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Modeling Improved Coverage of Rotavirus Vaccines

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Modeling Improved Coverage of Rotavirus Vaccines

By

ChinEn Ai

B.Sc., Taipei Medical University, 2016

Thesis Committee Chair: Benjamin Lopman, Ph.D

An abstract of
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Abstract

Modeling improved coverage of rotavirus vaccine

By Chin-En Ai

Background: Rotavirus is a leading cause of severe diarrhea in children under five years of age. Rotavirus vaccine coverage has remained low (70 – 75%) for several years in the U.S. Family practitioners offer rotavirus vaccines only 45% of the time while pediatricians routinely offer 85% of the time. Higher rotavirus vaccine coverage provided by family practitioners should be considered to decrease further rotavirus disease burden. This study adapted and used a dynamic transmission (SIR) model to assess the impact of rotavirus vaccine coverage offered by family practitioners versus pediatricians on the incidence of rotavirus in children under 5 in the U.S.

Methods: A deterministic age-structured dynamic model with susceptible, infectious, and recovered compartments (SIR model) was used to represent rotavirus transmission. We estimated the reduction of rotavirus severe gastroenteritis cases by 2 doses of rotavirus vaccine with three vaccination scenarios: (scenario 1: 85% coverage by pediatricians and 45% coverage by family practitioners; scenario 2: 85% coverage by pediatricians and family practitioners; scenario 3: 95% coverage by pediatricians and family practitioners). Scenario 2 and scenario 3 were initiated in 2018. In addition, we tested the sensitivity of the model to the assumption of mixing patterns between children visiting pediatricians and children visiting family practitioners by setting contact within a group to be higher than contact between groups to depict an assortative mixing pattern.

Results: In this model, higher vaccine coverage provided by family practitioners and pediatricians leads to lower incidence of severe rotavirus cases including indirect vaccine benefits. One critical impact of higher total vaccine coverage is the effect on rotavirus epidemic patterns in the U.S.; the biennial rotavirus epidemic patterns shifted to reduced annual epidemic patterns. Additionally, assortative mixing patterns in children visiting pediatricians and family practitioners amplify the impact of increasing vaccine coverage.

Conclusion: Under these high vaccine coverage levels (>85%), our model predicted that biennial patterns shifted to annual patterns with lower magnitude of rotavirus incidence peaks. Promoting vaccine coverage targeting children visiting family practitioners will provide population level benefits (both direct and indirect effects) and significant reduction of severe rotavirus incidence in children under 5 years of age in the U.S.

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INTRODUCTION

Burden of rotavirus

Globally, rotavirus is the leading cause of severe diarrhea, hospitalization, and diarrheal related deaths in infants and children younger than 5 years of age [1]. In 2016, rotavirus caused approximately 128,500 deaths among children younger than 5 years of age, the majority of which occurred in sub-Saharan Africa [2]. Before the introduction of rotavirus vaccines in the United States (2006), rotavirus led to more than 200,000 emergency room visit, 55,000 to 70,000 hospitalizations, and 20 to 60 deaths in children younger than 5 years of age. The total direct and indirect costs due to rotavirus were approximately $1 billion [3].

Classification

Rotavirus consists of 11 segments of double-stranded RNA (dsRNA). The segments range in size from 667 base pairs to 3,302 base pairs. The total genome possesses approximately 18,522 base pairs. Mature virus is nonenveloped and has a multilayered icosahedral protein capsid. These viruses are approximately 75 nm in diameter and composed of an outer layer, an inner layer and a core. Rotaviruses are capable of genetic reassortment. There are six distinct groups (A to F) of virus; groups A, B, and C are known to infect humans. Group A is the main cause of severe diarrhea in infants. Group B usually causes severe diarrhea in adults. Group C has been found to cause severe diarrhea in infants sporadically. Group A consists of six major serotypes: VP1, VP2, VP3, VP4, VP6, and VP7. VP4 and VP7 are two outer capsid proteins (VP4 as P protein and VP7 as G protein) induce antibodies with neutralizing activity. VP4 is associated with virulence of the virus and VP7 mainly forms the outer surface. These two proteins

are used to classify rotaviruses and are critical to vaccine development [4, 5]. There have been at least 12 G types and 15 P types identified in human infections. These types can theoretically lead to about 200 different G and P combinations; however five strains are most commonly associated with 80 – 90 % of rotavirus disease in worldwide: G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8]. New serotypes such as G5, G8, and G12 strains have emerged in the recent years [6].

Natural History and Epidemiology

Symptoms of disease include watery diarrhea, vomiting and abdominal pain. Infants with severe rotavirus diarrhea could become dehydrated, and if not treated properly can lead to death [7, 8]. Children younger than 5 years old are the most vulnerable population to rotavirus, and children between 6 and 24 months have the greatest susceptibility [5, 9]. Rotavirus is transmitted via the fecal-oral route and close person-to person contact [5, 10]. Rotavirus shedding is highest immediately after infection and during the first three days of illness. The incubation period is approximately 24 – 74 hours [10, 11]. The duration of illness can last 3 to 8 days and duration of immunity is 6 – 12 months after the primary infection [12]. Most of children after three years of age have gained rotavirus antibodies [5]. Natural rotavirus infection provides incomplete protection against reinfection [13]. Maternal immunity protects infants younger than 3 months from severe diarrhea [5]. Protection against rotavirus infection by maternal immunity through breastfeeding and placenta is not observed in developed countries [14] but may have adverse influences on vaccine efficacy in developing countries [15, 16]. The risk of rotavirus infection declines with each subsequent rotavirus infection. Each new rotavirus infection can build up partial immunity and reduce the severity of diarrhea [17].

Prior to rotavirus vaccination, rotavirus disease showed a winter-spring seasonality and geographic patterns that begin in the west in December-January, extending across to the U.S. and ending in the northeast during April-May. In the post-vaccine era, the rotavirus season was shorter, delayed and of smaller magnitude compared to seasons in the pre-vaccine era, but a biennial pattern of rotavirus incidence emerged [18-20]. Incomplete vaccination coverage that leads to a build-up of susceptible children may be an important factor driving this biennial pattern [21]. Baker et al. showed that unvaccinated children drive the higher hospitalizations due to rotavirus in the biennial patterns [22].

