Vaccination strategies against respiratory syncytial virus

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Respiratory syncytial virus (RSV) is the most common cause of US infant hospitalization. Additionally, RSV is responsible for 10,000 deaths annually among the elderly across the United States, and accounts for nearly as many hospitalizations as influenza. Currently, several RSV vaccine candidates are under development to target different age groups. To evaluate the potential effectiveness of age-specific vaccination strategies in averting RSV incidence, we developed a transmission model that integrates data on daily infectious viral load and changes of behavior associated with RSV symptoms. Calibrating to RSV weekly incidence rates in Texas, California, Colorado, and Pennsylvania, we show that in all states considered, an infected child under 5 y of age is more than twice as likely as a person over 50 y of age to transmit the virus. Geographic variability in the effectiveness of a vaccination program across states arises from interplay between seasonality patterns, population demography, vaccination uptake, and vaccine mechanism of action. Regardless of these variabilities, our analysis showed that allocating vaccine to children under 5 y of age would be the most efficient strategy per dose to avert RSV in both children and adults. Furthermore, due to substantial indirect protection, the targeting of children is even predicted to reduce RSV in the elderly more than directly vaccinating the elderly themselves. Our results can help inform ongoing clinical trials and future recommendations on RSV vaccination.

RSV | vaccination | model | viral load | social contact

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory tract infections worldwide (1, 2). The disease is highly contagious, infecting almost all individuals at least once by the age of 3 y (1). The virus continues to infect children and adults throughout their life (2–4). RSV most severely impacts the young and the old, accounting for over 230,000 hospitalizations and 14,000 deaths annually in the United States alone (2, 5).

There are currently no clinically available effective antiviral drugs against RSV (7). Although a monoclonal antibody preexposure prophylactic medication (palivizumab) is available, it is expensive and only recommended for a small percentage of infants who are born prematurely or who have exacerbating comorbidities (8, 9). Consequently, the WHO has designated vaccine development for RSV a top priority, and estimates that RSV vaccination will be commercially available in the next 5–10 y (10).

Several RSV vaccine candidates have been designed to target either young children or older adults. Nonreplicating candidates are considered most appropriate for vaccination of elderly individuals who have already been exposed previously to RSV (11). By contrast, replicating vaccines, some of which elicit mucosal immunity in the upper respiratory tract, are under development for children and adults (12). All vaccine types are designed to reduce disease severity by reducing viral load in the lower respiratory tract. However, if a vaccinated individual becomes infected, a replicating vaccine may be more effective at reducing the viral load within the mucosal secretions (13), thereby further reducing the probability of transmission. Thus, understanding population-based RSV transmission is critical in determining and prioritizing effective vaccination strategies with different vaccine types.

The two main drivers of RSV transmission are the viral load of respiratory secretions during the infection (14–17), as well as the contact patterns between infected and susceptible individuals (18–20). The levels and duration of infectious RSV loads in infants are greater than in adults (15, 21, 22). Contact patterns are highly assortative with age, where children have more frequent and extended physical contacts than adults (19, 23). A further complication is that the high RSV loads also increase disease severity (15), which tends to reduce social contact. Therefore, it is essential to account for these two factors simultaneously to assess RSV vaccination strategies accurately.

To evaluate the population-level impact of different strategies for age-group targeting of vaccination, we developed an RSV transmission model that incorporates data on infectious viral load and social contact. We use this model to identify age groups that contribute disproportionately to transmission, as well as to evaluate both the per-dose efficiency and population-level effectiveness of age-targeted vaccination strategies.

Results

In every state considered, we found that children younger than 5 y of age have both the highest risk of becoming infected with RSV

Significance

The WHO estimates that respiratory syncytial virus (RSV) vaccination will be available in the next 5–10 y. To evaluate the population effectiveness of an RSV vaccination program in the United States, we developed a transmission model that integrates data on daily infectious viral load and behavior changes while symptomatic. Our model simulations demonstrate that vaccinating children younger than 5 y of age will be the most efficient and effective way to prevent RSV infection in both children and older adults, a result that is robust across the US states considered. Accordingly, the population burden of RSV would be most effectively reduced if current vaccine candidates were to focus on children.

