Efficacy and Optimization of Palivizumab Injection Regimens Against Respiratory Syncytial Virus Infection

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IMPORTANCE Infection with the respiratory syncytial virus (RSV) is the leading cause of hospitalizations in children, accounting for more than 90 000 hospitalizations every year in the United States. For children who are at risk for severe RSV infections, the American Academy of Pediatrics recommends immunoprophylaxis with a series of up to 5 injections of the antibody palivizumab administered monthly, beginning on November 1 of each year. However, many practitioners initiate injections at the onset of RSV season as indicated by local surveillance.

OBJECTIVES To evaluate the effectiveness of current regimens for palivizumab injections across different cities and to design an optimized regimen.

DESIGN, SETTING, AND PARTICIPANTS We performed a mathematical modeling study of the risk for hospitalization due to RSV infection. The model accounted for the pharmacokinetics of the antibody, the timing of the injections, and seasonal patterns of RSV, including geographic and year-to-year variability. We used the model to estimate the efficacy of current regimens, including the American Academy of Pediatrics recommendation, and to design a more effective injection regimen, the optimized fixed start (OFS), which uses city-specific initiation dates. Participants were the approximately 700 000 individuals who had specimens tested for RSV by National Respiratory and Enteric Virus Surveillance System laboratories in 18 US cities from July 1, 1994, through June 30, 2011 (a total of 725 741 tests).

INTERVENTIONS Different palivizumab injection regimens.

MAIN OUTCOMES AND MEASURES The primary outcome measure was reduction in hospitalizations due to RSV infections. The secondary measures were cost (number of palivizumab doses) and duration of protection (in days).

RESULTS The American Academy of Pediatrics–recommended 5-injection regimen is expected to reduce hospitalization risk by a median of 2.7% (range, −2.2% to 6.1%) compared with the conventional regimen based on RSV surveillance. The 5-injection OFS regimen is expected to further reduce risk by a median of 6.8% (range, 4.9% to 14.8%), and the 4-injection OFS regimen is expected to achieve efficacy comparable to that of the conventional 5-injection regimen while reducing costs by 20%.

CONCLUSIONS AND RELEVANCE Modified palivizumab regimens can improve protection for children at risk for severe outcomes of RSV infection and thereby lower rates of hospitalization due to RSV.

Published online February 23, 2015.

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n the United States, the mortality burden of respiratory syncytial virus (RSV) infection in children younger than 1 year exceeds that of all influenza strains combined, and RSV infection is the leading cause of pediatric hospitalizations, resulting in more than 90,000 hospitalizations annually. Globally, RSV is estimated to cause an annual 23.8 million severe acute lower respiratory tract infections in children younger than 5 years. No vaccine protects against RSV, but palivizumab, a humanized monoclonal antibody marketed as Synagis (MedImmune), has been found to reduce hospitalizations by 55% (and as much as 72%) when delivered prophylactically to children at high risk. Palivizumab prophylaxis has been approved in 83 countries and is a primary control strategy for RSV infection worldwide. Dosing policies and target groups are similar among developed countries and are based on international clinical trials. Immunoprophylaxis is recommended for infants born at a gestational age of younger than 29 weeks and infants at risk for RSV-related hospitalization due to hemodynamically significant congenital heart disease, chronic lung disease of prematurity, congenital abnormalities, or lung conditions that compromise the handling of respiratory secretions. In the United States, palivizumab is administered by monthly intramuscular injection during the RSV season for a total of up to 5 doses per patient. Palivizumab administration is controversial because of its high cost, which exceeded $10,665 for a 5-dose regimen in 2013 and can reach $15,000 for some patients. The total annual cost of palivizumab worldwide is estimated to be $1.2 billion, which is primarily borne by insurance companies and national payers. Although the manufacturer provides some rebates, palivizumab has been the most costly pharmaceutical item in some fiscal quarters of the Medicaid program. Consequently, considerable interest exists in improving the effectiveness and reducing the costs of RSV prevention.