Impact of Rotavirus Vaccine

There are four rotavirus vaccine licensed worldwide in over 125 countries and available in the private medical sector in many countries [6]. RotaTeq (RV5) (Merck & Co) and Rotarix (RV1)(GlaxoSmithKline Biologicals) are two licensed vaccines and have been used in the U.S. since 2006 and 2008, respectively [23]. RotaTeq is a live, attenuated vaccine containing 5 rotavirus strains - G1, G2, G3, G4, and P[8], and given in 3 doses at age 2 months, 4 months and 6 months [24]; Rotarix is a live, attenuated vaccine containing a single strain - G1P[8] which is given in 2 doses at age 2 months and 4 months [25]. Globally, rotavirus-related deaths and hospitalizations have significantly decreased due to the introduction of rotavirus vaccines. The vaccine prevented approximately 20% of deaths attributed to diarrhea among children younger than 5 years old in sub-Saharan Africa in 2016 [2]. In 2006 – 2009, approximately a 30% reduction of deaths attributed to diarrhea among children younger than one year old was observed in Latin American countries with rotavirus vaccine introduction [26]. Reduction of rotavirus hospitalizations in European counties were estimated to be 65 – 84% after introduction of

rotavirus vaccine [27]. Data from the National Respiratory and Enteric Virus Surveillance System (NREVSS) in the United Stated indicates that rotavirus incidence in the U.S. has declined between 57% - 89% since the introduction of vaccines in 2006 [18]. Rotavirus hospitalization rates have reduced between 70% - 98%, and all cause diarrhea-associated hospitalization rates declined between 9% - 76% in children under the age of 5 [28]. Rotavirus vaccines have also provided indirect benefits to unvaccinated individuals across the age range [22].

Since the introduction of vaccines, the prevalence of rotavirus genotypes has changed. Prior to introduction, the most common genotype of rotavirus was G1P[8], and other common genotypes (G2P[4], G3P[8], G9P[8]) varied over time [29]. Since vaccine introduction, types G9 and G12 have become prevalent in a number of developing countries. During 2009-2011, G12 emerged in several outbreaks in the U.S., which accounted for approximately 10% of all rotavirus infections [30]. In the 2009 - 2010 season, G3P[8] was the predominant genotype (with 46% - 68% prevalence) in the U.S. In 2012 - 2013, G12P[8] replaced G3P[8] became the most common genotype (70%) [31]. However, in countries without rotavirus vaccines, changes of rotavirus genotype prevalence as well as dominant genotypes have been observed [32]. Therefore, the question still remains as to whether the introduction of rotavirus vaccine induces a shift in the distribution of rotavirus genotypes.

Regarding the effect of rotavirus vaccination, a study showed the direct rotavirus vaccine effectiveness (i.e. biological protection of a vaccine) ranged from 87% to 92%, the indirect effect (i.e. protection that unvaccinated individuals receive in the presence versus absence of a vaccine program) varied from 14% to 82% and the total effect (i.e. the

combination of biological and indirect protection received by vaccine individuals) ranged from 91% to 98% between 2007 – 2010 [33].

Epidemiological Models

Dynamic transmission models are a useful tool to evaluate and quantify the direct and indirect effects of vaccination. Transmission models, or Susceptible-Infected-Recovered (SIR) models, use sets of differential equations to track the health and disease states of a population over time. Individuals flow from one compartment to another according to a set of parameters [34]. SIR models had been used to understand the impact of environmental and demographic factors on rotavirus infection [35, 36]. Many studies have used SIR models to simulate and project the impact of introducing rotavirus vaccine programs to inform policy decisions [37-40]. Rotavirus transmission models have been used to forecast the direct and indirect effectiveness of rotavirus vaccines [41], predict epidemiological patterns [42] and predict changes in the distribution of rotavirus strains due to introducing national rotavirus vaccine programs in different countries [43, 44]. In addition, SIR models are used to understand the reason for lower rotavirus vaccine efficacy in low socio-economic settings [45]. Furthermore, many studies combined SIR models with cost-effectiveness evaluations to predict potential benefits and inform decision making on introducing national vaccine program [46-49]. As a result, dynamic transmission models can assist decision-making and provide insight of the impact of vaccination on rotavirus transmission in populations over time by forecasting the vaccine-induced rotavirus epidemiological changes.

Rotavirus vaccination in the United States

Estimates from the National Immunization Survey in 2009 show that rotavirus vaccine coverage increased from 68.6% in 2012 to 74.1% in 2016 in U.S. children 19 - 35 months of age. However, rotavirus vaccine coverage is still lower than other routine childhood recommended vaccines (DTap≥3 doses: 95%, Poliovirus≥3 doses: 93.7%, MMR ≥1 doses: 91.1%, Heb≥3 doses: 90.5% in 2016) and below the Healthy People 2020 goal of 80% coverage [50, 51]. Rotavirus vaccination coverage has remained around 70 - 75% for several years (2013 to 2016) [50]. Though significant reductions of rotavirus incidence were observed shortly after vaccine introduction, the overall incidence rates of rotavirus have hovered around 10 and 34 per 10,000 person-years during 2007 - 2010. Therefore, to meet the Healthy People 2020 goal of 80% coverage and decrease further rotavirus disease and economic burden, promotion of rotavirus coverage needs to be considered.

Attitude to Rotavirus Vaccination

Health care providers play a critical role in promoting vaccines [52]. Pediatricians and family practitioners are two essential rotavirus vaccine providers in the U.S. Pediatricians have higher rates of routinely providing rotavirus vaccine to all eligible infants than family practitioners. Data from a survey of physicians recruited from the American Academy of Family Physicians (AAFP) and the American Academy of Pediatrics (AAP) in 2007 showed pediatricians routinely provided rotavirus vaccines 85% of the time while family practitioners provide rotavirus vaccines only 45% of the time [53]. One possible reason for this discrepancy could be that family physicians are more concerned about vaccine safety and the burden of adding additional vaccines to the childhood vaccination

schedule [53]. Family practitioners have historically expressed more concern about the safety of rotavirus vaccines than pediatricians after the temporary suspension of RV1 by the Food and Drug Administration. Additionally, pediatricians and family practitioners have different perceptions of rotavirus vaccine effectiveness [54].