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(Figs. 1 *C* and *D* and 2) and the highest risk of transmitting RSV if infected (Fig. 2). Accordingly, targeting these young children between 0.5 and 5 y of age for RSV vaccination is predicted to be highly efficient, averting 0.1–0.5 cases per dose in this age class, as well as averting 0.1–0.4 cases in adults 50 y and above (Fig. 3). This indirect protection that arises from vaccinating children is so substantial that it is even predicted to avert more cases in adults than would a vaccination program that directly targeted the adults (Fig. 4). Our finding is robust across states, transmission settings, vaccine efficacies, and mechanisms of vaccine actions (Fig. 4 and *SI Appendix*).

The transmission model was calibrated to age-stratified RSV weekly incidence in four states across the United States (Texas, California, Colorado, and Pennsylvania) and accounted for the effects of viral load and social behavior during the course of infection (Fig. 1 *A* and *B* and *Methods*). With only seven free parameters, the model recapitulated RSV weekly trends and the age distribution of those individuals infected (Fig. 1 *C* and *D* and *SI Appendix*). For example, the calibrated model predicted the week 3 peak of RSV infections in Texas and the week 7 peak of RSV infections in California (Fig. 1*C*), and also yielded a mean age of infection that was lower in Texas than the mean age of infection in California (Fig. 1*D*).

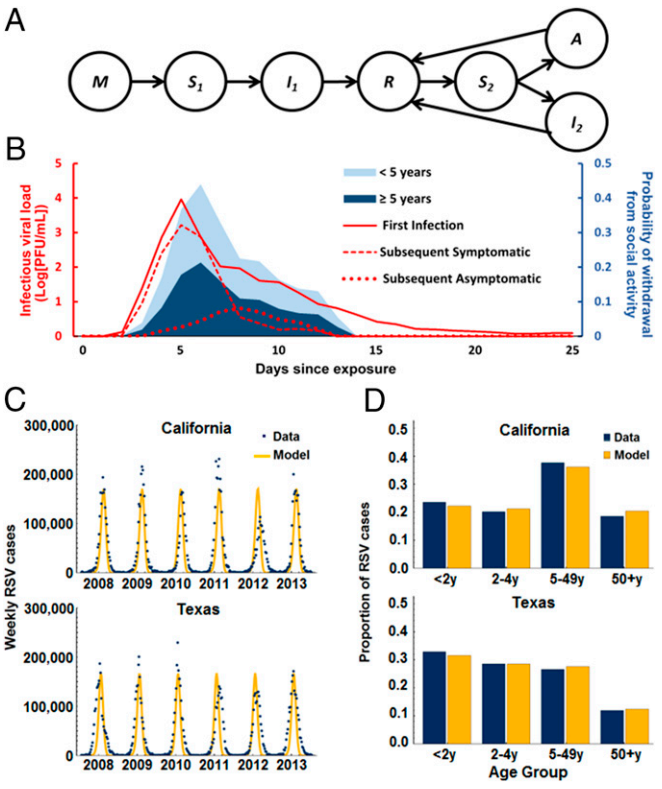

Fig. 1. Structure and fit of the model. (*A*) Compartmental diagram of the transmission model. Individuals are born into a maternal immunity compartment *M*, and then transition to the first susceptible compartment S_1, where they can become infected I_1. Following infection, individuals transition to a recovered compartment *R*, where they are temporarily immune. Following waning, individuals transition to S_2, where they might be reinfected, but with milder infection I_2, which can be asymptomatic in adults. For clarity of depiction, age stratification is not displayed (*SI Appendix*). (*B*) Infectious viral load of the first infection and subsequent infections, as well as daily behavior changes during RSV infection (based on refs. 22, 25, 44). (*C*) Time series of recorded weekly RSV cases and model fit to California and Texas (model fit to Colorado and Pennsylvania is provided in *SI Appendix*, Fig. S4). (*D*) Data and model fit to the age distribution among RSV infections.

