Adherence to Immunoprophylaxis Regimens for Respiratory Syncytial Virus Infection in Insured and Medicaid Populations

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Background. Immunoprophylaxis is the only pharmaceutical intervention for mitigating respiratory syncytial virus (RSV) infection. Patient level data on adherence to American Academy of Pediatrics (AAP) immunoprophylaxis recommendations are limited. This study characterizes adherence to AAP guidelines in privately insured and Medicaid populations.

Methods. We performed a retrospective birth cohort study of 211 174 privately insured children in Northern California; and 458 837 publicly insured children in Tennessee born between January 1, 1996 and December 31, 2008. Adherence to the AAP guideline was defined for eligible infants as the number of doses of RSV immunoprophylaxis administered over the number recommended for 4 mutually exclusive eligibility groups: chronic lung disease, prematurity <29 weeks, prematurity <32 weeks, and other eligibility.

Results. We identified 3456 California (Kaiser Permanente Northern California [KPNC]) and 12 251 Tennessee (Tennessee Medicaid [TennCare]) infants meeting AAP eligibility criteria. Immunoprophylaxis administration increased over the study period, from 15% for all eligible groups in 1998 to 54% in 2007. Adherence was highest among babies with chronic lung disease (KPNC 67% and TennCare 55%). Nonadherence (0% adherence) was greatest among infants of African American mothers (adjusted odds ratio [AOR] = 1.32; 95% confidence interval [CI] = .98–1.78); those with mothers with less than a high school education (AOR = 1.58; CI = 1.09–2.30) in KPNC; and in infants of Hispanic mothers in TennCare (AOR = 1.65; CI = 1.24–2.20). In KPNC, 0.11% of ineligible term infants and 5% of ineligible premature infants received immunoprophylaxis; the corresponding proportions in TennCare were 1% and 11%.

Conclusions. Overall adherence with AAP guidelines has increased over time. Considerable overuse and underuse of immunoprophylaxis are evident with identifiable risk groups to target for improvement.

Infection with respiratory syncytial virus (RSV) is common, with infection rates approaching 100% by age 3 years [1]. Attempts at developing an RSV vaccine have been unsuccessful [2–5]. Given the absence of viable treatment options, the only currently available option for decreasing morbidity among high risk infants is immunoprophylaxis. In 1997, the American Academy of Pediatrics (AAP) first issued recommendations for RSV immunoprophylaxis, recommending RSV immunoglobulin, and in 1998 recommending palivizumab administration, to selected infants at high risk (eg, premature infants <32 weeks gestation) [6]. These recommendations, based on contemporary data [7–13], were revised in 2003 [14] and 2009 [15].

A number of studies investigated the efficacy, effectiveness, and cost-effectiveness of RSV immunoprophylaxis with respect to hospitalization for bronchiolitis [16–24]. Our study, Prevention of RSV: Impact on Morbidity and Asthma (PRIMA), has been funded by the Agency for Healthcare Research and Quality to conduct a
PATIENTS AND METHODS

This study was approved by both the KPNC and Vanderbilt University Institutional Review Boards. Use of birth certificate data was approved by the State of California Committee for the Protection of Human Subjects and the Tennessee Department of Health, and use of Tennessee Medicaid data was approved by the Bureau of TennCare.

Study Population

Eligible infants met the following criteria: born between January 1, 1996 and December 31, 2008; birth weight of 500–6999 grams; gestational age between 24 0/7 and 45 5/7 weeks; and continuously enrolled in either TennCare or KPNC during the first year of life. In addition, KPNC infants had to be born at 1 of the 6 Northern California KPNC hospitals with a level III neonatal intensive care unit, representing 90% of all neonatal intensive care admissions in the program. Enrollment was considered continuous if there were no more than 90 days of nonenrollment during the first 12 months of life. Approximately 50% of infants in Tennessee are enrolled in TennCare.

Study Outcome

Our primary study outcome was receipt of the calculated recommended doses of RSV immunoprophylaxis for each infant within each eligibility category during the first year of life. For the purposes of our analyses, the window for RSV prophylaxis extended from November 1st to March 30th for all study years (1996–2008). This time frame is consistent with RSV surveillance data, defines the time period when eligible infants should receive immunoprophylaxis, and constitutes the time period during which one can assess completeness of adherence to AAP recommendations [26–29]. The outcome of calculated recommended doses of RSV immunoprophylaxis for each infant can be expressed as a percentage, as was done by Hampp et al [30] although our methodology was slightly different (detailed in Appendix 2).