This evidence suggests that education interventions about rotavirus vaccination should be considered for family practitioners to improve rotavirus vaccination rates. Family practitioners could play an essential role in increasing rotavirus vaccine coverage and could impact rotavirus incidence in the U.S. [55].

Our research aim is to adapt and use a dynamic transmission (SIR) model to assess the impact of rotavirus vaccine coverage provided by family practitioners versus pediatricians on the incidence and epidemiological patterns of rotavirus in children under 5 in the U.S. Our main hypothesis is that the incidence of rotavirus in the U.S. will decrease and epidemiological patterns will change if family practitioners provide higher rotavirus vaccine coverage. We used the statistical program R to adapt and analyze an existing transmission (SIR) model that incorporates probabilities that children under five receive vaccines either from pediatricians or family practitioners. With this model, we estimated the impact of higher rotavirus vaccine coverage provided by pediatricians or family practitioners on epidemiological patterns. In addition, we estimated the percent of severe rotavirus cases averted with increased vaccination coverage compared to present vaccination coverage in the U.S.

METHODS

Model design and model parameters

A deterministic age-structured dynamic model of rotavirus transmission with susceptible, infectious, and recovered compartments (SIR model) was used to represent rotavirus transmission and vaccination. The age structure includes 6 age groups: 0-1 month, 2 – 3 months, 4 – 11 months, 1 – 4 years, 5 – 24 years, and above 25 years. The full model equations are shown in Appendix. Individuals are born with maternal immunity which wanes at rate (e). Susceptible individuals are infected at a rate (λ) and enter the infectious compartment. Infected individuals either recover from infection and gain long-term immunity at rate (γ) or become susceptible to subsequent infections. Immunity wanes at rate (ω) and individuals become susceptible again. We also included a seasonal forcing term in our model (Appendix A).

Many parameters in our dynamic transmission model were informed by values from previous studies (Table 1). This model assumed individuals can have up to four rotavirus infections with decreasing probabilities of infection, disease and severe disease ($\varepsilon_{1\text{-}3}$) given the number of previous infections [17]. We assumed maternal immunity does not have an adverse effect on vaccine efficacy. In addition, we assumed only symptomatic individuals are infectious and primary infections contribute more to transmission than subsequent infections [56-59]. Only primary and secondary rotavirus infection were assumed to develop severe diarrhea. The proportion of symptomatic rotavirus infection in primary infection and subsequent infection, level of rotavirus infectiousness, and the proportion developing severe diarrhea in those symptomatic rotavirus infections are based on the Velazquez et al (1996) cohort study in Mexico [17]. Asymptomatic rotavirus infections were assumed not to be infectious. Additionally, we assumed primary

infection, secondary infection, tertiary infection, and quaternary infection have the same duration of infectiousness. Moreover, immunity was assumed to be "all or nothing;" some individuals develop long-term immunity while others become fully susceptible to the following infection.

We assumed the proportion of children visiting pediatricians was 84.4% while the proportion of children visiting family practitioners was 15.6% based on data from the MarketScan Research Dataset [60]. We separated children under one year of age into pediatrician and family practitioner groups in the model to predict the impact of different vaccine coverage in these two groups on rotavirus incidence and epidemiological patterns. In the model, children get the first dose vaccine at two months of age and second dose at four months of age. The birth rates were informed by data on the CDC Wonder database [61]. We assumed that the death rate equals the birth rate so that the total population remains constant. This model also assumed assortative contact structure between different age groups based on the POLYMOD study [62].

Parameters estimates

This model used age specific transmission parameters (q_{1-4}), seasonality parameters (A, θ) and a reporting rate that were previously estimated by using maximum likelihood to fit the model to data on monthly counts of severe rotavirus cases from the MarketScan Research Database. All analyses were conducted using the statistical program R version 1.1.423 [63], and the deSolve and foreach packages [64, 65]. We calibrated a parameter for rotavirus vaccine efficacy which allows us to capture biennial epidemic patterns (Table 1).

Vaccine scenario

The MarketScan Research Database showed rotavirus vaccine coverage among children whose provider were pediatricians was 85%, whereas rotavirus vaccine coverage among children whose provider were family practitioners was 45%. We estimated the reduction of rotavirus severe gastroenteritis cases by 2 doses of rotavirus vaccine with three vaccination scenarios: 85% coverage of the pediatrician population and 45% coverage of the family practitioner population, which is the present vaccine coverage (scenario 1); 85% coverage of the pediatrician population and 85% coverage of the family practitioner population, which is improved vaccine coverage among the family practitioner population (scenario 2); and 95% coverage of the pediatrician population and family practitioner populations, which is improved coverage among both populations (scenario 3). Scenario 2 and scenario 3 were initiated in 2018. We calculated the percent of severe rotavirus cases averted by comparing the rate of severe rotavirus cases in scenarios 2 and 3 to average rate of severe rotavirus cases in 2000 – 2006, prior to the introduction of vaccines, and each year from 2007 to 2030 in scenario 1. The percent of severe rotavirus cases averted for each vaccination scenario compared to current vaccine coverage and prior vaccine era was calculated by the following equation:

$$Percent\ averted = \frac{Rate\ of\ severe\ case_{Current} - Rate\ of\ severe\ case_k}{Rate\ of\ severe\ case_{Current}}$$

where k is the vaccine scenario (k=2, 3). The percent of severe rotavirus cases averted for each rotavirus vaccination scenario compared to prior vaccine era was calculated by the following equation:

$$Percent\ averted = \frac{Rate\ of\ severe\ case_{pre-vaccine} - Rate\ of\ severe\ case_i}{Rate\ of\ severe\ case_{pre-vaccine}}$$

where i is the vaccine scenario (i=1, 2, 3).