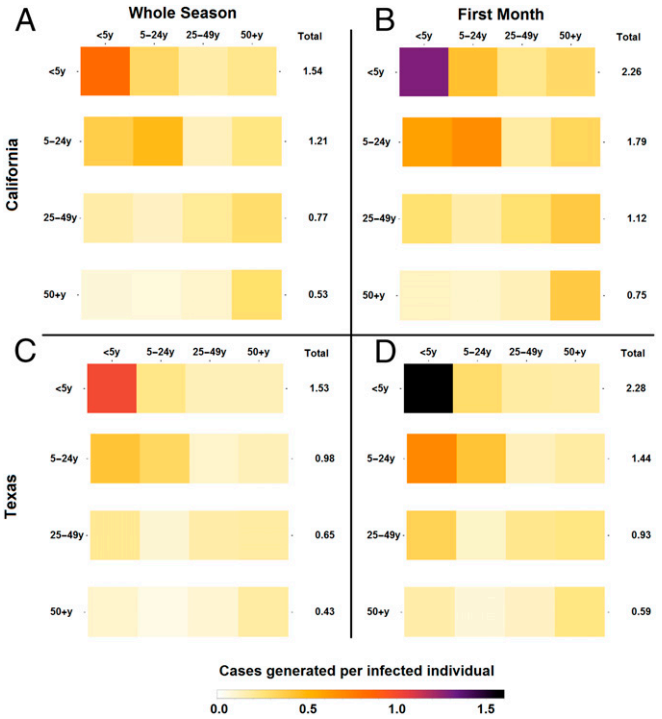

Fig. 2. Age-specific average number of secondary infections generated per case. Each row identifies an age group that can be a source of infection. Each column identifies an age group that can be infected. The color at the intersection of the row and column indicates the number of secondary infections attributed to a single infective case. The average number of secondary cases from the source age group is tabulated in the rightmost column of each panel. California (*A* and *B*) and Texas (*C* and *D*) model predictions are shown for the entire RSV season (*A* and *C*) and for the first month of the RSV season (*B* and *D*). Similar trends are observed in Colorado and Pennsylvania (*SI Appendix*, Fig. S6).

To explore the effect of age on transmission, we stratified the population into four age groups (0–4 y, 5–24 y, 25–49 y, and ≥50 y) and evaluated the mean number of secondary cases attributable to a single case throughout the RSV season (*Methods*). We found that the younger age groups, particularly children under 5 y of age, were the groups in which a single case would typically transmit the disease to more than one individual (<5 y: 1.53–1.57, 5–24 y: 0.98–1.21, 25–49 y: 0.65–0.77, ≥50y: 0.45–0.55) (Fig. 2*A* and *SI Appendix*, Fig. S6), indicating that children are predominantly responsible for transmission. In contrast, the infected elderly will transmit less than an individual in any other age group. This finding was robust across all of the US states considered (*SI Appendix*). In California, for example, an infected individual younger than 5 y of age is predicted to transmit RSV to 2.9-fold as many people as an individual older than 50 y of age (1.54 vs. 0.53; Fig. 2*A*). In addition, arising both from the high-contact mixing of people within the same age group and from the higher susceptibility of children, all age groups were most likely to infect either individuals in their own age group or individuals under 5 y of age (Fig. 2*A*).

