

EPIDEMIOLOGY

Surveillance data confirm multiyear predictions of rotavirus dynamics in New York City

Donald R. Olson^{1*}, Benjamin A. Lopman^{2,3}, Kevin J. Konty¹, Robert W. Mathes¹, Vikki Papadouka¹, Alexandra Ternier¹, Jane R. Zucker^{1,2}, Lone Simonsen^{4,5†}, Bryan T. Grenfell⁶, Virginia E. Pitzer^{7*}

Prediction skill is a key test of models for epidemic dynamics. However, future validation of models against out-of-sample data is rare, partly because of a lack of timely surveillance data. We address this gap by analyzing the response of rotavirus dynamics to infant vaccination. Syndromic surveillance of emergency department visits for diarrhea in New York City reveals a marked decline in diarrheal incidence among infants and young children, in line with data on rotavirus-coded hospitalizations and laboratory-confirmed cases, and a shift from annual to biennial epidemics increasingly affecting older children and adults. A published mechanistic model qualitatively predicted these patterns more than 2 years in advance. Future efforts to increase vaccination coverage may disrupt these patterns and lead to further declines in the incidence of rotavirus-attributable gastroenteritis.

INTRODUCTION

Before vaccine licensure in 2006, rotavirus-associated gastroenteritis (RVGE) was estimated to cause more than 500,000 outpatient visits and 60,000 hospitalizations annually in the United States (1), with epidemics occurring every year beginning in the southwestern states in November to January and peaking in northeastern states in March and April (2, 3). Since 2008, observational studies have shown significant declines in rotavirus-related outpatient clinical and emergency department (ED) visits and inpatient hospitalizations in the United States, with evidence of both direct and indirect protection of children and adults (4–7). Delays in the timing of peak rotavirus activity and the emergence of an every-other-year (biennial) pattern of epidemics have also been described (8). Mathematical models previously linked the prevaccination pattern of epidemics to underlying variation in birth rates across states and predicted that vaccination would lead to a delay in the timing of rotavirus activity in the second year following vaccine introduction as well as a shift to biennial epidemics when coverage with a full vaccine course reached 70 to 80% (9). These predictions were made years before the emergence of biennial epidemics, providing an unprecedented example of the potential predictability of infectious disease dynamics.

Mechanistic models of infectious disease dynamics are often developed with the goal of predicting the future trends in incidence, but thus far, most predictions have been limited to forecasting incidence on the order of weeks to months (10–12), and notable failures have occurred, particularly for emerging pathogens (13, 14). In principle, multiyear predictions should be possible for communicable diseases because—unlike the atmospheric conditions that determine weather, for example—there is often just one dynamic nonlinearity

(the feedback between infectious and susceptible individuals). However, environmental and demographic stochasticity, evolution, and behavioral change in response to infectious disease threats can greatly complicate the predictive ability of models (15). Furthermore, even if the disease dynamics are potentially predictable, the lack of appropriate and timely surveillance data can inhibit our ability to train models and test predictions in a meaningful way.

The availability of multiple complementary data sources from New York City, including data on vaccine coverage, rotavirus-coded hospitalizations, laboratory-reported cases, and ED visits for syndromic diarrhea, provides a unique opportunity to monitor changes in the underlying epidemiology of rotavirus. Here, we validate previous mathematical model predictions while evaluating the use of syndromic surveillance—which is available in near real time—to assess the impact of rotavirus vaccination (16, 17) and examine strategies to further mitigate the burden of RVGE.

RESULTS

Before vaccine introduction (2002–2006), rotavirus-coded hospitalizations in New York City were elevated each winter, with epidemics typically beginning in January, peaking in March, and declining by May (Fig. 1), consistent with national data on laboratory-confirmed rotavirus (18). The number of hospitalizations began to decrease in 2008, and from 2010 to 2016, the overall number remained well below levels observed during the prevaccine period (Fig. 1 and table S1). The number of laboratory-reported cases was highly correlated with the hospitalization data for the period following the beginning of mandated reporting in 2008 [correlation coefficient (r) = 0.76, $P < 1 \times 10^{-20}$]. Both rotavirus-coded hospitalizations and laboratory-reported cases showed a biennial pattern of odd-year increases beginning in 2011, with limited sporadic reports in even years starting in 2012 (Fig. 1). The age distribution of rotavirus-coded hospitalizations and laboratory-reported cases shifted from occurring predominantly among young children during the prevaccine period to a more equal proportion occurring among older children and adults in the postvaccine years (table S1). In 2015, 15% of hospitalizations and 39% of laboratory-confirmed cases occurred among children and adults ≥ 5 years of age, compared to only 3.7% of

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¹New York City Department of Health and Mental Hygiene, New York City, NY, USA.

²Centers for Disease Control and Prevention, Atlanta, GA, USA. ³Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA.

