time. (4) Both models assuming assortative mixing and unique rates of transmission (*W*2–3) gave reasonable model fit. We note that differences in AIC scores between the best raked models were small, and the present data was not adequate to identify a single model as superior compared to the other candidate models ranked 2–3. However, we note that the relative incidence of severe infection following 5 years of vaccination in these models only varied 1–2%. Also the basic reproductive rate of the primary infection was found to be ($R_0 \sim 21$–22) in all three models, implying that the importance of the youngest age groups in driving the rotavirus epidemics was comparable. Finally, we observe that the vaccine effect increases by assuming a shorter infectious period. For example, a fitted base case model with $1/\gamma = 5$ days instead of $1/\gamma = 10$ days decreases the expected 5-year incidence after vaccination with 4.3% compared to the base case scenario.

A.4. Direct protection and herd immunity

Vaccine efficacy (VE) is calculated from:

$$\text{VE} = \frac{\text{ARU} - \text{ARV}}{\text{ARU}} \quad (1.7)$$

where ARU is the attack rate in the unvaccinated and ARV is the attack rate in the vaccinated. The direct protection against incidence of severe infection for the secondary infection and the baseline vaccination scenario is

$$E_{\text{sec}} = \left(1 - 0.65\left(\frac{0.25 \times 0.17}{0.47 \times 0.28}\right)\right) = 0.790$$
$$\text{VE}_{\text{vacc}} = \left(1 - 0.7\left(\frac{0.35 \times 0.1975}{0.47 \times 0.28}\right)\right) = 0.632 \quad (1.8)$$

The relative endemic prevalence in the age group just prior to vaccination ($j = 2$) of susceptible to the primary and secondary infection is $p_1 = 0.853$ and $p_2 = 0.147$. The overall efficacy is estimated from:

$$\text{VE}_{\text{sev}} \simeq p_{\text{sero}}(1 - p_{\text{inc}})(p_1\text{VE}_{\text{vacc}} + p_2(1 - E_{\text{sec}})) = 0.487 \quad (1.9)$$

where p_{sero} is the seroconversion rate and p_{inc} is the relative reduction in vaccine efficacy due to incomplete rotavirus vaccination regimen. The direct effect of vaccination is the calculated from

$$f(cov) = (1 - \text{VE}_{\text{sev}})cov \quad (1.10)$$

where cov is the coverage. This function is plotted in Fig. 6A.

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