Nonetheless, these averages belie temporal evolution of the average number of secondary cases over the RSV season. At the beginning of the season, when the RSV transmission is highest, an infected individual will transmit, on average, more than an individual who was infected later in the season. For example, in the first month of the season, children are predicted to transmit RSV to 3.2- to 3.9-fold as many people as individuals older than 50 y of age (Fig. 2*B* and *SI Appendix*, Fig. S6). Transmissibility evolves not only as the RSV season progresses but also during the course of individual infections. Although infants are potentially infectious for 26 d (21),

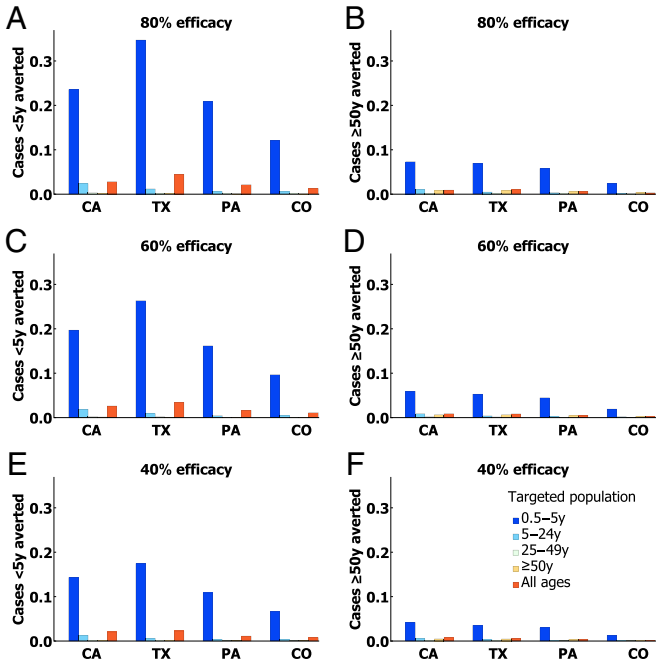

Fig. 3. Model predictions of RSV cases averted per vaccinated individual in California, Texas, Pennsylvania, and Colorado, assuming vaccine efficacies of 80% (*A* and *B*), 60% (*C* and *D*), and 40% (*E* and *F*). We assumed age-specific monthly vaccination coverages as observed for the influenza vaccine between 2010 and 2014. No reduction in viral load is imposed for vaccinated individuals who became infected. Cases averted are tallied for the two at-risk age groups: individuals younger than 5 y of age (*A*, *C*, and *E*) and individuals older than 50 y of age (*B*, *D*, and *F*).

we found the majority of the secondary infections occur during the 4 d associated with the most severe symptoms (*SI Appendix*, Fig. S5).

We also evaluated the efficiency of age-dependent vaccination strategies for RSV, defined as the number of cases averted per dose. Given plans to administer the RSV vaccine together with the influenza vaccine (24), we specified the vaccination coverage observed monthly for the influenza vaccine between 2010 and 2014 for every age group in each state. Across all scenarios and states (*Methods*), targeting adults aged 50 y and older had only minimal indirect benefit in terms of reducing RSV transmission to the other age groups (Fig. 3). In contrast, vaccinating children between 6 mo and 5 y of age was found to be more efficient for individuals over 50 y of age than vaccinating these adults directly (Fig. 3). For example, each dose of an RSV vaccine with 80% efficacy that is targeted toward children is predicted to avert 0.12–0.35 cases in children and 0.03–0.07 cases in adults, whereas the vaccination of an adult is predicted to avert only 0.0001–0.0014 cases in children and 0.0036–0.0086 cases in other adults (Fig. 3).

We also evaluated the effectiveness, defined as the overall reduction in RSV cases, of age-targeted vaccination strategies. Compared with targeting any of the other age groups, the targeting of children under 5 y of age was predicted to be the most effective strategy to reduce RSV infection in both children and adults. This result was obtained even though substantially fewer RSV doses would be needed to vaccinate young children than other age groups. For example, vaccinating children in Pennsylvania with a 60% efficacious vaccine is predicted to avert 56% of infections in children, as well as to reduce infection in adults aged 50 y and older by 54%. In contrast, if the entire population is vaccinated, about 10-fold more doses would be needed to achieve reductions of 65% in children and 75% in adults.