Sensitivity analysis to assumption of assortative mixing patterns between children visiting pediatricians and family practitioners

Initially we assumed random mixing patterns between children visiting pediatricians and family practitioners; however, it is possible that there is assortative mixing within these groups. Children within a group may have more contact with children in the same group and less contact with children in the other group. Therefore, we tested the sensitivity of the model to this assumption of mixing by setting contact within a group to be higher than contact between groups to depict an assortative mixing pattern. We assumed that 80% of contacts occur within a group and 20% of contacts occur between groups in assortative mixing patterns.

RESULTS

Severe rotavirus incidence cases reduction

Before rotavirus vaccine introduction, the model estimated that the average incidence of severe rotavirus cases was 327 per 10,000 between 2000 and 2006 (Table S1, Appendix B). The average incidence of severe rotavirus cases was 70 cases per 10,000 after vaccine introduction with scenario 1. Biennial patterns were captured with high peak years having around 80 cases and low peak years having around 65 cases per 10,000. In scenario 1, the incidence after 2018 was 78 cases per 10,000 in odd years and 70 cases per 10,000 in even years while in scenario 2 was 56 cases per 10,000 and scenario 3 was 32 cases per 10,000, representing a 71%, 83% and 90% decrease of severe rotavirus cases compared to the pre-vaccine era, respectively. Moreover, compared to the rate of severe rotavirus cases in scenario 1, the percent of severe rotavirus cases averted fluctuated between 21% and 26% in scenario 2 and between 54% and 58% in scenario 3.

Four-year average of severe rotavirus incidence reduction

The four-year average rates of severe rotavirus cases in scenario 1, scenario 2, and scenario 3 were 75, 57, and 33 per 10,000 people, respectively (Table 2). The four-year average percent of severe rotavirus averted for new vaccine coverage strategies was 23% for scenario 2 and 57% for scenario 3 compared to scenario 1.

Epidemic patterns shift

The model predicted that rotavirus epidemic patterns shift from biennial epidemic patterns to reduced annual epidemic patterns after 2018. This model reproduced the patterns of winter seasonality and biennial epidemic patterns for severe rotavirus cases

after rotavirus vaccination introduction in the U.S. In the pre-vaccine years, the peak of monthly number of severe rotavirus cases was around 3200 and troughs were around 700, and had annual seasonal pattern with a sharp peak during winter (Figure 1). Most importantly, the biennial patterns in 85% and 95% vaccine coverage disappeared and annual epidemic patterns returned.

Indirect benefits of improved rotavirus vaccine coverage in family practitioner population

In children 0 - 11 months old, the model estimated the percent of severe rotavirus cases averted for new vaccine coverage strategies were 23% in the pediatrician population and 37% in the family practitioner for scenario 2 compared to scenario 1 (Table S3, Appendix B). The percent of severe rotavirus cases averted in the pediatrician population after 2018 compared to the pre-vaccine era was 85% in scenario 1 and 89% in scenario 2. Since there is no improved vaccine coverage in the pediatrician population in scenario 2, this additional 4% of severe cases averted in pediatrician population are indirect benefits of improved vaccine coverage from family practitioner population.

Sensitivity to assumptions about mixing patterns of children visiting pediatricians and family practitioners

In the sensitivity analysis (Table S2, Appendix B) assuming assortative mixing patterns with 80% of contacts occurring within a group and 20% of contacts occurring between groups, the average percent of severe rotavirus averted in scenario 2 was 83% compared to pre-vaccine era and 29% compared to scenario 1 after 2018. The average percent of

severe rotavirus averted in scenario 3 was 90% compared to the pre-vaccine era and was 58% compared to scenario 1 after 2018. These impacts were slightly higher than the impacts with the random mixing assumption (Table S2, Appendix B). Moreover, assortative mixing patterns in scenario 1 resulted in an increase of 5 per 10,000 population of the four-year average severe rotavirus incidence relative to severe rotavirus incidence with random mixing patterns. Assortative mixing patterns resulted in around 5% higher four-year average percent of severe rotavirus cases averted in scenario 2 and scenario 3 compared to scenario 1 than the random mixing patterns (Table 3). Scenario 2 and scenario 3 had on average 30% and 60% of severe rotavirus cases averted compared to scenario 1 under the assortative mixing assumption. Comparing epidemic patterns between random mixing patterns and assortative mixing patterns, there were obvious fluctuations scenario 2 for 3 years and lower rates of severe rotavirus cases in the honeymoon period after 2018 in assortative mixing patterns (Figure 2). Daily severe rotavirus cases became stable a few years after new vaccine coverage strategies in 2018.

DISCUSSION

In this model, higher vaccine coverage provided by family practitioners and pediatricians leads to lower incidence of severe rotavirus cases including indirect vaccine benefits. One critical impact of higher total vaccine coverage is the effect on rotavirus epidemic patterns in the U.S.; biennial rotavirus epidemic patterns shift to reduced annual epidemic patterns. Additionally, assortative mixing patterns in children visiting pediatricians and family practitioners amplify the impact of increasing vaccine coverage.

To compare the value of severe rotavirus cases predicted by our model to literatures using Marketscan dataset, we multiplied the value of severe rotavirus cases in the model by the reporting rate to get the hospitalization rate. The hospitalization rate under five years of age in our model were similar to the rate of rotavirus-coded diarrhea hospitalization in high peak years while higher in low peak years than the hospitalization rate in literatures using Marketscan dataset [28, 66]. That is, the magnitude of the cases difference between high peak year and low peak years in the biennial epidemic patterns was not obvious as the surveillance result.