⁴Department of Science and Environment, Roskilde University, Roskilde, Denmark.

⁵Department of Global Health, George Washington University, Washington, DC, USA. ⁶Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ, USA. ⁷Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA.

*Corresponding author. Email: dolson@health.nyc.gov (D.R.O.); virginia.pitzer@yale.edu (V.E.P.)†Present address: Department of Science and Environment, Roskilde University, Denmark.

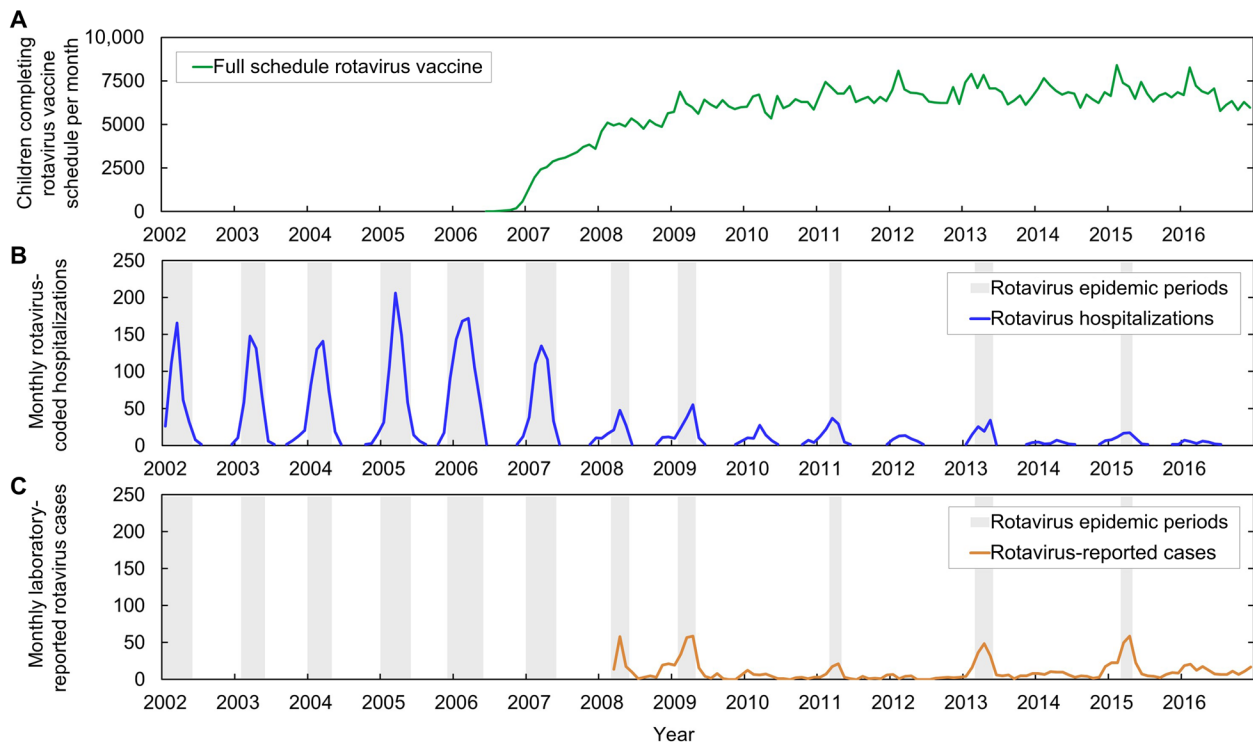


Fig. 1. Vaccination registry, rotavirus hospitalization, and laboratory-reported case data in New York City, January 2002 through December 2016. (A) Monthly counts of children age 8 months to <2 years receiving the complete series of rotavirus vaccine as recorded in the Citywide Immunization Registry (CIR) are shown in green. (B) Monthly counts of rotavirus-coded inpatient hospitalizations from January 2002 through December 2016 are shown in blue, and (C) notifiable laboratory-reported cases from February 2008 through December 2016 are shown in yellow. Epidemic rotavirus periods are shaded in gray and are identified as months, in which both the number of rotavirus-coded hospitalizations and laboratory-reported cases met or exceeded their respective upper quartile of cases observed over the entire period of available data.

hospitalized cases reported in this age group before vaccine introduction (table S1).

Diarrheal syndrome ED visits during the prevaccine period were elevated each winter and spring, coincident with the timing of rotavirus activity, particularly among children <5 years of age (Fig. 2). The timing and magnitude of diarrheal syndrome ED visit increases shifted in 2008 and 2009, with winter season peaks occurring before periods of confirmed rotavirus circulation, and with a lesser magnitude during the rotavirus epidemic periods (Fig. 2). After 2010, diarrheal syndrome ED visits remained consistently reduced by >90% compared to prevaccine levels among children <2 years of age; more modest declines were observed among 2- to 4-year-olds (Table 1 and Fig. 2). In contrast, the timing and magnitude of rotavirus epidemic period increases among children ages 5 to 12 years were higher compared to prevaccine levels, most notably during peak rotavirus circulation periods in 2013 and 2015, when excess diarrheal ED visits were, respectively, 1.81 and 2.36 times greater than the average prevaccine level (Table 1 and Fig. 2).