We determined receipt of RSV immunoprophylaxis using International Classification of Diseases, Ninth Revision (ICD-9) [31] and Current Procedural Terminology (CPT4) codes [32]. We captured total number of doses and date of each dose. The number of recommended doses of RSV immunoprophylaxis was calculated for each infant depending on recommendations for each eligibility group and infant age in relation to RSV season. Our main dichotomous outcome for multivariable analysis was the receipt of ≥70% (yes vs no) of the recommended number of doses for each infant. Because of data limitations, we assigned a birth hospitalization discharge date to 62% of TennCare children using imputation methods (Appendix 4). During the study period, palivizumab was used exclusively in KPNC after 1998, whereas both palivizumab and RespiGam were used in TennCare.

Adherence to Guidelines and Predictors of Receipt and Nonreceipt

Details on our data sources and methods are available in the appendices or have been published elsewhere [10, 33–44]. Using the available data, we placed infants into 5 hierarchical and mutually exclusive eligibility categories based on the above-mentioned AAP guidelines (Figure 1). These were as follows: (1) chronic lung disease requiring medical therapy in the 6 months preceding the RSV season; (2) prematurity <29 completed weeks; (3) prematurity <32 weeks; (4) other eligibility (eg, 32–34 week infants with 2 or more risk factors, infants with congenital heart disease, etc); and (5) ineligible for RSV immunoprophylaxis. In this scheme, children in groups 1–4 constitute the total population eligible for RSV immunoprophylaxis. During data collection, we learned that internal communications for immunoprophylaxis in KPNC specified a gestational age range that was higher (≤32 weeks vs <32 weeks) than that in the AAP guideline.

To analyze adherence within eligibility groups 1–4, we considered the following predictors in our bivariate and multivariable analyses: infant sex, maternal race, gestational age, small for gestational age status (birth weight <5th percentile) [45], season of discharge, maternal age, maternal...
education, maternal smoking, maternal gravidity, and discharge year. Nonadherence was defined as an eligible infant who received 0% of the recommended doses of RSV immunoprophylaxis. In addition, we report on receipt of RSV immunoprophylaxis among the ineligible group.

**Statistical Analysis**

We conducted all analyses using SAS version 9.1.3 (SAS Institute Cary, NC) and R version 2.12.1 (http://www.r-project.org). For descriptive analyses, we treated adherence as a categorical variable in 2 ways (any vs none; or 3 categories: 0%–69%, 70%–99%, 100%) across the eligibility groups. We assessed the association of the predictors with the dichotomous outcome of receipt of ≥70% with adjusted odds ratios (AORs) and corresponding 95% confidence intervals (CIs) using a multivariable logistic regression model. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test, and model discrimination and overall explanatory power were assessed using the c-statistic (area under the receiver operator characteristic curve) and the Nagelkerke pseudo-$R^2$, as
We estimated the relative contribution of predictors using the method described by Render et al [47].

RESULTS

During the study period, a total of 211,174 babies were discharged alive from the KPNC sites. Of these infants, 3456 (1.6%) were eligible for immunoprophylaxis. The corresponding figures for TennCare were 458,837 and 12,251 (2.7%). Figure 1 shows the distribution of patients within the defined eligibility categories in both programs.

Table 1 summarizes the 2 cohorts, which have important differences in baseline characteristics. Babies born in KPNC had longer mean gestational age (38.8 ± 2.1 weeks vs 38.5 ± 2.4 weeks; \( P < .001 \)), higher birth weight (3365 ± 617 grams vs 3179 ± 599 grams; \( P < .001 \)), and a lower proportion of small for gestational age infants (1% vs 4%; \( P < .001 \)). The increased proportion of eligible infants in the TennCare group is largely driven by prematurity: for example, infants born at <28 weeks constituted 0.6% (2271 of 364,612) of the TennCare cohort but only 0.4% (650 of 166,463) of the KPNC cohort.