The results from this model are consistent with to what has been predicted with previously published rotavirus transmission models; high rotavirus vaccine coverage (>85%) predicted reductions of annual severe rotavirus incidence by 56% [39], 70% [37, 38], 84% [40] for children under five years of age, compared to pre-vaccination levels in different model studies. One modeling study in Germany [40] predicted no rotavirus biennial epidemic patterns after high national rotavirus vaccine coverage (90%). However, other models had different predicted effects on rotavirus epidemic patterns after high national rotavirus vaccine coverage (90%) [37, 38, 41]. These models predicted biennial epidemic patterns in medium vaccine coverage (70%) and elimination of

rotavirus at 90% coverage, whereas other models predicted potential biennial epidemic patterns with 90% vaccine coverage. Differences in the assumptions and parameters of these models may explain the different predictions for epidemic patterns. For example, in our model we assumed vaccines and natural infection induce partial immunity (i.e. subsequent infection at reduced rate) that wanes after 44 years. The models from Pitzer et al.'s study that predicted high vaccine coverage with biennial patterns assumed one-year duration of complete immunity after previous infection, and partial immunity when individuals are susceptible [41]. In addition, those models assumed life-long immunity to symptomatic infection with waning immunity. Moreover, our model fit to data from the U.S. whereas other rotavirus models were fit to rotavirus data from England and Wales. Differences in demographic conditions between the U.S. and England and Wales may also partly explain the differences in these results.

The emergence of biennial epidemic patterns of rotavirus incidence in the U.S. after the introduction of a national vaccine programs may be driven by modest vaccine coverage. Other developed countries with high coverage of rotavirus vaccination (>85%), such as Belgium, Austria, Australia, Finland, and Germany, did not have the biennial epidemic patterns after the introduction of vaccines [67-71]. Our model predicted that rotavirus incidence shifted from a biennial pattern to an annual pattern when vaccine coverage reached 85%. Thus promoting rotavirus vaccination in children visiting family practitioners lowers disease incidence rates and results in a shift from biennial to annual epidemic patterns. Higher vaccination coverage leads to lower susceptible population compared to the susceptible population in current vaccine coverage. Therefore, the slower accumulation of susceptible children over two successive birth cohorts that induces biennial patterns may not happen. Shah et al. found that increased rotavirus

vaccine coverage in the U.S. may change the rotavirus epidemiological patterns since the biennial epidemic patterns may be driven by incomplete vaccination [21]. The shift of epidemic patterns from biennial patterns to reduced annual patterns may benefit the public health preparedness since there is no need for health care facility to face variable burden of rotavirus-related hospitalization in alternating years.

Our model predicted assortative mixing patterns in children visiting pediatricians and family practitioners had higher impact of increasing vaccine coverage on severe rotavirus incidence and higher severe rotavirus incidence in scenario 1 than random mixing patterns had. Our model had higher force of infection in assortative mixing patterns than that in random mixing patterns that may explain the phenomenon above. Effelterre et al. showed that the estimated value for basic reproductive number (R_0) of rotavirus is higher if mixing patterns are assumed to be assortative in rotavirus related gastroenteritis (RV-GE) models. However, this study showed that reduction in any grade of severity RV-GE incidence in children under 5 years of age after vaccination is higher when the assortative mixing is lower, which is contradictory to our results [72]. One potential reason for this contradictory result is that Effelterre et al. focused on the reduction of any grade of severity RV-GE but our study focused on the reduction of severe RV-GE. This difference influences the vaccine impact on the reduction of RV-GE since rotavirus vaccines have better efficacy against severe rotavirus disease [28, 73, 74]. In their study, Choe and Lee indicated that the higher degree of assortative mixing had higher R_0 than random mixing. Furthermore, after treatment introduction, disease incidence decreased faster with lower incidence over time in higher degree of assortative mixing [75]. We have no data to inform mixing patterns the pediatrician and family population group. Under with scenario, promoting vaccine coverage rates in children visiting family practitioners can

have significant impacts on reducing severe rotavirus incidence in children younger than 5 years of age in the U.S. based on our model. Future rotavirus vaccine promotion strategies in the U.S. can concentrate on children visiting family practitioners.

Our model had several limitations. First, though we took the assortative contact patterns for children visiting pediatricians and family practitioners into account, there currently are no data that describe the true assortative contact patterns within and between patients who attend physician groups. Furthermore, the assortative contact structure between different age groups used in this model is based on the POLYMOD study, which is a population-based contact survey in Europe. This may not accurately represent the contact structure in the U.S. Future studies of social contacts and mixing patterns regarding the spread of infectious diseases in the U.S. are needed to inform more accurate parameters and model predictions. Second, some of the parameters in our model were estimated and calibrated from model fitting rather than based on evidence-based research. For example, we calibrated the vaccine effectiveness to capture the rotavirus biennial epidemic patterns and estimated the duration of immunity induced by vaccine. However, most of the rotavirus natural history parameters in our model were based on Velazquez et al, which was widely used in other rotavirus transmission dynamic models. Last, we used a model that was fitted to a commercial insurance dataset. While this database covers most states, it may not be representative of the whole U.S. population. For example, children who fall under the coverage of Medicaid, may have lower childhood vaccination coverage and higher incidence of rotavirus than the children represented in the MarketScan commercial insurance database [50].

In conclusion, we used a dynamic transmission model to predict the impact of higher rotavirus vaccine coverage provided specifically by family practitioners. This model

predicted reductions of severe rotavirus cases compared to pre-vaccine era and present vaccine coverage if vaccine coverage provided by family practitioners increased from 45% to 85% and both vaccine providers increased vaccine coverage to 95%. Under these high vaccine coverage levels, our model predicted that biennial patterns shifted to annual patterns with lower magnitude of rotavirus incidence peaks. Promoting vaccine coverage targeting children visiting family practitioners will have more indirect vaccine benefits and significant reduction of severe rotavirus incidence in children younger than 5 years of age in the U.S.

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TABLES

Table 1. Natural history, demographic and estimated parameter values used in epidemiological model.