A previously developed rotavirus transmission model fit to statewide monthly rotavirus-coded hospitalizations from 1993 to 2004 predicted strongly seasonal winter epidemics occurring each year during the prevaccination period (Fig. 3) (9). Model predictions varied depending on assumptions about the relative efficacy of an incomplete vaccine course (fig. S1); the closest match to the observed laboratory surveillance data was obtained when we assumed a relative efficacy of 88% (fig. S2). However, models did a better job of capturing the annual seasonal incidence in 2008–2010 at lower

values of the relative efficacy (fig. S1), which we hypothesize may be related to the increase in the proportion of infants completing the vaccine series (fig. S3). Following vaccine introduction, the calibrated model predicted that the incidence of rotavirus would remain high in 2007 (when vaccine coverage was <50%) and then exhibit a reduced and delayed peak in 2008, which was predicted to extend through the summer and fall months and into 2009 (Fig. 3). Beginning in 2010–2011, the model predicted the emergence of a biennial pattern of epidemics occurring in odd years. While the incidence of severe RVGE was predicted to remain substantially reduced in <2- and 2- to 4-year-olds, the model predicted that peak rotavirus incidence among ≥ 5 -year-olds in 2013 and 2015 would exceed the prevaccination seasonal peaks in incidence (Fig. 3). The model was also able to predict the shift in the age distribution of cases (fig. S4).

Increasing vaccine coverage with a full series of rotavirus vaccine to 93.2%, comparable to coverage with diphtheria-tetanus-acellular pertussis (DTaP) vaccine, was predicted to reduce the future incidence of RVGE (Fig. 3). The timing of the increase in coverage affected the pattern of epidemics predicted by the model, leading to either progressively smaller odd-year biennial epidemics or a gradual return to annual epidemics (Fig. 3).

DISCUSSION

The implementation of routine immunization against rotavirus in the United States has led to substantial changes in the epidemiology of RVGE, including the emergence of odd-year epidemics and the

