intelligence. If \( \beta_{\text{break}} \) indicates a statistically significant upward shift in a carefully calibrated estimation model, which also includes all plausible and available environmental controls, there is strong evidence that the resulting partial regression coefficient of duration of breastfeeding is still not reflecting pure nutritional effects.

The pattern shown in this study also helps explain why studies comparing children who have ever been breastfed and those who have never been breastfed find no difference in intelligence.6

Fabian Kosse, Dr rer pol

Author Affiliation: Institute for Applied Microeconomics, University of Bonn, Bonn, Germany.

Corresponding Author: Fabian Kosse, Dr rer pol, Institute for Applied Microeconomics, University of Bonn, Adenauerallee 24-42, 53113 Bonn, Germany (kosse@uni-bonn.de).


Conflict of Interest Disclosures: None reported.

Additional Contributions: Data access was provided by Bernardo Lessa Horta, PhD, Universidade Federal de Pelotas. He was not compensated for his contribution.


Outcomes of Respiratory Syncytial Virus Immunoprophylaxis in Infants Using an Abbreviated Dosing Regimen of Palivizumab

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants younger than 1 year. Premature infants, infants with chronic lung disease, infants with major congenital heart diseases, or infants with severe immunodeficiencies are at highest risk of hospital admission for RSV. Palivizumab, a monoclonal antibody, reduces pulmonary viral replication by 100-fold on serum drug levels greater than 40 μg/mL in the cotton rat model.1

On the basis of randomized clinical trials, monthly administration of 15 mg/kg of palivizumab reduces hospitalizations by approximately 55% in these infants.2 However, the costliness of this drug restrains its broader use. The American Academy of Pediatrics recommends a maximum of 5 palivizumab doses in selected risk groups during the RSV season,3 although pharmacokinetic analyses suggest that equivalent antibody protection may be sustainably achieved with fewer doses.3,4

Methods | In British Columbia, administration of palivizumab necessitates central approval through the British Columbia RSV Immunoprophylaxis Program, and eligible infants are closely followed up by program-coordinated clinics across the province. The RSV season extends from November to April, with the first and last palivizumab doses given the closest day to November 15 and on April 15, respectively. All infants receive a maximum of 3 or 4 doses based on criteria listed in the Table, with maximal dose intervals of 28 days after the first dose and 35 days after the second and subsequent approved doses (prospectively defined as the scheduled dosing period). Hospitalizations in the preceding month are assessed in program clinics before each dose and up to April 30 each year. Program data were linked to the Discharge Abstract Database of the British Columbia Health Authorities to confirm hospitalizations, according to 7 diagnostic codes for RSV bronchiolitis or acute respiratory infection of unspecified cause using the International Classification of Diseases, Tenth Revision, and International Classification of Diseases, Tenth Revision, Clinical Modification. The study was approved by the Children’s & Women’s Research Ethics Board. Written informed consent was obtained from all participants in whom blood samples were obtained for RSV neutralizing antibody measures.

### Table. Administration Criteria for Respiratory Syncytial Virus Immunoprophylaxis in British Columbia

<table>
<thead>
<tr>
<th>Indication</th>
<th>Maximum No. of Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD or CLD requiring oxygen or continuous positive airway pressure at &gt;28 days of age and &lt;1 year of age by November 1 AND receiving supplemental oxygen on or after July 1</td>
<td>4</td>
</tr>
<tr>
<td>Born at &lt;29 weeks of gestation and discharged home on or after September 1</td>
<td>4</td>
</tr>
<tr>
<td>Tracheostomy, receiving home oxygen, or receiving home ventilatory support on or after November 1 and &lt;2 years of age by November 1</td>
<td>4</td>
</tr>
<tr>
<td>Multiples (twins or triplets) of approved child and born on or after November 1, 2012 Same as approved sibling</td>
<td></td>
</tr>
<tr>
<td>Hemodynamically significant CHD and &lt;2 years of age by November 1</td>
<td>4</td>
</tr>
<tr>
<td>Severe immunodeficiency (eg, stem cell transplantation) and &lt;2 years of age by November 1</td>
<td>4</td>
</tr>
<tr>
<td>Cystic fibrosis with lung disease and born on or after January 1</td>
<td>4</td>
</tr>
<tr>
<td>Trisomy 21 without hemodynamically significant CHD and discharged home on or after October 1 and with a risk factor score ≥42 points*</td>
<td>4</td>
</tr>
<tr>
<td>Significant pulmonary disability (pulmonary hypertension, pulmonary malformations, severe BPD, progressive neuromuscular disease, other) and &lt;2 years of age by November 1</td>
<td>4</td>
</tr>
<tr>
<td>Infants born between 29 and &lt;35 completed weeks of gestation without BPD or CLD and discharged home on or after October 1 and with a risk factor score ≥42 points*</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; CLD, chronic lung disease.