Variability between the effectiveness and efficiency of RSV vaccination programs was predicted across states. Specifically, vaccination was projected to be most efficient in Texas, followed by California, Pennsylvania, and Colorado. In contrast, vaccination would be most effective in California, followed by Pennsylvania, Colorado, and Texas. The variability in the discrepancies between effectiveness and efficiency across states arises through a combination of differences in expected vaccine uptake, seasonality pattern, annual RSV rates, and population demography. For example, the high birth rate in Texas fuels transmission. Thus, the per-dose number of cases averted for Texas is predicted to be more efficient than in other states (Fig. 3). However, the higher underlying rate of transmission in Texas leads to a lower reduction in overall population-level effectiveness achieved for a given vaccination program. With the exception of Pennsylvania, in which influenza vaccination coverage typically exceeds 75% in children, all other states had vaccination uptake within the range of 60–70% for both children and adults (*SI Appendix*).

Given that the RSV season typically starts earlier than the influenza season, a further complication is that RSV peaks are expected to occur before all individuals are vaccinated, with the earliest peaks occurring in Texas, followed by Pennsylvania, California, and Colorado (*SI Appendix*, Fig. S8). If the RSV and influenza vaccines were administered together, around 30% of those individuals vaccinated in Texas would not be vaccinated until after the RSV season had started. By contrast, the RSV season in Colorado peaks 6 wk later than in Texas, and nearly 90% of those individuals who will be vaccinated already have been vaccinated before the RSV season begins. This variation in misalignment between vaccination timing and RSV trajectories across states is consistent with predictions of more moderate effectiveness of RSV vaccination programs in Texas than in Colorado or other states (Fig. 4).

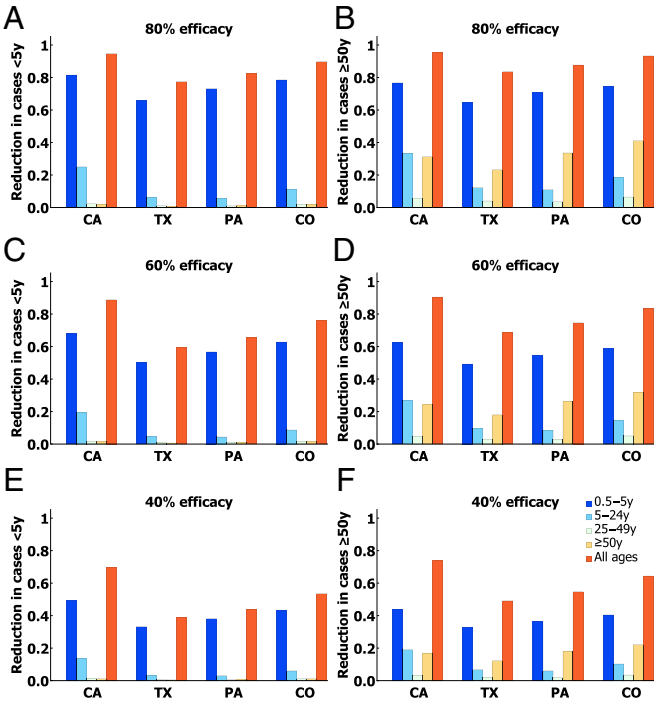

Fig. 4. Model predictions of proportion reduction in RSV cases in California, Texas, Pennsylvania, and Colorado, assuming vaccine efficacies of 80% (*A* and *B*), 60% (*C* and *D*), and 40% (*E* and *F*), respectively. We assumed age-specific monthly vaccination coverages as observed for the influenza vaccine between 2010 and 2014. No reduction in viral load was imposed on vaccinated individuals who became infected. Cases averted are tallied for the two at-risk age groups: individuals younger than 5 y of age (*A*, *C*, and *E*) and individuals 50 y of age or older (*B*, *D*, and *F*).