Adherence to RSV Immunoprophylaxis Regimens

Among eligible groups in KPNC, the proportion of infants who received no immunoprophylaxis over the entire study period ranged from 19% among infants with chronic lung disease (CLD) to 84% among infants in the other eligibility group, whereas the proportion of infants who received 100% of recommended doses ranged from 11% among infants in the other eligibility group to 58% among infants in the <29 weeks gestation group (Table 2). In the TennCare cohort, the proportion of infants who received no immunoprophylaxis ranged from 7% among infants in the other eligible group to 37% among infants in <32 weeks group, whereas the proportion of infants who received 100% of recommended doses ranged from 29% among infants in <32 weeks group to 49% in the CLD group. Additional tabular data on the other eligibility group are provided in Appendix 3.

Predictors of Adherence to RSV Immunoprophylaxis Guidelines

Predictors of \( \geq 70\% \) adherence to RSV immunoprophylaxis among infants discharged in 1998–2007 are listed in Table 3. Figure 2 shows changes in adherence over
time in the 2 cohorts for the entire study period. With respect to temporal factors, the AORs for epochs after 1998–1999 were significant in both programs, although some leveling off occurred in the last epoch. Across all years, in both cohorts, discharge epochs later than 1998–1999 were significantly associated with increased adherence. Maternal factors also had significant effects. In KPNC, children of African American mothers were less likely to be adherent (AOR = .53; CI = .41–.69), whereas in TennCare this effect was seen in children of Hispanic mothers (AOR = .65; CI = .52–.83). In both cohorts, younger maternal age was associated with lesser adherence, although this was more pronounced in the KPNC cohort than in TennCare. In KPNC, first time mother status was associated with adherence (AOR = 1.37; CI = 1.13–1.67) and maternal smoking was associated with nonadherence (AOR = .67; CI = .49–.91). In TennCare, children of mothers with more than a high school education were more likely to be adherent (AOR = 1.18; CI = 1.05–1.32).

With respect to neonatal factors, prematurity was associated with increased adherence in both cohorts: for example, compared with term infants, the AORs for children born at <28 weeks were 16.10 (CI = 8.74–29.65) in KPNC and 2.09 (CI = 1.56–2.79) in TennCare. Small for gestational age status was also associated with increased adherence, with an AOR of 1.79 (CI = 1.07–2.99) in KPNC and 2.48 (CI = 2.01–3.05) in TennCare.

In models, the most important predictor for adherence in the KPNC cohort was gestational age group, with a relative explanatory power of 65.7%, followed by calendar year (17.0%) and maternal race (6.1%). In the TennCare cohort, the most important predictor was calendar year (79.5%), followed by small for gestational age status (5.2%) and gestational age group (5.2%).

**Predictors of Nonadherence to RSV Immunoprophylaxis Guidelines**

The results of our alternative logistic regression model, in which the dependent variable was 0% adherence, were directionally similar. Children born in later time periods and children discharged during RSV season were less likely to have 0% adherence. In KPNC, children of African American mothers were more likely to have 0% adherence (AOR = 1.32; CI = .98–1.78), and this result was also found among children of Hispanic mothers in TennCare (AOR = 1.65; CI = 1.24–2.20). KPNC children whose mothers lacked a high school education were more likely to have 0% adherence (AOR = 1.58; CI = 1.09–2.30); in TennCare, children of women with more than a high school education were less likely to have 0% adherence (AOR = .80; CI = .69–.94). Results for neonatal factors were also directionally similar, with premature infants <28 weeks significantly less likely to be 0% adherent in KPNC (AOR = .039; CI = .021–.072), and the same effect, although not statistically significant, occurred in TennCare (AOR = .87; CI = .53–1.43).

The other aspect of nonadherence is receipt of RSV immunoprophylaxis among children not meeting our predefined AAP eligibility categories. The total proportion of infants in the ineligible group who received immunoprophylaxis was 0.11% among term infants and 5% among premature infants in KPNC; the corresponding proportions in the TennCare cohort were 1% and 11%. Most of these children were born between 32 and 35 weeks gestation: among KPNC babies 32–35 weeks gestation who did not meet other eligibility criteria, 690 of 9350 (7%) received immunoprophylaxis, whereas in TennCare this proportion was 4431 of 27928 (16%). Among the remaining ineligible children 32–37 weeks gestation, 89 of 7275 (1%) received immunoprophylaxis in KPNC and 1028 of 21717 (5%) received immunoprophylaxis in TennCare.