* Risk factor score is calculated as follows: Infant attends day care regularly during first 3 months after discharge (22 points); discharged home in December, January, or February (20 points); discharged home in November or March (10 points); gestational age at birth of 29 weeks to less than 31 weeks of completed gestation (10 points); more than 5 people living in household (12 points); sibling younger than 5 years (14 points); remote community, travel of more than 1 hour or of more than 100 km required to the nearest hospital (10 points); girl not receiving breast milk, or boy (8 points); birth weight less than 10th percentile (8 points); and 2 or more smokers in household (8 points).
A subset of infants approved to receive either 3 or 4 doses of palivizumab were tested before any palivizumab dose, between 1 and 5 days after a first dose of palivizumab, and at the end of the RSV season (at least 30 days after the last palivizumab dose or after April 15, whichever came last). The RSV neutralizing antibody titers were also determined in season-matched healthy adults. The RSV neutralizing serum antibody titer equivalents (NT95) are based on the ability of a serum dilution (expressed as 1/titer) to inhibit 95% or more of viral infection. In this assay, we determined that palivizumab serum concentrations of 40 μg/mL correspond to a median neutralizing antibody titer of 1:32 (dotted line with minimum and maximum values [shaded area from 3 independent experiments performed in duplicate]). Detection limit was NT95 of approximately 4 (or 1/4), equivalent to a serum concentration of palivizumab of approximately 6.25 μg/mL except for predose serum samples for which the detection limit of the assay was NT95 of approximately 2. Error bars represent median with interquartile range.

Results | We report our population-based intent-to-treat analysis with 100% follow-up rate. Since we adopted this abbreviated program, 514 infants and 666 infants have been approved in the 3- and 4-dose schedules for 4 (2010-2014) and 2 seasons (2012-2014), respectively. In the 3-dose cohort, 1 of 514 infants (0.2%) was hospitalized with RSV during the scheduled dosing period, and 1 was hospitalized 58 days after the third dose. In the 4-dose cohort, 10 infants (1.5%) were hospitalized with RSV during the scheduled dosing period, and 2 twins (0.3%) were hospitalized 65 days after the fourth dose. Moreover, 7 infants (1.4%) and 18 infants (2.7%) in the 3-dose and 4-dose cohorts, respectively, were hospitalized for acute bronchiolitis with no viral studies performed (unspecified cause) within the scheduled dosing period. No infants in either cohort were hospitalized for unspecified bronchiolitis beyond the same period. These data have considerable resource implications for RSV vaccine schedule in infants at higher risk for RSV hospitalization.

Discussion | The RSV neutralizing antibodies comprise palivizumab and natural immunity against the virus, which is important because preexisting antibodies correlate best with protection against infection in humans. In summary, our experience in British Columbia provides real-world evidence of adequate protection using an abbreviated palivizumab dosing schedule in infants at higher risk for RSV hospitalization. These data have considerable resource implications for RSV prevention in other medical jurisdictions.
Hospitalizations of Low-Income Children and Children With Severe Health Conditions: Implications of the Patient Protection and Affordable Care Act