In scenario analyses, we also considered the possibility that if vaccinated individuals are infected in the same season, they might be less infectious than infected unvaccinated individuals (25). For a vaccine that reduces viral load by 50%, a vaccine dose in children is predicted to avert an additional 0.02–0.04 infection in children and 0.001–0.007 infection in adults older than 50 y of age. Such a vaccine would also further reduce total infections by 2–7% in children and 2–13% in adults, compared with a vaccine that does not affect viral load (*SI Appendix*, Figs. S11 and S12). Furthermore, the vaccination of children younger than 5 y of age remained the most efficient and effective strategy for averting RSV in both children and adults (*SI Appendix*, Figs. S9 and S10) even when we calibrated the annual attack rate in adults to the highest observed in six RSV seasons (5, 49) (*SI Appendix*).

Discussion

Our analyses indicate that vaccination of children under 5 y of age could effectively and efficiently reduce RSV in young children and older adults. This impact of vaccinating children arises because children are disproportionately responsible for transmission, attributable to a combination of factors. First, children have higher infectious viral loads than adults, with longer durations of infection (22, 26, 27). Second, children have both greater frequency and duration of contacts than adults. Additionally, children are more likely to mix with individuals in their own age group, who are more susceptible to become infected with RSV. Specifically, although children under 5 y of age represent less than 10% of the US population, vaccinating these children with a 60% efficacious vaccine could reduce as much as 75% of RSV infection in children and the elderly combined.

RSV and influenza vaccines may be coadministered; a clinical trial has already been completed to evaluate their safety together (24). A challenge is that the RSV season typically occurs earlier than the influenza season. Recent studies have demonstrated that protection conferred by the influenza vaccine wanes rapidly (28, 29). Thus, future studies should focus on optimizing the schedule of both influenza and RSV vaccination. As a component of such an optimization analysis, it should be taken into account that influenza infection results in more hospitalizations among the elderly, whereas RSV is responsible for more hospitalizations in young children. However, the indirect protection to the elderly from targeting children is substantial against both influenza (30, 31) and, as we have found, RSV.

We found that targeting children younger than 5 y of age is highly efficient per dose, and is also the most effective strategy to reduce RSV in both young children and older adults across all states and transmission settings. Nevertheless, vaccinating the rest of the population could further decrease the number of cases, albeit with substantially lower efficiency that varies across states. These results suggest that future cost-effectiveness analysis of RSV vaccination should be tailored to specific states.

Ongoing clinical trials on RSV for different age targeting do not explicitly consider the effect of indirect protection via reduced transmission (10). However, we found that the indirect protection arising from vaccinating children is so substantial that it is even predicted to avert more cases in older adults than would a vaccination program directly targeting the adults. This finding underscores the importance of measuring the infectious viral load and disease severity for vaccinated individuals who become infected, which can be assessed by swab tests and survey studies.

As for any modeling study, we made a number of simplifying assumptions. Because RSV is typically mild in older children and adults under 50 y of age, limited data are available on RSV incidence in these age groups. Nevertheless, even when we assumed an annual attack rate of 8.3% (*SI Appendix*), more than double the base case, vaccinating young children remained the most efficient and effective strategy. Given there is no commercially available vaccine against RSV, we were required to make certain assumptions about the potential vaccine and its uptake. For example, we assume that immune protection elicited by vaccination is equivalent to natural infection. We also assume that the efficacy of the vaccine is the same for all ages, whereas many vaccines have lower efficacy in the elderly (32, 33). Nonetheless, this assumption is conservative with regard to our finding that vaccinating children is much more effective and efficient than vaccinating the elderly.

In conclusion, allocating vaccine doses to children under 5 y of age is more effective not only for the children but also for older adults, due to reduced transmission. Our finding that indirect protection can avert even more infections than direct protection of adults over 50 y of age highlights the importance of accounting for population-level effectiveness rather than solely for individual-level efficacy. Given several types of vaccine candidates currently targeting different age groups (10, 11, 34), focusing on children is likely to be the most promising for reducing the incidence, morbidity, and mortality of RSV.