**DISCUSSION**

To our knowledge, this is the first and largest study that includes both a privately insured and Medicaid population, to systematically assess and compare adherence to RSV immunoprophylaxis recommendations in 2 representative US populations. Overall adherence to the AAP recommendations was fairly high and improved over time, an important finding given the fact that adherence, which requires identification of eligible infants with different therapy requirements and 4–5 monthly intramuscular injections, can be difficult. We also found that a number of infants (992 of 207718 or 0.48% of such children in KPNC and 8171 of 446586 or 1.83% in TennCare) who did not meet our criteria for receipt of immunoprophylaxis did in fact receive it, a finding that merits further study given the costs of administration. Our findings expand upon the findings of a study with a much smaller population describing the use of palivizumab among fee-for-service Medicaid recipients in Florida [30]. Like that study, we report high overall adherence rates, increasing uptake over time followed by a plateau in adherence, decreased use among certain racial groups, and significant use among children not meeting eligibility criteria.

In multivariable analyses, we determined factors associated with receipt of ≥70% of the calculated number of
African American former preterm infants [48]. In con-

management in KPNC that showed a similar effect among

light of the results of a previous study on asthma man-

was evident in the KPNC cohort, which is important in

Decreased adherence among African American infants

cohort and younger gestational age in the KPNC cohort.

strongly associated with adherence in the TennCare

greatly between sites, with later years being more

effects of year of birth and gestational age differed

between the cohorts. The magnitude of the

slowly in later years.

In general, adherence improved over time, although more

slowly in later years.

In contrast, a number of factors associated with adher-

differed between the cohorts. The magnitude of the

effects of year of birth and gestational age differed

greatly between sites, with later years being more

strongly associated with adherence in the TennCare

cohort and younger gestational age in the KPNC cohort.

Decreased adherence among African American infants

was evident in the KPNC cohort, which is important in

light of the results of a previous study on asthma man-

agement in KPNC that showed a similar effect among

African American former preterm infants [48]. In con-

trast, decreased adherence among Hispanic infants was

observed in the TennCare cohort. These program-specific

findings suggest that different types of barriers (including

possible cultural or language barriers) may be present in

these 2 programs. During the course of conducting

audits for this study, we discovered that medical centers

included risk factors in addition to those outlined in the

AAP guidelines, such as lack of breastfeeding, small for

gestational age status, and male sex, to determine eligibil-

ity for immunoprophylaxis. As noted previously, internal

communications for immunoprophylaxis in KPNC speci-

fied a gestational age range that was higher (≤32 weeks

vs <32 weeks), which highlights how small modifications

that occur at a local level can affect implementation of

nationally promulgated guidelines.

With respect to adherence, it is important to consider

our findings from 3 perspectives. First, in some respects,

RSV immunoprophylaxis is analogous to vaccination,

and our finding of a plateau effect is similar to that seen

with new vaccinations in young children, such as the one

for varicella [49]. From this perspective, improvements in

adherence to immunoprophylaxis could be achieved

using approaches similar to those used for vaccines.

Second, because immunoprophylaxis is not recommend-

ed for all infants, (1) determination of eligibility is not

straightforward, (2) strict timing of injections is required,

and (3) improvements in RSV immunoprophylaxis ad-

herence may require different approaches, including en-

hanced understanding of acceptability and uptake in the

targeted populations. This process begins with first un-

derstanding whether the target populations have a per-

ceived risk of infection and knowledge of the benefits of

immunoprophylaxis. It also includes considering patient

beliefs, clinician beliefs, and other factors likely to impact

immunoprophylaxis initiation and completion. Third,

because the immunoprophylaxis regime is complex and

at present there is no evidence of harm due to nonreceipt,

it is essential to remember that using the term “adher-

ence” must be more nuanced, because whether an infant

receives immunoprophylaxis may be more dependent on

system-level factors (eg, outreach) than on patient- or

family-specific factors.