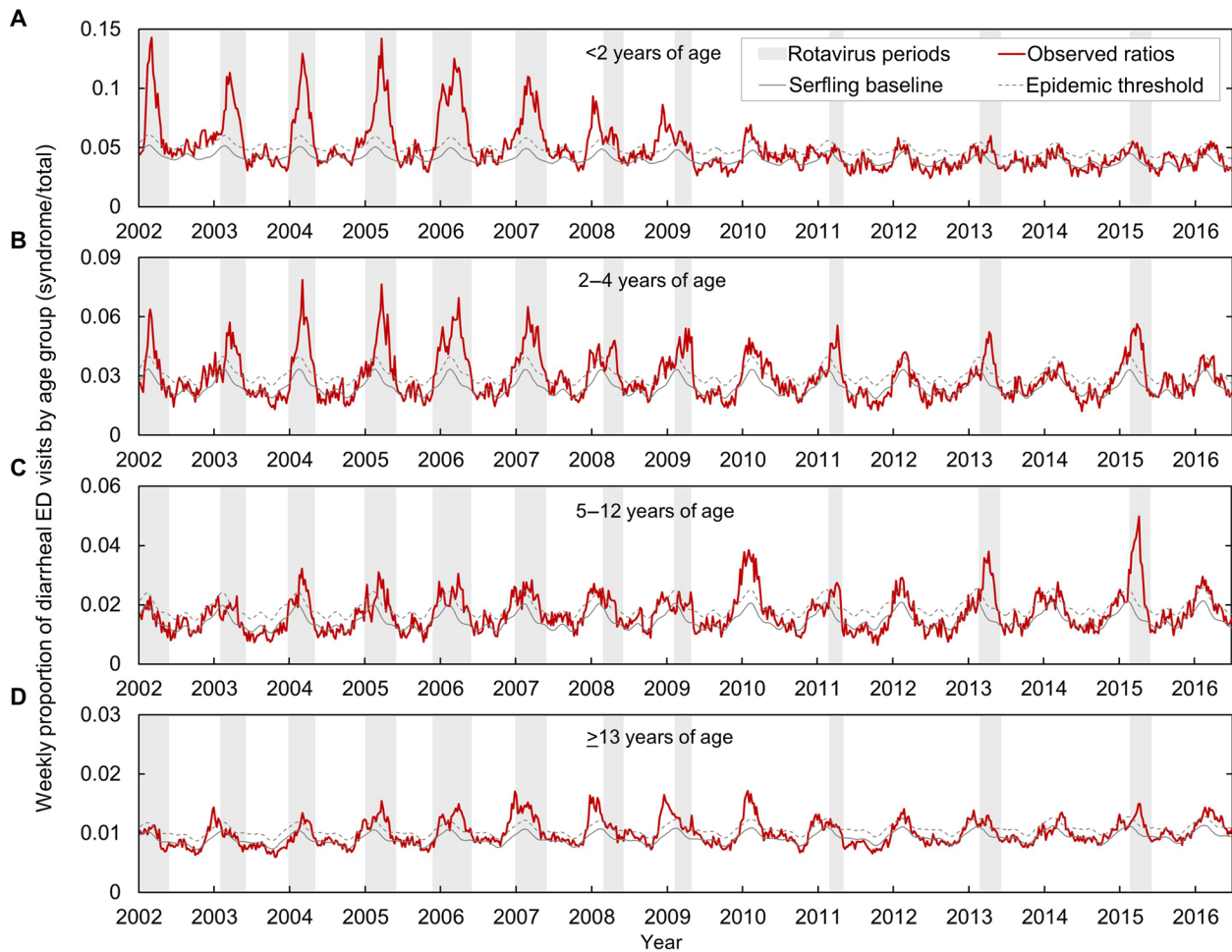


Fig. 2. Weekly diarrheal syndrome ED visit proportions by age group, January 2002 through June 2016 in New York City. Weekly percentage of diarrheal syndrome ED visits are shown (red lines) with periodic regression baseline expected percentages (gray lines) with 95% threshold levels (dashed lines) by age group: (A) <2, (B) 2 to 4, (C) 5 to 12, and (D) ≥13 years. Epidemic rotavirus periods are shaded in gray, as identified on the basis of rotavirus-coded hospitalization and laboratory-reported data.

Table 1. Seasonal excess ED diarrheal syndrome visits in New York City, 2003–2016. Average seasonal rotavirus epidemic period excess ED diarrheal visit rates per 10,000 population (per age group) are shown by age group and for all ages for the prevaccine period 2003–2006. Seasonal rotavirus epidemic period excess ED diarrheal visit rates are given for each year, excluding 2010, 2012, and 2014, when only low-level or sporadic rotavirus circulation was detected without sustained rotavirus epidemic periods. Seasonal prevaccine excess ED diarrheal syndrome visit rate ratios are calculated (in parentheses) as the diarrheal syndrome excess ED visit rate for each epidemic season divided by the average seasonal excess ED visit rate for 2003–2006, for each postvaccine epidemic season since 2008.

Seasonal epidemic excess diarrheal syndrome ED visit rates before (2003–2006) and after (2008–2016) rotavirus vaccine introduction

Age in years	2003–2006 average	2008	2009	2010	2011	2012	2013	2014	2015	2016
Excess diarrhea syndrome ED visits, rate per 10,000 by age group (prevaccine rate ratio)										
<2 years	194.7	23.0 (0.12)	18.1 (0.09)	–	7.0 (0.04)	–	13.0 (0.07)	–	15.3 (0.08)	–
2–4 years	47.0	14.4 (0.30)	20.3 (0.43)	–	19.6 (0.42)	–	20.4 (0.43)	–	24.2 (0.51)	–
5–12 years	7.7	3.0 (0.39)	2.8 (0.36)	–	6.0 (0.79)	–	13.9 (1.81)	–	18.1 (2.36)	–
≥13 years	3.3	0.5 (0.16)	1.3 (0.41)	–	0.7 (0.21)	–	2.5 (0.77)	–	3.9 (1.20)	–
All ages	10.6	1.9 (0.18)	2.6 (0.25)	–	2.1 (0.20)	–	4.5 (0.43)	–	6.3 (0.60)	–