Methods

Model Overview. We developed a dynamic model for age-stratified RSV infection progression and transmission in Texas, California, Colorado, and Pennsylvania. Our model is a modified susceptible-infected-recovered compartmental framework (35) in which transitions between the compartments occur over time (Fig. 1). To model age-dependent transmission, we stratified the population into eight age groups: 0–5 mo, 6–11 mo, 1 y, 2–4 y, 5–24 y, 25–49 y, 50–64 y, and ≥65 y. Consistent with immunological observations (36, 37) and previous transmission models (38–41), we assumed individuals to be born with temporary protection conferred by maternal antibodies. Immunity is elicited following the first infection and leads to a lower viral load and severity in any subsequent infection (14, 15, 22) (also *SI Appendix*). Consistent with a previous model (41), we assumed that upon recovery, individuals are fully, albeit temporarily, protected with mean waning of 6.7 mo. This assumption is also supported by prospective studies demonstrating that reinfection in the same season is rare (1), yet possible (42). Immunological studies in adults show that preexisting serum RSV-neutralizing antibodies reduce susceptibility to subsequent infection (15, 43). However, if infection does recur, there is little to no reduction in infectious viral load in individuals with preexisting antibodies (15). Therefore, no further reduction in viral load beyond the reduction conferred by the partial immunity of a first infection was incorporated (model equations in *SI Appendix*).

Force of Infection. The rate at which individuals transmit RSV depended on (*i*) age-specific contact rates between the infected individual *n* and his or her contact *j*, (*ii*) infectiousness of the infected individual based on his or her daily viral loads and time in the RSV season, and (*iii*) age-specific susceptibility to infection. Age-specific contact rates were parameterized using data from an extensive survey for daily contacts (19). These contact data reveal frequent mixing between similar age groups, moderate mixing between children and people of their parents' age, and infrequent mixing among other groups (*SI Appendix*). To account for the evolution in transmissibility over the course of RSV infection, we parameterized transmissibility from daily estimates of infectious viral load as determined by viral culture (15, 22). We combined the daily viral load data with daily probabilities of withdrawal from daily social interaction for children (25) and symptomatic adults based on surveys of individuals infected with RSV (Fig. 1*B* and *SI Appendix*). Specifically, we used the individual-level data (15) reported from an analysis of 35 volunteers who were experimentally infected with RSV in the United States. Perceived severity of RSV symptoms and the consequent change in social activity was measured twice daily for 2 wk. The patterns of daily withdrawal from social activity exhibited in the survey were consistent with results from other experimental studies that followed individuals infected with RSV throughout their infection period (27, 44). For children younger than 5 y of age, we took into account that an RSV infection has been found to result in 2.3 d of missed daycare (25). We assumed that these 2.3 d of withdrawal from social mixing occurred around the peak of viral load, given the correlation between viral load and severity of symptoms in both children (25) and adults (15, 27) (*SI Appendix*). To consider conservatively the daily mixing patterns of those individuals who withdraw from social interaction while infected, we assumed that children stopped interacting within their age group but that contact with people from different age groups, for example, the parents of infected children, was unaffected.

RSV incidence is seasonal, with a peak typically striking in the winter (45), yet the driver for this seasonality remains uncertain (40). Thus, we included general seasonal variation in the susceptibility rate of the model as

$$T(t) = \Gamma\left(1 + \cos\left[\frac{2\pi}{365}(t-\phi)\right]\right),$$

in which Γ is the seasonal amplitude and ϕ is a seasonal offset. This formulation was previously shown to capture the seasonal variations of RSV incidence by US state accurately (40).

Modeling Vaccination. Given provisional plans to administer the RSV vaccine together with the seasonal influenza vaccine (46), we parameterized vaccination uptake from state-specific monthly influenza vaccine coverage data for different age groups as observed from 2010 to 2014.

RSV vaccines under development fall into two categories (34): replicating or nonreplicating candidates. The latter is likely to elicit only a systemic response and not a mucosal response, whereas the former stimulates both. Recent clinical data that measured immune markers in volunteers experimentally exposed to RSV (46) demonstrated that both IgA (which mimics response to the live-attenuated vaccine) and serum neutralizing antibodies (which mimic response to the nonreplicating vaccine) reduced susceptibility to infection. However, if infected, viral load was unaffected (46). Accordingly, in our base case, we assumed that vaccination will reduce susceptibility, but not the viral load, for those individuals who are infected. Given that those studies were conducted only in adults who already experienced multiple RSV infections, this assumption is conservative. We also conducted a sensitivity analysis of this assumption, where we considered a reduction in viral load of up to 50% (*SI Appendix*) for a vaccinated versus unvaccinated individual who became infected in the same RSV season.