Prevention of RSV is complicated by the considerable variation in the timing of the RSV season. According to the Centers for Disease Control and Prevention (CDC), the onset of the RSV season in a particular city is the first of 2 consecutive weeks with at least 10% of specimens tested for RSV returned with positive findings. The end of the season is defined as the last of 2 consecutive weeks with 10% or more of specimens tested for RSV returned with positive findings. Based on this definition, the duration of the RSV season in the United States is typically 4 to 5 months, running approximately from November through March. However, the season starts earlier and ends later in Florida and several other southern states. Because of this variability, a palivizumab regimen optimized for one location will not necessarily be optimal for another location.

The American Academy of Pediatrics (AAP) 2014 Red Book recommends, as in 2009 and 2012, that at-risk infants receive up to 5 doses of palivizumab beginning in November except in Alaska and Florida. Although some practitioners have adopted this recommendation, a large number continue to initiate injections at the onset of the RSV season, which may vary annually and geographically. The injection regimen is ultimately prescribed by the pediatrician and is based on interpretation of the CDC definition and RSV surveillance information from regional laboratories, but Medicaid and insurance companies typically limit the number of injections per patient. Thus, the timing of the treatment can affect clinical outcomes significantly. Starting too early or too late may leave patients vulnerable for a portion of the season.

Herein, we use RSV surveillance data provided by the CDC for 18 major cities and 17 RSV seasons to evaluate the efficacy of the AAP-recommended regimen. We also evaluate a recently suggested regimen that initiates injections 30 days before the median start date across the 5 most recent seasons (MED30). We compare these regimens with the conventional regimen, in which injections are initiated with the local start of the CDC-defined RSV season (hereinafter termed the seasonal regimen). All 3 regimens inject palivizumab every 30 days. However, a single injection protects the patient for longer than 1 month, resulting in an accumulation of excess antibodies during the course of the season. Specifically, 30-day regimens have been shown to reach antibody concentrations exceeding 100 μg/mL far surpassing the 99% neutralizing level for RSV antibodies of 30 to 40 μg/mL. To address this inefficiency, we designed an alternative regimen termed the optimized fixed start (OFS) regimen—that increases the duration of protection with the same number of injections. We further optimized the OFS regimen to begin on fixed dates determined by local RSV seasonality to ensure coverage during the months of highest RSV risk.

Methods

This study was exempt from institutional review board approval. Informed consent was not required; data were deidentified by the National Respiratory and Enteric Virus Surveillance System and the CDC. We estimated the risk for hospitalization owing to RSV infection based on the diagnostic data from the National Respiratory and Enteric Virus Surveillance System from July 1, 1994, through June 30, 2011, reported in the following 18 US cities: Atlanta, Georgia; Birmingham, Alabama; Cleveland, Ohio; Columbia, South Carolina; Corpus Christi, Texas; Honolulu, Hawaii; Indianapolis, Indiana; Long Beach, California; Los Angeles, California; Nashville, Tennessee; New Orleans, Louisiana; Oklahoma City, Oklahoma; Richmond, Virginia; San Antonio, Texas; San Diego, California; Seattle, Washington; Sioux Falls, South Dakota; and St Louis, Missouri. These cities were selected by a prior study based on consistency of reporting, by submitting at least 30 weekly RSV reports to the CDC per season from 1992 through 2007. For each city, the data include weekly reports of the number of samples undergoing testing for RSV, the number of samples with findings that are positive for RSV, and the percentage of test results that returned positive results for RSV. In the absence of palivizumab administration, the daily probability of hospitalization was estimated by interpolating the weekly number of RSV tests with positive findings divided by 7 (with results remaining robust to alternative measures of RSV hospitalization risk). On administration of palivizumab, the probability of hospitalization was reduced by 55% while serum levels remained greater than 40 μg/mL.

We modeled the palivizumab concentration over time using a compartment model in which palivizumab is elimi-
in the Supplement). The half-life of palivizumab was assumed to be 20 days based on the US Food and Drug Administration label. This estimate is conservative and ensures that sufficient concentrations of palivizumab are available despite the large interindividual variability and any hemodynamically significant congenital heart disease (eAppendix 2 in the Supplement). Following the US Food and Drug Administration label, we assumed that each palivizumab injection is given at a dose of 15 mg/kg of body weight. Because only a small fraction of infants receives palivizumab, these interventions are not expected to affect the overall course of RSV outbreaks.