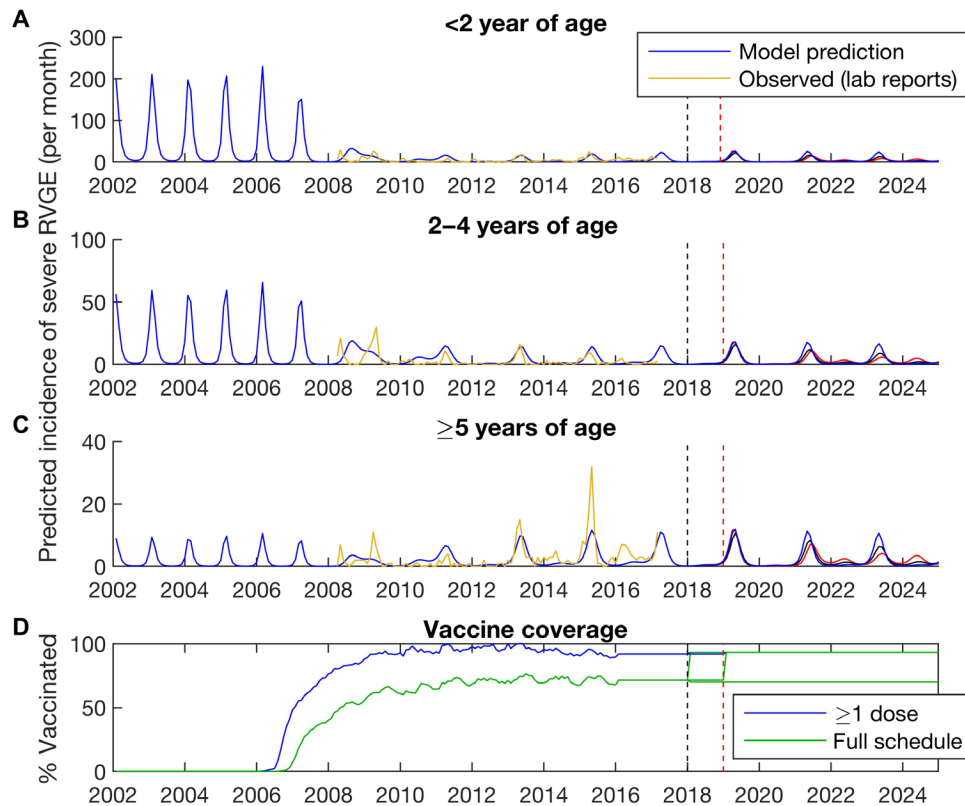


Fig. 3. Predicted incidence of severe RVGE in New York, 2002–2024. Dynamic model predictions are based on a previously described mathematical model fit to monthly hospitalization data from New York State (1993–2004), which was simulated to predict the impact of vaccination through 2024. Model predictions for the monthly number of moderate-to-severe RVGE cases in individuals (A) <2, (B) 2 to 4, and (C) ≥ 5 years old are plotted in blue, while the observed laboratory-reported cases are plotted in yellow. (D) Vaccine coverage in the model is based on estimates of rotavirus vaccine coverage with at least one (blue) and the full series (green) from the CIR. Coverage with a full course of rotavirus vaccine was increased to the current vaccine coverage with the DTaP vaccine beginning in January 2018 (black dashed lines) or 2019 (red dashed lines). We assumed that the relative efficacy of an incomplete vaccine course was 88% (see the Supplementary Materials).

shift in burden to slightly older age groups, as confirmed by multiple data sources from New York City. These changes are associated with the herd immunity conferred by rotavirus vaccination and were portended by mathematical models years before their emergence (9). This provides a remarkable example of the multiyear predictability of a dynamic infectious disease system, at least in qualitative terms, which stands in stark contrast to the predictability of weather systems, for example, (19).

Unlike the multiple nonlinear interactions that hamper the ability to predict weather more than a few days in advance, infectious disease systems often feature fewer nonlinear feedbacks (19, 20). Changes to the periodicity and age distribution of epidemics in response to vaccination have been predicted for other pathogens, such as measles (21, 22) and pertussis (23, 24), although future validations of these predictions are rare. The predictability of infectious disease systems has thus far proven elusive, with notable recent failures. Early models for the spread of Ebola vastly overestimated the epidemic potential, in part because they failed to account for behavioral changes in response to the epidemic (13, 14). Furthermore, there were limited data from previous epidemics that could be used to parameterize Ebola models and anticipate the behavioral response. Influenza forecasting has become more adept at predicting the peak and size of the epidemic a few weeks in advance, but antigenic changes to the virus lead to year-to-year variations in the size and

timing of influenza epidemics that remain beyond the scope of these forecasts (10–12).

Despite the relative simplicity of our model for rotavirus transmission, we were able to capture the qualitative epidemic dynamics in response to vaccination—including the shift to biennial epidemics and increased burden of disease among older children—although the emergence of biennial epidemics and their exact timing depended on assumptions about the relative efficacy of an incomplete vaccine course. We speculate that our success in capturing the qualitative epidemic dynamics was enabled by the relative lack of behavioral modifications in response to changes in rotavirus incidence, since rotavirus is just one of many causes of diarrhea and transmission is driven primarily by infants. Infant behavior is unlikely to be influenced by perceptions of risk, and children and adults are probably no more or less likely to wash their hands on the basis of how much rotavirus is circulating in their community. However, reliable long-range quantitative forecasts for rotavirus remain elusive, in part because we do not fully understand the relative efficacy of an incomplete vaccine course.