Parameter	Symbol	Parameter value	Description	Reference
Transmission probability	q_i	$q_1 = 0.9998$ $q_2 = 0.4494$ $q_3 = 0.0472$ $q_4 = 0.0019$	Probability of transmission per contact. q= 1…4 represent age group <1 year, 1-4 years; 5-24 years, > 25 years, respectively	Estimated
Seasonal transmission amplitude	*A*	0.0866	Proportion change in disease incidence	Estimated
Seasonal offset	θ	0.4942		Estimated
Reporting rate	δ	0.0538	Probability that severe rotavirus case is reported	Estimated
Vaccine Efficacy	ψ	0.5		Calibrated
Daily rate of loss of immunity	ω	1/21,154	Rate at which immune individuals become re-susceptible infection	Atchison 2010
Daily rate of loss of maternal immunity	e	1/90	Maternal immunity against rotavirus infection wane at a constant rate on average 90 days	Linhares, 1989
Daily rate of loss of infection	γ	1/5	Symptoms last 2-7 days but on average 5 days	Heymann, 2015
Risk of infection after previous infection	ε_i	ε_1=0.62 ε_2=0.37 ε_3=0.37	After first infection After second infection After third infection	Velazquez et al., 1996
Proportion of symptomatic infection in nth infection	α_i	α_1=0.47 α_2=0.25 α_3=0.32 α_4=0.20	At first infection At second infection At third infection At fourth infection	Velazquez et al., 1996
Proportion of symptomatic infection associated with severe disease at nth infection	σ_i	σ_1=0.28 σ_2=0.19	At first infection At second infection	Velazquez et al., 1996
Level of infectiousness after primary infection	r	r=0.25		Velazquez et al., 1996
Daily aging rates for age group j	a_j	a_1=1/60 a_2=1/120	*j*=1...4 represent age group 0-3 months, 4-11	

		a_3=1/365 a_4=1/7,300	months, 1-4 years, and 5-24 years, respectively	
Counts of total contacts	c_i	c_1=5.43 c_2=8.56 c_3=15.65 c_4=14.16	Counts for age <1 year Counts for age 1-4 years Counts for age 5-24 years Counts for age >25 years	Mossong et al., 2008
Birth rate (Daily)	μ	1/30,827.7	U.S. 2017 birth rate	CDC Wonder

Table 2. Four-year average incidence rates and percent of severe rotavirus cases averted in new vaccination strategies assuming random mixing patterns between children visiting pediatricians and family practitioners.

Four-year average rate of severe rotavirus cases per 10,000	**78.6% vaccine coverage [a]**	**85% vaccine coverage [b]**	**95% vaccine coverage [c]**
2018-2021	73	57	35
2022-2025	74	56	32
2026-2029	74	57	33
Four-year average percent of severe rotavirus cases averted compared to 78.6% coverage			
2018-2021		23%	52%
2022-2025		24%	57%
2026-2029		23%	56%

a. 85% vaccination coverage for children visiting pediatricians and 45% for children visiting family practitioners (total 78.6% current vaccination coverage).
b. 85% vaccination coverage for children visiting pediatricians and family practitioners.
c. 95%vacccination coverage for children visiting pediatricians and family practitioners.

Table 3. Four-year average incidence rates and percent of severe rotavirus cases averted in new vaccination strategies with assortative mixing patterns assuming 80% of contacts occur within a group and 20% of contacts occur between groups.

Four-year average rate of severe rotavirus cases per 10,000	**78.6% vaccine coverage [a]**	**85% vaccine coverage [b]**	**95% vaccine coverage [c]**
2018-2021	78	55	34
2022-2025	79	57	31
2026-2029	79	57	33
Four-year average percent severe rotavirus cases averted compared to 78.6% coverage			
2018-2021		30%	56%
2022-2025		28%	60%
2026-2029		28%	58%

a. 85% vaccination coverage for children visiting pediatricians and 45% for children visiting family practitioners (total 78.6% current vaccination coverage total 78.6%).
b. 85% vaccination coverage for children visiting pediatricians and family practitioners.
c. 95%vacccination coverage for children visiting pediatricians and family practitioners.

FIGURES

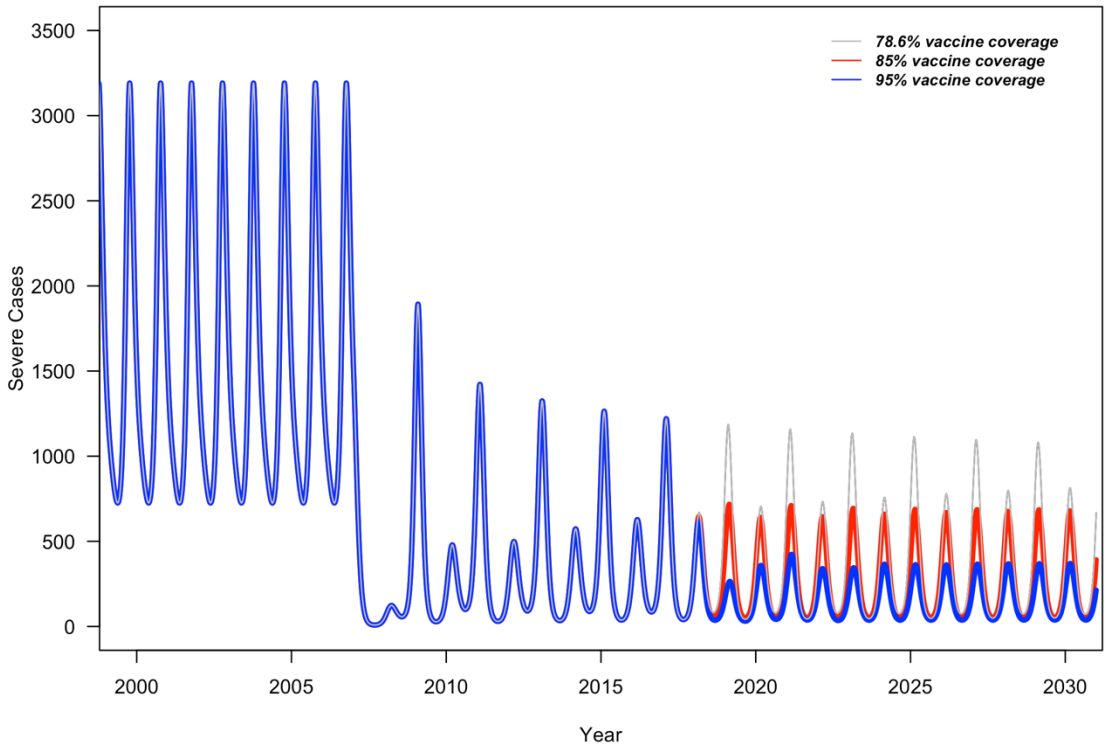

Figure 1. Monthly number of severe rotavirus cases in children under 5 years of age with 78.6% (grey), 85% (red), and 95% (blue) vaccine coverage assuming random mixing patterns between children visiting pediatricians and family practitioners.