We designed several different palivizumab regimens aimed at minimizing the risk for RSV-related hospitalization during a typical season (Table 1). Each regimen uses a fixed start date and is constrained by 1 of 3 different injection budgets (5, 4, or 3 injections). Our OFS regimen allows for 5 injections and specifies fixed injection dates for each city. Specifically, we used the palivizumab pharmacokinetic model to determine an injection spacing schedule that maximizes the duration of continuous protection and historical RSV incidence to determine the start date expected to maximize the overlap between antibody protection and local RSV infection risk. We followed the same procedures for optimizing local injection schedules under reduced budgets of 4 (OFS4) and 3 (OFS3) injections. Finally, we designed regimens that combine the optimized injection intervals of the OFS with a variable start date triggered by local RSV surveillance, but we found them to provide protection comparable or inferior to that provided by the OFS while having the additional requirement of real-time access to accurate surveillance data (eAppendix 3 in the Supplement). To evaluate the optimized regimens, we used the leave-one-out cross-validation procedure. Each regimen was optimized based on data from all but 1 season and then evaluated on the held-out season.

We compared the designed regimens with 3 existing regimens in which injections are separated by 30 days (Table 1). First, the seasonal regimen, which is widely practiced and indicated in the US Food and Drug Administration label, prescribes the first injection at the onset of the RSV season (ie, after the first 2 successive weeks of >10% positive RSV test results reported by local National Respiratory and Enteric Virus Surveillance System laboratories). Second, the AAP-recommended regimen advises administration of the first injection on November 1 for most regions outside Alaska or Florida (NOV1). Third, the MED30 regimen is discussed as recommended by Panozzo et al.

### Results

#### Timing Injections to Improve Protection

We determined the optimal timing of injections to maximize the duration of protection derived from maintaining palivizumab serum levels above an empirically determined threshold for immunologic protection. The resulting OFS, OFS4, and OFS3 regimens include an induction phase of 29 days between doses 1 and 2 and a maintenance phase in which subsequent doses are delivered 38 days apart. For example, if the optimal local start date is November 1, then subsequent doses should be given on November 30, January 7, February 14, and March 24 (assuming 28 days in February).

Our optimized 5-dose regimen (OFS) is predicted to provide continuous protection for 181 days. For comparison, 5-dose regimens with 30-day spacing between subsequent injections are expected to achieve only 160 days of protection and a temporary loss of protection at day 30. Thus, the OFS regimen that we propose herein is expected to achieve 22 additional days of protection compared with the seasonal (Figure 1), NOV1, and MED30 regimens. The OFS4 and OFS3 regimens are expected to attain 143 and 105 days of protection, respectively.

The OFS is a particularly effective strategy in locations that typically experience extended seasons, such as the southern United States. When determining start dates, the optimization method considers entire seasonal burdens and can delay injections to ensure coverage in regions where RSV infection rates peak relatively late in the season. In contrast, the seasonal regimen initiates injections at the initial rise in RSV infection rates regardless of the ultimate duration and magnitude of the season and thus runs the risk of protection waning too early, as illustrated in Figure 1B.

The second step in optimizing the regimens is to use longitudinal data from prior RSV seasons to determine the fixed start date that is likely to avert the most hospitalizations in each city. We found that most of the optimized start dates for OFS are earlier than November 1, with a median date of October 24 (Figure 2 and Table 1). By extending the window of protection to 181 days, injections are initiated earlier in the OFS regimen, enabling early season protection without compromising late season protection.

### Reduction in RSV Hospitalization Risk

For each regimen, we computed the relative reduction in hospitalization risk beyond that achieved by the seasonal regi-
The AAP-recommended regimen (NOV1) with 5 injections is estimated to reduce hospitalization risk by a median of 2.7% across the 18 cities, reaching a maximum of 6.1% in Los Angeles (Figure 3). The OFS strategy is expected to reduce risk even further, with a median reduction of 6.8% and a maximum of 14.8% in Sioux Falls (Figure 3). In some cases, the regimens approach the greatest possible reduction in RSV hospitalization risk (55%), which is expected under year-round palivizumab treatment. Paired t tests indicate that the NOV1 regimen is significantly more protective than the seasonal regimen ($P < .05$) in 9 cities, and the OFS regimen is superior to the seasonal regimen ($P < .02$) and to the NOV1 regimen ($P < .006$) in all 18 cities (eTables 1 and 2 in the Supplement).