Our analysis benefited from multiple complementary sources of surveillance data, each with their own strengths and biases. While the laboratory and hospitalization data provide specific evidence of the emergence of the biennial pattern of rotavirus activity and an indication of its severity, the syndromic surveillance data demonstrate

the more recent shift in burden to older children and provide an estimate of the overall and age-specific burden of disease. The increase in RVGE among older children may not be as apparent from the hospitalization and laboratory data because of biases in the testing, coding, and reporting of RVGE cases or to its recent emergence (since it is also apparent in the 2015 laboratory data from New York City). Nonsignificant increases in RVGE hospitalizations have also been reported for children in the United States in 2013 (7). Traditionally, RVGE has been considered primarily a disease of children <5 years of age. Treatment does not depend on laboratory confirmation. Therefore, cases of RVGE in older children and adults are likely underdiagnosed. Furthermore, ED cases likely represent the less severe end of the rotavirus disease spectrum.

The increased incidence of RVGE among 5- to 12-year-old children should not be taken as a sign of vaccine failure or waning vaccine protection. Because of the herd immunity provided by routine rotavirus vaccination, unvaccinated infants and young children, and those not fully protected by vaccination, likely experience fewer opportunities for natural infection. Unlike in the prevaccination era when nearly all infants were infected by 2 years of age, it is possible that older children are only experiencing their first or second rotavirus infection, which studies suggest are more likely to result in disease (25). Therefore, the reduced circulation of rotavirus and the fewer opportunities for gaining immunity from natural infection can explain the apparent increase in ED visits among children 5 to 12 years of age absent of any waning of vaccine-induced immunity (9, 16). Our model suggests that increasing vaccine coverage by ensuring children complete the full two- or three-dose series would help to reverse this pattern and lead to lower incidence in all age groups.

Our analysis has several limitations. First, this study was ecologic; we had no direct information about the vaccination status of ED patients, laboratory-confirmed cases, or hospitalized individuals and no information about the infection status of ED patients in the syndromic surveillance system. Second, laboratory testing for rotavirus is not commonly done in New York City, and the data are not necessarily representative of population-level rotavirus incidence. Third, our ED visit data were based solely on diarrheal syndrome complaints and not on vomiting or other potentially related syndromes or clinical visit codes. Winter seasonal increases in acute gastroenteritis can be due to other causes such as norovirus; it is conceivable that other causes could explain the unusual pattern seen in diarrheal ED visits in 2013 and 2015 among children 2 to 12 years of age. Last, it was not possible to generate true out-of-sample predictions from the original mathematical model, since the future vaccine coverage, as well as the proportion of infants who received a full course of vaccination, was not known at the time.

Despite these limitations, all the data used in this study were aligned with the qualitative model predictions made in our 2009 study (9). Moreover, we demonstrate the value of testing model predictions by comparing them to out-of-sample data from different electronic surveillance systems. As electronic public health systems continue to be further developed and become increasingly adopted for disease surveillance (26, 27), these types of analyses will enable a more refined and timely examination of the long-term impact of vaccination and other public health interventions so that strategies to further mitigate the burden of disease can be devised. At a minimum, infectious disease models and novel surveillance systems should be judged by their ability capture major shifts in the epidemiology

of the disease—such as changes to the timing, age distribution, and severity of epidemics—in response to vaccination and other interventions or shocks to the system.

MATERIALS AND METHODS

Surveillance data

Four sources of surveillance data were used for this study. Three electronic surveillance systems operated by the New York City Department of Health and Mental Hygiene (DOHMH) provided data covering portions of the period from January 2002 through December 2016. These systems maintain ongoing surveillance data on laboratory-reported cases of rotavirus, diarrheal syndrome ED visits, and childhood rotavirus vaccinations in New York City. The fourth data source consisted of inpatient hospitalization data, available retrospectively for the period from January 2002 through December 2016. The study was deemed not to involve human participants by the New York City DOHMH Institutional Review Board.

Rotavirus-coded hospitalizations and laboratory-reported cases

The New York Statewide Planning and Research Cooperative System (SPARCS) is a comprehensive all-payer reporting system that has collected data on hospitalizations in the state of New York since 1979 (28). The system provided monthly counts of all inpatient hospitalizations that occurred in New York City facilities coded with a rotavirus-specific ICD-9-CM of “008.61” or ICD-10-CM of “A08.0” from January 2002 through December 2016. Counts of hospitalizations were aggregated by age group (<2, 2 to 4, and ≥ 5 years). These groupings were used to avoid restrictions on small cell sizes with potentially identifiable cases counts in SPARCS; no values below 6 are shown in figures or tables. Laboratory-confirmed rotavirus cases in New York City became reportable by laboratories to the DOHMH in January 2008 (29). Laboratory-reported case counts for February 2008 to December 2016 were summarized by month of diagnosis and age group (<2, 2 to 4, and ≥ 5 years). Rotavirus seasons were identified each year as the consecutive months from July through June (e.g., the 2006 rotavirus season spanned from July 2005 to June 2006). Epidemic rotavirus periods from 2002 to 2007 were identified as consecutive months that reached the upper-quartile level of monthly rotavirus-coded hospitalizations, and from 2008 to 2016 as consecutive months when hospitalizations and laboratory-reported cases both reached their respective upper-quartile threshold levels (e.g., for the 2008 rotavirus epidemic, hospitalizations and laboratory reports exceeded their respective upper-quartile thresholds for the months March through May; while for the 2010 season, the threshold for laboratory-reported rotavirus cases was reached only in January, and rotavirus hospitalizations reached only in March, indicating no clear epidemic period (Fig. 1).