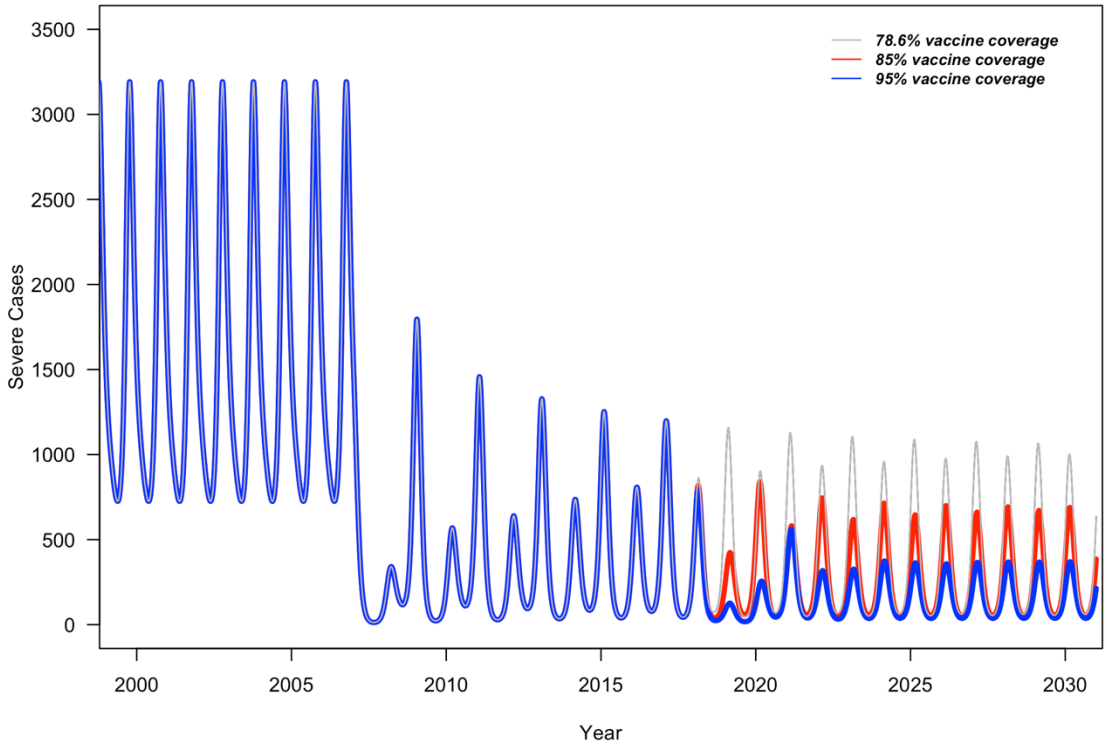

Figure 2. Monthly number of severe rotavirus cases in children under 5 years of age with 78.6% (grey), 85% (red), and 95% (blue) vaccine coverage with assortative mixing patterns assuming 80% of contacts occur within a group and 20% of contacts occur between groups.

APPENDECES

Appendix A:

Our model is a system of ordinary differential equations, the full model equations are:

$$\frac{dS_{ni}}{dt} = \varepsilon_{(n-1)}\gamma I_{(n-1)i} - \lambda_i S_{ni} - \delta S_{ni} + \delta S_{n(i-1)} \ldots\ldots n = 1 - 3$$

$$\frac{dS_{4i}}{dt} = \omega R_i + \varepsilon_3 \gamma I_{(3)i} - \lambda_i S_{ni} - \delta S_{ni} + \delta S_{n(i-1)}$$

$$\frac{dI_{ni}}{dt} = \lambda_i S_{ni} - \gamma I_{ni} + \delta I_{ni} + \delta I_{n(i-1)} \ldots\ldots n = 1 - 4$$

$$\frac{dR_{ni}}{dt} = \sum_n \left((1 - \varepsilon_n)\gamma I_{ni}\right) + \gamma I_{4i} - \omega R_i - \delta R_i + \delta R_{(n-i)} \ldots\ldots n = 1 - 3$$

where:

i = 1 … 6 represent age groups 0 – 1 month, 2 – 3 months, 4 – 11 months, 1 – 4 years, 5 – 24 years, and above 25 years, respectively.

S_{ni} = susceptible to nth rotavirus infection (n =1-4) in age group i

I_{ni} =infected by nth rotavirus infection (n = 1-4) in age group i

R_i = recovered and immune to rotavirus infection in age group i

δ = rate at which individuals in age group i age into age group (i +1)

γ = rate of loss of infection

ω= rate of loss of immunity

ε_n = risk of becoming re-susceptible after nth rotavirus infections

λ_i= force of infection; rate at which susceptible individuals become infected in age group i

Susceptible individuals are infected at a rate (λ) and enter the infectious compartment. Infected individuals either recover from infection at rate (γ) or become susceptible to subsequent infections. Immunity wanes at rate (ω) and individuals become susceptible again. This model assumes individuals can have up to four rotavirus infections with

decreasing probabilities of infection, disease and severe disease ($\varepsilon_{1\text{-}3}$) given the number of previous infections [14].