Our study also identifies eligible infant groups in

whom targeted strategies to increase coverage should be

developed. The data also identify the problem of

administration of a costly medication to a group not

recommended to receive it and delineate this group’s

characteristics. An easier system for assessment of eligi-

bility seems to be needed, and it could be refined in an era

that focuses on personalized medicine. Finally, data from

this study lead to the next set of questions that need to

be addressed to impact outcomes for these children,

which is to understand why these groups are not covered

and to implement and study strategies for improving

<table>
<thead>
<tr>
<th>Table 2. Adherence to Immunoprophylaxis Regimen by Eligibility Group</th>
<th>Chronic Lung Disease</th>
<th>Prematurity &lt;29</th>
<th>Prematurity &lt;32</th>
<th>Other Eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KPNC</td>
<td>TennCare</td>
<td>KPNC</td>
<td>TennCare</td>
</tr>
<tr>
<td>N</td>
<td>328</td>
<td>990</td>
<td>1020</td>
<td>3958</td>
</tr>
<tr>
<td>Receipt of immunoprophylaxis</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>62</td>
<td>19</td>
<td>170</td>
<td>17</td>
</tr>
<tr>
<td>Any</td>
<td>266</td>
<td>81</td>
<td>820</td>
<td>83</td>
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<tr>
<td>0%-69%</td>
<td>108</td>
<td>33</td>
<td>448</td>
<td>45</td>
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<td>70%-99%</td>
<td>45</td>
<td>14</td>
<td>115</td>
<td>58</td>
</tr>
<tr>
<td>100%</td>
<td>183</td>
<td>56</td>
<td>484</td>
<td>49</td>
</tr>
</tbody>
</table>

Abbreviations: KPNC, Kaiser Permanente Medical Care Program; TennCare, Tennessee Medicaid.

*aSome discrepancies in percents due to rounding.

*bEligibility groups are mutually exclusive; see text and Figure 1 for details of hierarchical assignment of categories.

*cSee text details on how receipt of immunoprophylaxis was ascertained. Adherence is quantified as the percentage of the recommended doses (given an infant’s discharge date from the hospital) that an infant received.
adherence for eligible infants while avoiding administration to ineligible infants.

It is important to note a number of study limitations. We relied entirely on electronic data, which have important gaps, including data on additional eligibility factors (eg, childcare) as well as factors that could lead to adherence (eg, clinician knowledge of additional reasons to provide immunoprophylaxis, outreach efforts to specific families) or nonadherence (eg, parental refusal, medical contraindications). In the absence of a widely recognized metric for immunoprophylaxis, we made what we considered a reasoned choice for an outcome variable—70% adherence—but other investigators might not select this. Furthermore, our simplified definition does not completely address issues with respect to late provision of immunoprophylaxis (eg, an April dose). Finally, given our reliance on electronic data, we may have misclassified some infants.

Despite these limitations, our findings have important implications for understanding the use, uptake, and

### Table 3. Factors Associated With ≥70% Adherence Among Infants Eligible for Immunoprophylaxis, Discharged in 1998–2007