ED syndromic surveillance

We analyzed data from the New York City syndromic surveillance system classified as a “diarrheal” syndrome based on ED patient chief complaint (30). The New York City syndromic surveillance system was established in 2001 to monitor ED visits citywide with the goal of early detection of outbreaks or bioterrorism events. Routinely collected patient chief complaint and demographic information from hospital EDs were transmitted electronically to the DOHMH and analyzed each day for statistically significant temporal

increases or spatial clusters. From January 2002 through June 2016, more than 52 million ED visits were recorded in the DOHMH syndromic surveillance system, of which 1.4% were classified into a diarrheal syndrome based on patient chief complaint. Only diarrheal syndrome ED visit data were analyzed in this study; other syndromes based on chief complaint terms and classified as febrile or vomiting syndromes that could potentially indicate rotavirus infection were not included.

Coverage of the ED syndromic surveillance system increased from an estimated 65% of all ED visits citywide in 2002 to more than 95% after 2008. Chief complaint reporting by hospitals in the ED system was not standardized across facilities or through time, and considerable variation existed in the syndrome coding and completeness of reporting. Diarrheal syndrome ED visits have been monitored daily, year-round since 2001 for temporal changes in disease trends and spatial clustering of cases in New York City by the DOHMH. To characterize age-specific trends in this study, weekly counts of diarrheal syndrome and total ED visits were calculated as weekly syndrome proportions as the sum of age-specific diarrheal visits divided by the total number of visits each week by age group (<2, 2 to 4, 5 to 12, and ≥ 13 years).

Estimating rotavirus epidemic excess ED visits

Periodic regression models originally developed for monitoring and measuring the impact of seasonal epidemic and pandemic influenza (31–34) were used to estimate seasonal baseline patterns of diarrheal syndrome ED visits and to quantify epidemic period excess visits as a proxy for RVGE. To determine the magnitude of excess diarrheal syndrome ED visits during documented peak rotavirus periods, models were fit to weekly time series of the proportion of diarrheal syndrome ED visits during baseline periods, defined as the consecutive weeks between predominant rotavirus circulation periods, with the remaining upper-quartile weeks removed before model fitting. The periodic regression models included secular trend and annual (52-week) and semiannual (26-week) harmonic terms to approximate seasonal baseline patterns expected in the absence of winter seasonal epidemic increases, as routinely used with surveillance data for monitoring influenza-like syndrome ED visits in New York City (33) and diarrheal syndrome clinic visits in the French Sentinel Network (34).

The periodic regression models were fit to data for each age group. Rotavirus epidemic periods were defined as consecutive weeks during peak rotavirus circulation when observed diarrheal ED visits exceeded the all-ages periodic regression threshold. Weekly rotavirus epidemic period excess diarrheal syndrome ED visit estimates were calculated as the observed minus expected proportions multiplied by the observed weekly total of ED visits for each group. Average seasonal rotavirus epidemic period excess diarrheal ED visits for 2003 to 2006, before widespread vaccine use, were compared to each postvaccine season from 2008 to 2016 as the ratio of the seasonal excess diarrheal ED visit rate for each postvaccine epidemic to the average epidemic prevaccine excess diarrheal ED visit rate by age group. Age-specific excess diarrheal ED visit rate ratios were calculated to determine the relative change by season in each age group.

Citywide Immunization Registry

Vaccine coverage was estimated on the basis of data from the Citywide Immunization Registry (CIR), a population-based registry

that captures immunizations administered to children less than 19 years of age in New York City. New York State Public Health Law requires providers to report immunizations to the CIR within 2 weeks of administration (35). The CIR has been in existence since 1996 and is currently one of the sites selected by the Centers for Disease Control and Prevention to provide data to monitor immunization trends nationally (36). As a sentinel site, the CIR captures more than 90% of the childhood population with immunizations, with 94% of pediatric providers reporting regularly and with more than 94% of immunizations reported within 30 days of administration (37). We used the CIR to determine the number of children 8 to 23 months old as of December 31 of each year from 2005 to 2015 who received three valid doses of RotaTeq (Merck, recommended for ages 2, 4, and 6 months), two valid doses of Rotarix (GlaxoSmithKline, recommended for children at 2 and 4 months of age), or three valid doses of a combination of the two products, as recommended (38). The denominators used to calculate coverage were based on annual New York City population estimates. Monthly vaccine coverage estimates were based on a 3-month moving average of the number of doses administered (first and last dose) divided by the 3-month moving average of the number of births occurring 1 to 3 months (first dose) or 4 to 6 months (last dose) previously. Vaccine coverage estimates for 2016–2017 were assumed to plateau at the average monthly vaccine coverage observed in 2015.