The force of infection was calculated as:

$$\lambda_j(t) = \beta_{(t)} c_j \sum_{j=1}^{4} s_{jk} \left(\frac{I_{nj}}{N_j} \right)$$

where:

j = k = 1 … 4 represent contact patterns in age group 0 – 1 year, 1 – 4 years, 5 – 25 years, and above 25 years, respectively.

c_j= Count of total contacts in each age group

s_{jk}= proportion of contact between group j and *k* (*j*=1-4, *k*=1-4)

I_{nj}= infected by nth rotavirus infection (*n* = 1-4) in contact patterns *j*

N_j=Total population in contact pattern *j*

We modeled seasonal variation of rotavirus transmission $\beta(t)$:

$$\beta(t) = q_l(1 + A \cos(2\pi t + \theta))$$

where q_l represents probability of transmission per contact from children in age group *l*, A is the amplitude of the seasonal fluctuation and θ is the phase angle in years (t).

l=1…4 represent age group <1 year, 1 – 4 years, 5 – 24 years, > 25 years, respectively.

Appendix B:

Table S1. Rate of severe rotavirus cases (per 10,000) and percent of severe cases averted for each rotavirus vaccination scenario in 2000 to 2030 assuming random mixing patterns between children visiting pediatricians and family practitioners.

Year	78.6% vaccine coverage [a]	85% vaccine coverage [b]			95% vaccine coverage [c]		
	Rate	Rate	Percent Averted compared to 2000-2006	Percent Averted compared to 78.6% coverage	Rate	Percent Averted compared to 2000-2006	Percent Averted compared to 78.6% coverage
2000 – 2006 average	327	327			327		
2007	50	50	85%		50	85%	
2008	40	40	88%		40	88%	
2009	100	100	69%		100	69%	
2010	65	65	80%		65	80%	
2011	82	82	75%		82	75%	
2012	62	62	81%		62	81%	
2013	80	80	75%		80	75%	
2014	65	65	80%		65	80%	
2015	79	79	76%		79	76%	
2016	67	67	80%		67	80%	
2017	79	79	76%		79	76%	
2018	68	56	83%	17%	46	86%	32%
2019	78	58	82%	26%	25	92%	68%
2020	69	55	83%	20%	33	90%	51%
2021	78	57	82%	26%	36	89%	54%
2022	70	55	83%	21%	30	91%	56%
2023	77	57	83%	26%	31	90%	60%
2024	70	56	83%	21%	32	90%	54%
2025	77	57	83%	26%	32	90%	58%
2026	71	56	83%	21%	32	90%	54%
2027	77	57	83%	26%	32	90%	57%
2028	71	56	83%	21%	33	90%	54%
2029	77	57	83%	26%	33	90%	57%
2030	72	57	83%	21%	33	90%	54%

a. 85% vaccination coverage for children visiting pediatricians and 45% for children visiting family practitioners (total 78.6% current vaccination coverage).
b. 85% vaccination coverage for children visiting pediatricians and family practitioners.
c. 95% vaccination coverage for children visiting pediatricians and family practitioners.

Table S2. Rate of severe rotavirus cases (per 10,000) and percent of severe cases averted for each rotavirus vaccination scenario in 2000 to 2030 with assortative mixing patterns assuming 80% of contacts occur within a group and 20% of contacts occur between groups.

Year	78.6% vaccine coverage [a]	85% vaccine coverage [b]			95% vaccine coverage [c]		
	Rate	Rate	Percent Averted compared to 2000-2006	Percent Averted compared to 78.6% coverage	Rate	Percent Averted compared to 2000-2006	Percent Averted compared to 78.6% coverage
2000 – 2006 average	326	326			326		
2007	51	51	84%		51	84%	
2008	68	68	78%		68	78%	
2009	91	91	73%		91	73%	
2010	65	65	77%		65	77%	
2011	83	83	75%		83	75%	
2012	65	65	78%		65	78%	
2013	81	81	75%		81	75%	
2014	68	68	77%		68	77%	
2015	79	79	76%		79	76%	
2016	70	70	77%		70	77%	
2017	79	79	76%		79	76%	
2018	71	53	82%	23%	46	84%	33%
2019	78	45	86%	44%	15	96%	84%
2020	72	60	81%	18%	27	91%	62%
2021	78	51	84%	33%	40	86%	44%
2022	73	55	82%	24%	28	91%	63%
2023	78	53	83%	32%	27	91%	62%
2024	73	54	82%	25%	30	90%	57%
2025	77	54	83%	30%	31	90%	59%
2026	74	54	82%	26%	30	90%	59%
2027	77	54	83%	29%	30	90%	58%
2028	74	54	82%	27%	31	90%	58%
2029	77	54	83%	28%	31	90%	58%
2030	75	54	83%	27%	31	90%	58%

a. 85% vaccination coverage for children visiting pediatricians and 45% for children visiting family practitioners (total 78.6% current vaccination coverage).
b. 85% vaccination coverage for children visiting pediatricians and family practitioners.
c. 95%vacccination coverage for children visiting pediatricians and family practitioners.

Table S3. Children 0 – 11 months old percent of severe rotavirus cases averted in post-vaccine era and new vaccine scenario after 2018 in pediatrician and family practitioner populations assuming random mixing patterns between children visiting pediatricians and family practitioners.

	78.6% vaccine coverage [a]		85% vaccine coverage [b]	
Average rate of severe rotavirus cases per 10,000	**Pediatricians**	**Family practitioners**	**Pediatricians**	**Family practitioners**
2000-2006	993	993	993	993
2010-2017	143	176	143	176
2018-2029	148	182	114	115
2018 – 2029 average percent of averted severe rotavirus cases compared to 78.6% coverage	--	--	23%	37%
2018 – 2029 average percentage averted severe rotavirus cases compared to 2000 – 2006	85%	82%	89%	88%
Additional percentage averted from improved vaccine coverage in family practitioner group	--	--	4%	--

a. 85% vaccination coverage for children visiting pediatricians and 45% for children visiting family practitioners (total 78.6% current vaccination coverage total 78.6%).

b. 85% vaccination coverage for children visiting pediatricians and family practitioners (0% improved vaccine coverage in pediatrician population, 45% improved vaccine coverage in family practitioner population).