<table>
<thead>
<tr>
<th>Factor</th>
<th>KPNC</th>
<th>95% CI</th>
<th>TennCare</th>
<th>95% CI</th>
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<tr>
<td>Year of discharge</td>
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<td>1998–1999</td>
<td>Reference</td>
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<td>Reference</td>
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<tr>
<td>2000–2001</td>
<td>2.49</td>
<td>1.87–3.31</td>
<td>4.50</td>
<td>3.76–5.40</td>
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<tr>
<td>Season of discharge</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outside of RSV season</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>During RSV season</td>
<td>1.08</td>
<td>.91–1.30</td>
<td>1.58</td>
<td>1.44–1.73</td>
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<td>Maternal race&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>.53</td>
<td>.41–.69</td>
<td>1.02</td>
<td>.93–1.12</td>
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<tr>
<td>Hispanic</td>
<td>1.08</td>
<td>.84–1.39</td>
<td>.65</td>
<td>.52–.83</td>
</tr>
<tr>
<td>Asian</td>
<td>.93</td>
<td>.71–1.22</td>
<td>.64</td>
<td>.39–1.04</td>
</tr>
<tr>
<td>Other</td>
<td>1.09</td>
<td>.79–1.49</td>
<td>.94</td>
<td>.61–1.44</td>
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<tr>
<td>Maternal age, y</td>
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<td></td>
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<tr>
<td>&lt;18</td>
<td>.35</td>
<td>.17–.75</td>
<td>.74</td>
<td>.58–.95</td>
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<tr>
<td>18–24</td>
<td>.57</td>
<td>.43–.75</td>
<td>1.01</td>
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<td>25–34</td>
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<td>.87–1.22</td>
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<td>≥35</td>
<td>Reference</td>
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<td>Reference</td>
<td></td>
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<tr>
<td>Maternal gravidity at delivery</td>
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<tr>
<td>Primigravida</td>
<td>1.37</td>
<td>1.13–1.67</td>
<td>1.06</td>
<td>.95–1.18</td>
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<td>Multigravida</td>
<td>Reference</td>
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<td></td>
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<tr>
<td>Maternal cigarette smoking during pregnancy</td>
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</tr>
<tr>
<td>Smoked</td>
<td>.67</td>
<td>.49–.91</td>
<td>.96</td>
<td>.86–1.06</td>
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<td>Never smoked</td>
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<td>Maternal education</td>
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<td>Less than high school</td>
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<td>.51–1.01</td>
<td>.91</td>
<td>.82–1.00</td>
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<td>College</td>
<td>1.17</td>
<td>.95–1.45</td>
<td>1.18</td>
<td>1.05–1.32</td>
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<td>Infant Sex</td>
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<tr>
<td>Male</td>
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<td>.95</td>
<td>.88–1.04</td>
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<td>28–31</td>
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<td>3.39–10.82</td>
<td>1.61</td>
<td>1.22–2.13</td>
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<td>32–36</td>
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<td>≥37</td>
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<td>c-statistic</td>
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<td>.70</td>
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<td>R&lt;sup&gt;2&lt;/sup&gt;</td>
<td>.28</td>
<td></td>
<td>.18</td>
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<td>Hosmer-Lemeshow P value</td>
<td>.221</td>
<td></td>
<td>.016&lt;sup&gt;d&lt;/sup&gt;</td>
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</table>

Boldface text indicates significance (P < .05).
Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; KPNC, Kaiser Permanente Medical Care Program; RSV, respiratory syncytial virus; TennCare, Tennessee Medicaid.
<sup>a</sup>See text for details on how maternal race was assigned.
<sup>b</sup>See text for details on how gestational age was assigned.
<sup>c</sup>Small for gestational age determined as birth weight <5th percentile, based on the algorithm developed by Brenner et al.<sup>39</sup>
<sup>d</sup>Although P value is significant, model is well calibrated; see decile plot in the web appendix (Appendix 6).
adherence to immunoprophylaxis among infants for whom it is recommended and use outside of these recommended groups. Unlike a randomized trial, demonstration of an intervention’s beneficial effect in a community setting can be very difficult, and our results show that nonadherence is not randomly distributed (we observed a differential receipt of immunoprophylaxis among infants at highest risk). Consequently, analyzing the relationship between receipt of immunoprophylaxis and the occurrence of severe RSV infection requires use of more sophisticated methods, including propensity scores [50].

First, our study has additional implications for improving adherence to guidelines, because it identifies groups in whom rates of administration are significantly lower, who are targets for improved adherence. Second, although the uptake of RSV immunoprophylaxis is similar to other preventive interventions, the proportion of eligible patients receiving it has not reached that of early childhood vaccines, and this group also differs within the risk groupings for which RSV immunoprophylaxis is recommended. Finally, because RSV immunoprophylaxis is a costly intervention, decreasing use among ineligible infants would result in cost savings.

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Author contributions. G. J. E. was responsible for drafting of the manuscript and overseeing the analyses included therein; he also worked with T. H. in writing the original grant proposal that led to this study being funded and is also the principal investigator of record for this project within Kaiser Permanente Northern California (KPNC). The Agency for Healthcare Research and Quality (AHRQ) grant awarded funding for this project to T. H. (the principal investigator); she participated in editing of the manuscript as well as in overseeing the overall creation of the study dataset as well as the analyses included in this manuscript. T. G., statistician, conducted all of the analyses and also ensured their statistical integrity under the supervision of T. H. and G. J. E. Moreover, K. C., S. X. L., E. M. W., P. W., E. M., and C. S. provided intellectual input and assisted in editing of the manuscript. In addition, K. C. and P. W. assisted T. H. and G. J. E. in establishing the definitions and variables for the study, whereas S. X. L. and E. M. W. prepared the KPNC dataset and E. M. prepared the TennCare dataset. Both T. H. and G. J. E. had full access to all data in the study, and they take responsibility for the integrity of the data and the accuracy of the data analyses.

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