To examine the potential impact of strategies aimed at increasing rotavirus vaccine coverage, we assumed that coverage with the full series of rotavirus vaccine (two doses of Rotarix or three doses of RotaTeq) would equal the coverage with ≥ 3 doses of DTaP vaccine among infants 19 to 35 months of age in New York City (93.2% in 2017) (39). Note that this is similar to assuming that all infants who receive at least one dose of rotavirus vaccine would complete the full course (Fig. 3). We assumed that coverage would increase beginning in either January 2018 (during a low epidemic year) or January 2019 (just before an odd-year epidemic) to explore how the timing of the increase could potentially affect the epidemic dynamics.

Description of rotavirus transmission model

We simulated the transmission dynamics of rotavirus and predicted impact of vaccination using an age-structured compartmental model that we previously developed and fit to statewide data on rotavirus hospitalizations in New York (9). Briefly, the model assumes that individuals are born at a rate $B(t)$ (equal to the annual mean crude birth rate in New York State) with maternal immunity (M) and are protected from infection for a period of $1/\omega_M$ and then become susceptible to first infection (S_0). First infections (I_1) occur at a rate λ , and individuals recover at a rate γ_1 into a temporarily immune (R_1) state. This immunity wanes at a rate ω_1 , and individuals become susceptible again (S_1) but are reinfected at a reduced rate $\sigma_1\lambda$. Second infections (I_2) are assumed to have infectiousness reduced by a factor ρ_2 and a faster recovery rate γ_2 . Individuals are again assumed to be temporarily immune (R_2) following infection, then lose this immunity, and become partially susceptible (S_2). Once in S_2 , individuals can be reinfected at a rate $\sigma_2\lambda$, but subsequent infections (I_A) are assumed to be subclinical and have reduced infectiousness (ρ_A). Recovery from subclinical infection is again assumed to occur at an increased rate γ_2 and lead to temporary immunity (R_A) that wanes at a rate ω_2 . We assumed that individuals with first rotavirus infection (I_1) have a probability d_1 of developing severe

diarrhea, while those with second infection (I_2) develop severe diarrhea with probability $d_2 < d_1$. The fixed and estimated parameter values (table S2), as well as the differential equations describing the model, are presented in the Supplementary Materials.

To model the impact of vaccination, we assumed that each dose of the vaccine was equivalent to one natural infection, thereby moving individuals from M or S_0 to R_1 (bypassing I_1) following the first dose and from R_1 or S_1 to R_2 (bypassing I_2) following the second dose. Contrary to our 2009 analysis, we had data on both the proportion of infants receiving at least one dose of rotavirus vaccine as well as the proportion receiving a full course of vaccination. We assumed that 95% of individuals responded to vaccination (and thus received any benefit of the vaccine) following two or more doses, consistent with seroconversion data from vaccine trials in the United States and Finland (40), and assumed that the relative efficacy of an incomplete vaccine series (i.e., protection following receipt of the first dose) was 70 to 90% (fig. S1), consistent with our previous analysis (9). The long-term pattern of predicted seasonality and age-specific impact from the model were compared with the observed hospitalization and laboratory-based surveillance data for January 2008 to December 2016. We calibrated the model by determining the value of the relative efficacy conferred by one dose of the vaccine that minimized the sum of squared errors between the model-predicted number of cases and both the hospitalization and laboratory-reported postvaccination data (fig. S2).

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at <http://advances.sciencemag.org/cgi/content/full/6/9/eaax0586/DC1>

Supplementary Materials and Methods

Fig. S1. Predicted incidence of severe RVGE in New York, 2002–2016, for different values of the relative efficacy of the first vaccine dose.

Fig. S2. Fit of model to laboratory-reported rotavirus cases for different values of the relative efficacy of one vaccine dose.

Fig. S3. Proportion of infants completing a full rotavirus vaccine series.

Fig. S4. Age distribution of rotavirus-coded hospitalizations, laboratory-reported cases, and model-predicted RVGE cases.

Table S1. Rotavirus-coded hospitalizations and laboratory-reported cases in New York City, 2002–2016.

Table S2. Fixed and estimated parameter values.

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