We also compared the OFS regimen with the seasonal, NOV1, and MED30 strategies by tallying the number of years and cities in which it was predicted to outperform the alternatives. Among the 305 seasons considered, the OFS regimen would have conferred superior protection in 290 (i.e., 95.1%) of cases. The seasonal, MED30, and NOV1 regimens performed best in 11, 7, and 7 cases, respectively; some, but not all, of these 25 seasons exhibited strong early outbreaks.

Optimal Scheduling With Fewer Doses

The OFS4 regimen uses 4 rather than 5 injections and provides coverage for an estimated 143 days, which is 16 days less than the 5-dose seasonal regimen and 38 days less than the OFS. Nonetheless, the OFS4 regimen is expected to perform at least as well as the seasonal regimen in 11 of the 18 cities considered, significantly better in 3 cities, and significantly worse in 3 cities (paired t test, $P < .05$). Across all cities, the OFS4 regimen reduced the expected risk for RSV-related hospitalization by a median of 1.9% (range, −4.2% to 9.5%) compared with the 5-dose seasonal regimen. Some payers restrict the number of covered injections to 3 according to the 2012 AAP recommendations but not the updated 2014 recommendations. We estimate that reducing the seasonal regimen from 5 to 3 doses is expected to increase the relative hospitalization risk by a median of −10.3% (range, 1.7% to −31.6%). Use of November 1 as the start date for a 3-dose regimen increases risk by 11.8% (range, 8.0% to 38.6%) relative to the 3-dose seasonal regimen. In comparison, the locally optimized OFS3 regimen is expected to provide a median of 3.2% (range, −0.1% to 10.3%) more protection than the 3-dose seasonal regimen and to be more protective in 15 of 18 cities.
Discussion

We proposed a novel regimen (OFS) that is based on geographically determined fixed start dates for initiating immunoprophylaxis for RSV infection. In the OFS, the interval between injections is extended to 38 days after the second injection (rather than the 30-day intervals of current regimens). This regimen is based on an empirical pharmacokinetic threshold and extends the total protection by 3 weeks. The additional pro-

Figure 2. Recommended Dates for Initial Injections in the Optimized Fixed Start (OFS) Palivizumab Strategy in 17 US Cities

The OFS strategy is detailed in Table 2. Varied shades in data points correspond to the shading in the date line.

Table 2. Efficacy of Alternative Regimens Relative to Seasonal Regimen and Dates of Dose 1 for OFS, OFS4, and OFS3

<table>
<thead>
<tr>
<th>City</th>
<th>Efficacy of Seasonal Regimen, %</th>
<th>RRR of Alternative, %</th>
<th>Start Date</th>
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</thead>
<tbody>
<tr>
<td>City</td>
<td>NOV1</td>
<td>MED30</td>
<td>OFS</td>
</tr>
<tr>
<td>Atlanta, GA</td>
<td>48.6</td>
<td>-2.2</td>
<td>-0.3</td>
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<td>Birmingham, AL</td>
<td>50.7</td>
<td>2.7</td>
<td>2.1</td>
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<td>Cleveland, OH</td>
<td>48.5</td>
<td>4.9</td>
<td>6.7</td>
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<td>Columbia, SC</td>
<td>47.7</td>
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<td>-53.6</td>
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<td>Corpus Christi, TX</td>
<td>51.2</td>
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<td>4.2</td>
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<td>Los Angeles, CA</td>
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<td>Nashville, TN</td>
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<td>New Orleans, LA</td>
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<td>1.1</td>
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<td>Oklahoma City, OK</td>
<td>50.7</td>
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<td>4.3</td>
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<td>Richmond, VA</td>
<td>46.1</td>
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<td>4.2</td>
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<tr>
<td>San Diego, CA</td>
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<td>2.7</td>
<td>1.2</td>
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<td>Seattle, WA</td>
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<td>0.8</td>
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<tr>
<td>Sioux Falls, SD</td>
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<td>5.4</td>
<td>10.4</td>
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<tr>
<td>St Louis, MO</td>
<td>48.2</td>
<td>5.4</td>
<td>-4.1</td>
</tr>
<tr>
<td>Median</td>
<td>49.4</td>
<td>2.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 1. RRR, relative risk reduction.
* Computed over seasons relative to the 5-dose seasonal regimen.
tection is particularly beneficial in cities that experience long RSV seasons and allows protection to start earlier and end later in the year. With 5 doses, this new regimen is expected to decrease hospitalization risk relative to the conventional seasonal regimen in all 18 US cities considered ($P < .02$), with a median decrease of 6.8%. Although the OFS regimen does not entail additional injections, costs associated with variable spacing between injections may accrue. We suggest that these costs constitute a relatively low barrier given the expected improvements in hospitalization rates and mortality.