Model Calibration. To estimate empirically unknown epidemiological parameters (*SI Appendix*, Table S2), we calibrated our model to weekly cases of RSV (confirmed by viral isolation, antigen detection, or PCR) (47). These data were collected by the CDC's National Respiratory and Enteric Virus Surveillance System by the CDC and state health departments from four different states in the United States from 2010 to 2014. For children under 5 y of age, we used a prospective cohort study from Texas to scale the following age-specific incidences of RSV: 0–11 mo, 1 y, and 2–4 y of age (1).

Given the variability of attack rates during the first year of life, we used an additional prospective study to stratify between the ages of 0–5 mo and 6–11 mo (2). No prospective studies estimating rates of RSV in children are available in Pennsylvania, Colorado, or California. However, given that in the RSV season, 20–41% of the influenza-like illness (ILI) cases are attributed to RSV infection in children younger than 5 y of age (48), we used ILI data from 2010–2014 to evaluate RSV rates in these states. Specifically, we calculated the quotients between the ILI rates observed at the RSV seasons in children under 5 y of age in each of the three states and the ILI rates observed at the RSV season for the same age group in Texas. The state-specific RSV rates used in the calibration of our model were calculated as a product between these quotients and the RSV rates observed in the prospective cohort study from Texas.

For individuals over 5 y of age, we used a prospective cohort study in adults to scale incidence of RSV in all four states (5). Due to the uncertainty related to the actual incidence in adults, we calibrated our model parameters for each state using two settings that correspond to the lowest and highest attack rates, respectively, of RSV seasons observed in the elderly (5, 49).

To assess the balance between including additional parameters and the potentiality of overfitting the model, we applied the Akaike information criterion, derived from information theory. We further confirmed the optimality of the model structure using the alternate Bayesian information criterion (*SI Appendix*). The final transmission model included seven parameters without constraints imposed from previous data: seasonal offset ϕ; seasonal amplitude A; relative transmissibility r; and susceptibility rates σ_j for individuals in age groups j: <2, 2–5, 5–50, and ≥50 y of age (Fig. 1 *C* and *D* and *SI Appendix*).

Calculation of Secondary Cases. We calculated the average number of secondary cases generated per infected individual in each age group by evaluating the total number of new cases for which members of an age group had been the source of infection divided by the total number of that age group that been infected (cf. refs. 30, 50). Specifically, we simulated entire RSV seasons in each US state. Throughout the season, we calculated the daily probability that an individual within age group e, day of infection τ, and type of infection l (first, subsequent asymptomatic, or subsequent symptomatic) would be the source of transmission to individuals from age group j (*SI Appendix*). The total number of new cases for which members of an age group had been the source of infection is the summation of the probabilities for every individual within each age group. The probability of infection from a host within an age group was calculated as a function of three data-driven factors, which evolve during the progression of infection: (*i*) the infectious viral load, (*ii*) the probability of withdrawal from social activity, and (*iii*) the expected number of contacts between the age group of the host i and the age group of the contact j. These factors were parameterized with clinical, epidemiological, and behavioral data, respectively (*SI Appendix*).

Model Simulations. To determine the population-level effectiveness and per-dose efficiency of age-specific vaccination strategies against RSV, we simulated 10 y following vaccination implementation. We evaluated the targeting of specific age groups (0.5–4 y, 5–24 y, 25–49 y, and ≥50 y) and of the entire population for a range of vaccine efficacies in all eight settings. We compared the reduction of RSV incidence achieved both per dose and overall in children under 5 y of age and adults aged 50 y and older across a 10-y period of implementation.

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