Medicaid reimbursement often falls below health care costs (Medicaid shortfall). Therefore, hospitals face financial losses from caring for both uninsured and Medicaid-insured patients. The US government provides disproportionate share hospital (DSH) payments to institutions with large uninsured and Medicaid populations. Anticipating decreased numbers of uninsured patients, the Patient Protection and Affordable Care Act (ACA) reduces DSH payments.1 The ACA also penalizes hospitals for readmissions.2 There will not be large decreases in the number of uninsured children since only a small percentage of children are uninsured. In contrast, a high percentage of children have Medicaid insurance, and institutions will continue to face Medicaid shortfalls. The loss of DSH payments may not be matched by reductions in financial losses from decreases in the number of uninsured patients. In addition, the readmission penalties of the ACA may not adequately adjust for low-income patients or patients with severe health conditions, thereby adversely affecting hospitals with high proportions of these patients.3 We sought to determine which hospitals with pediatric patients may be at highest financial risk from decreases in DSH payments and readmission penalties by identifying hospitals with a disproportionate per-hospital number of discharges of pediatric patients receiving Medicaid and those with a disproportionate per-hospital number of discharges of low-income patients or those who have severe health conditions, respectively.

Methods | We analyzed 1174 540 discharges of patients younger than 18 years from 2207 hospitals in the 26 states providing hospital identifiers to the 2009 Kids Inpatient Database (Agency for Healthcare Research and Quality)4 from March 5, 2013, through February 27, 2015. The main outcome was hospital type categorized by teaching status (as defined by the Agency for Healthcare Research and Quality)4 and children’s hospital status (as defined by the Children’s Hospital Association). Children’s hospital status was subcategorized as free-standing and within a general hospital or specialty children’s hospital. The main exposures were patient household income (HI) (quartile of median HI by zip code), insurance type, severity (quartile of charge weight),5 and complexity (complex chronic condition).6 We excluded pregnancy-related (All Patient Refined Diagnosis Related Group [APR-DRG] codes 540-566) and normal newborn discharges (DRG code 391 or newborn discharges with a length of stay <5 days unless death occurred). This study was deemed exempt from institutional board review by Children’s Mercy Hospital and Clinics.

We used χ² tests to compare patients’ HI, insurance type, illness severity, and disease complexity levels by hospital type. To determine the relative per-hospital burden of patients with these characteristics, we created ratios of observed-to-expected number of discharges by dividing the percentage of discharges by the percentage of hospitals for each hospital type.

Results | Most discharges (range, 232 605 of 404 835 [57.5%] to 212 147 of 313 649 [67.6%]) of pediatric patients with Medicaid insurance, lowest HI, and highest severity of illness were from non-children’s hospitals (Table 1). Although children’s hospitals represented 3.4% (n = 75) of all hospitals, they accounted for 32.4% (n = 101 502) of the lowest HI, 33.8% (n = 185 905) of Medicaid recipients, and 42.5% (n = 172 230) of patients with the highest severity of health conditions. Children’s hospitals cared for most patients with complex chronic conditions (152 872 [52.8%]).

For patient mix within hospital types, there were similar distributions of payor type (range, 46%–47% for Medicaid recipients 2%–4% for the uninsured) and HI (range, 24%–29% for the lowest HI) (Table 2). In contrast, 172 230 (43.0%) children’s hospital discharges were children in the highest illness severity category compared with 94 119 (24.5%) discharges of such children from nonteaching hospitals. Similarly, 78 408 (41.0%) children discharged from a freestanding children’s hospital had a complex chronic condition compared with 46 520 (12.1%) children discharged from nonteaching hospitals.

Discussion | Analysis of more than 1 million pediatric hospitalizations in 26 states demonstrated that, although non-children’s teaching hospitals were the most common hospital type for patients with Medicaid, those with the lowest HI, and those with the highest severity of health conditions, the per-hospital burden of those discharges was much greater for children’s hospitals. Moreover, children’s hospitals cared for most of the chronically ill patients and had the greatest proportion of discharges of patients with complex chronic conditions.

Our study has several limitations, including the use of community-level HI as a proxy for patient-level socioeconomic status and the exclusion of “observation status” discharges in the Kids Inpatient Database.

Children’s hospitals may face disproportionate financial risk from the ACA. Reductions in DSH payments may disproportionately affect children’s hospitals because of their high per-hospital number of Medicaid discharges. In addition, readmission penalties may disproportionately affect children’s hospitals...