We also found that the AAP-recommended 5-dose palivizumab regimen, with its national fixed start date, is expected to be more protective than the seasonal regimen, which uses variable start dates triggered by local seasonal circulation of RSV. The AAP regimen is estimated to reduce RSV-related hospitalizations significantly in 9 of the 18 US cities considered, and the protection increases from a median of 49.4% (range, 39.1%-52.0%) to a median of 50.3% (range, 38.1%-53.4%), which translates to a relative decrease in risk of 2.7% (range, −2.2% to 6.1%). Under the AAP regimen, Atlanta would see an increase of 2.2% in the hospitalization risk. The MED30 regimen would reduce the national hospitalization risk by a median of 1.2% (range, −53.6% to 10.4%) relative to the seasonal regimen, with an outlier expected increase of 53.6% in Columbia.

The fixed start dates used by the AAP-recommended and OFS regimens are more robust to high variability in early-season RSV.
activity than the seasonal regimen that uses surveillance-triggered start dates.\textsuperscript{19-27} Some seasons exhibit multiple waves, with an initial wave that is short and unseasonably early followed by more typical, larger waves. In such years, regimens triggered by real-time data would start too early and exhaust the available doses while the threat of RSV remains. We also saw this effect when we modified the OFS regimen to allow an adaptive rather than a fixed start date and then optimized the surveillance trigger (eAppendix 3 in the Supplement). Even with an optimized incidence trigger, which often differs from the 10\% RSV positive test results in 2 consecutive weeks used in the seasonal regimen, these adaptive regimens are not projected to provide as much protection as the OFS regimen (although they are expected to outperform the seasonal regimen). The optimized start date does not apply to children born after the start of the season, who should receive palivizumab as early as possible.

A fixed start date also brings a practical advantage because patients who qualify for palivizumab could schedule appointments at pediatric practices in advance of the RSV season, thereby reducing congestion and administrative burdens at the beginning of the RSV season. However, an overly inflexible schedule might create barriers to care, decrease adherence to the injection regimen, and amplify existing disparities in treatment. Therefore, in clinical practice, if one of the injection dates cannot be scheduled or is likely to be missed by the patient, pediatricians should schedule the patient's appointment before the fixed date and, if necessary, reschedule. Although rescheduling shortens the duration of protection, this flexibility would ensure uninterrupted protection at the peak of the RSV season.

We evaluated palivizumab regimens in 18 US cities for which historical RSV laboratory data were available from the CDC. This method could be applied readily to other cities worldwide where similar epidemiologic data are available. The first step is to extend the window of palivizumab protection by using 38-day intervals between injections after the second injection; the second step, to use historical RSV data to optimize a fixed start date for the initial injection. For cities in the United States (outside Alaska or Florida) where no such data are available, practitioners might consider the median start date across the 18 OFS regimens (for 5 doses, October 24).

With the growing emphasis on efficient delivery of health care, strategies for improving health care while reducing costs are paramount. Although some studies\textsuperscript{28-30} have found that current palivizumab regimens are cost-effective and even cost-saving for some indications, its cost-efficiency is controversial,\textsuperscript{12,13,31} and one could imagine a scenario in which health care practitioners must reduce the number of palivizumab injections. We found that an optimized 4-injection regimen (OFS4) is often expected to achieve similar or greater protection than the conventional 5-dose seasonal regimen, particularly in cities that experience short RSV seasons. Thus, compensation for reductions in palivizumab availability through more efficient dispensation may be possible, contingent on the approval of the payers.

Because we used historical data to evaluate regimens, their future performance is uncertain. Nevertheless, we assessed the robustness of our findings with respect to several assumptions and confirmed that our estimates for the efficacy of the OFS regimen were consistent across a large number of historical years (eAppendix 2 in the Supplement) and cities (eAppendix 3 in the Supplement) using several metrics of RSV hazard. Furthermore, the city-specific start date of the OFS regimen was robust to uncertainty in the pharmacokinetics of palivizumab (eAppendix 1 in the Supplement).

Our method uses published estimates of pharmacokinetic properties\textsuperscript{11} and the efficacy of palivizumab (eAppendix 1 in the Supplement).\textsuperscript{6,23} but considerable variability across patients exists that is not well understood.\textsuperscript{32-33} This variability might leave some patients with inadequate antibody levels, particularly just before each injection. This risk is slightly larger with the OFS regimen than with the NOV1 regimen given that the mean antibody levels maintained during 180 days are expected to be 83 and 86 μg/mL, respectively. In the absence of reliable predictors that allow physicians to tailor palivizumab dosing schedules to individual patients, we emphasize the importance of testing the OFS and other proposed regimens in randomized trials to validate their efficacy under clinical conditions.

In addition, our estimates of RSV hospitalization risk are based on RSV laboratory test data. Although other investigators\textsuperscript{25,27,29-30} have demonstrated a significant correlation between the two and although RSV test positivity is used to determine the RSV season, positivity is only an approximate indicator of risk. Finally, our findings are limited to 18 geographically diverse US cities; extrapolation to other cities or rural areas requires further analysis of site-specific RSV data, particularly in Alaska and Florida, where the RSV season is unusually long.\textsuperscript{11,19}

Conclusions

Our evaluation of the AAP-recommended palivizumab regimen of 5 injections initiated on November 1 broadly supports its adoption compared with the seasonal regimen, which initiates injections based on RSV surveillance data. Additional protection is possible with the OFS 5-dose regimen, which is expected to achieve a 6.8\% median risk reduction compared with the seasonal regimen. The OFS is based on fixed initiation dates that differ by region and uses variable injection intervals (29-, 38-, 38-, and 38-day intervals rather than fixed 30-day intervals). The OFS4 regimen is expected to achieve risk reductions comparable to those of the seasonal 5-dose regimen while reducing the number of doses by 20\%.
Statistical analysis: All authors. Obtained funding: Galvani, Meyers. Study supervision: Meyers.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by Models of Infectious Disease Agent Study grant U1GMO87779 from the National Institutes of General Medical Sciences (Drs Galvani and Meyers). Dr. Gutfraind is also supported through the Oak Ridge Institute for Science and Education Fellowship Program and a pilot grant from the University of Illinois at Chicago.

Role of the Funder/Sponsor: The fundings sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Previous Presentation: This paper was presented as a poster at the Conference on Evolution and Ecology of Infectious Diseases, May 23-24, 2012; Ann Arbor, Michigan.

Additional Contributions: Rosalind M. Eggo, PhD, University of Texas at Austin, and Ed Goldstein, PhD, Harvard University, provided guidance on interpreting the surveillance data. Marilyn Felkner, DrPH, and Lesley Brannan, MPH, Texas Department of State Health Services, provided guidance on RSV surveillance and palivizumab administration policies. The Centers for Disease Control and Prevention shared National Respiratory and Enteric Virus Surveillance System outbreak data on RSV. MedImmune provided information on palivizumab. Anonymous reviewers provided excellent suggestions for improving both clarity and rigor. No compensation was provided for these contributions.

REFERENCES