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Cover Impressions

About Our Cover Artist


John Chehak, a former pharmacist, has been chosen as the cover artist for JMCP’s annual issue featuring an artist with a pharmaceutical, medical, or scientific background. Born and raised in Cedar Rapids, Iowa, he always knew that he could draw and paint, but art was not his first career choice. While growing up, Chehak dreamed of becoming a pharmacist like his grandfather, Milo Chehak, who started Paramount Pharmacies. He fulfilled that dream in 1973 by earning a pharmacy degree from the University of Iowa in Iowa City. For the next 8 years, Chehak worked as operational vice president and staff pharmacist for the family business.

In the early 1980s, he stopped practicing pharmacy and started a computer systems company that customized computer software for businesses. In 1989, Chehak accepted a job offer as director of marketing and public relations at Mercy Medical Center in Cedar Rapids. He left there 3 years later and purchased a wholesale distribution business which sold non-grocery items to convenience stores. Then, in 2000, Chehak took a position as business manager for Professional Home Health Services in Cedar Rapids. In mid 2009, he became president of U.S. Nameplate Company in Mt. Vernon, Iowa. The company produces product identification including nameplates, decals, asset tags, safety labels, control panels, and dials for thousands of original-equipment manufacturers. Chehak is responsible for the decision making and daily operational results of U.S. Nameplate Company, focusing on their tradition of high production quality and exceptional customer service, while pursuing new product development, technology research, and sales opportunities. Regarding his various business choices, he thinks that people should follow their heart. “Don’t be afraid of failure,” he advises. “If you succeeded all the time, you would never know the meaning of success.”

By the time he was in his late 40s, Chehak had begun to fully realize his artistic talents. Now that he is 10 years older, his work has come full circle. It is described on the Kavanaugh Gallery’s Web site: “His muted colors and distinct choice of subject matters have attracted collectors throughout the nation. Many of Chehak’s paintings emerge directly from his imagination. All of his work is original—no prints or copies.” A self-taught artist, he paints in acrylics on canvas or paper, and has recently produced 3-dimensional works in mixed media. Chehak says that painting helps him to express his emotions. Although his subjects have included urban scenes in New York, Chicago, and New Orleans, he prefers the sedate, yet captivating, landscapes of the Midwest. Rural compositions of rolling hills, farmlands, red barns, and the like characterize his unique style. “I’m particularly fond of the symmetry and beauty of buildings and other structures, both urban and rural,” he says.

Chehak’s Rooftops painting bears a slight resemblance to a Georges Braque Cubist landscape. Cubism was an early 20th century avant-garde art movement pioneered by Braque and Pablo Picasso that revolutionized European painting and sculpture. It is characterized by the process of construction—of creating a pictorial rhythm, and converting the represented forms into the essential geometric shapes, which are the cube, sphere, cylinder, and cone. Even though the geometric shapes of the buildings in Rooftops form a multitude of angles, the overall effect is harmonious. Chehak achieved a sense of depth in this picture by gradually reducing the color saturation of the buildings as they recede into the background. The scene, reminiscent of an Italian village, appears to be impossibly crowded, yet believable at the same time. Perhaps the composition is a metaphor for urban overcrowding. Or it could represent the artist’s state of mind—his attempt to convey all of the feelings that he was experiencing at the time.

Chehak is currently represented by 2 major art galleries in Iowa: the Kavanaugh Art Gallery in West Des Moines (kavanaughgallery.com) and The Chait Galleries Downtown in Iowa City (thegalleriesdowntown.com). His work has also been featured on The University of Iowa’s Web site called The Daily Palette (dailypalette.uiowa.edu). This site features the work of a different Iowa artist every day. Chehak’s Landscape Three painting appeared on The Daily Palette on September 2, 2006. Another interesting composition of his can be found on the Kavanaugh Art Gallery Web site; it is a triptych (3-part) set of paintings titled Town Triptych 1, Town Triptych 2, and Town Triptych 3.

Although his full-time job keeps him busy, Chehak somehow finds the time to create paintings for the 2 art galleries and some art fairs, such as the Powderhorn Art Fair, which is held every August in Powderhorn Park in Minneapolis, Minnesota. In addition, he accepts commissions and will paint from patrons’ favorite photographs or other images.

Sheila Macho
Cover Editor

Cover Credit

Sources
Interview with the artist.
JMCP EDITORIAL POLICY

EDITORIAL MISSION AND POLICIES

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- Research
- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Brief Communications
- Commentary/Editorials
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These are well-referenced, comprehensive reviews of subjects relevant to managed care pharmacy. The Methods section in the abstract and in the body of the manuscript should make clear to the reader the source of the material used in the review, including the criteria used for inclusion and exclusion of information.

FORMULARY MANAGEMENT

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     - P values that are > 0.01 should be expressed as P = 0.xxx, to 3 decimal places. P values less than 0.001 should be shown as P < 0.001.
     - Include succinct, quantitative bullet points for (a) what is already known about this subject, and (b) what this study adds.
     - Electronic submission of cover letter, manuscript, and native files for figures at: http://jmcp.msubmit.net

3. **DISCLOSURES AND CONFLICT OF INTEREST**: completed and signed author attestation forms for the principal author and each coauthor, including source(s) of funding and financial support.

**REFERENCE**

DESCRIPTION OF THE OUTCOMES OF PRIOR AUTHORIZATION OF PALIVIZUMAB FOR PREVENTION OF RESPIRATORY SyncYTIAL VIRUS INFECTION IN A MANAGED CARE ORGANIZATION

Brieana C. Buckley, PharmD; Derek Roylance, PharmD; Matthew P. Mitchell, PharmD, MBA; Sushma M. Patel, PharmD; H. Eric Cannon, PharmD; and Jeffrey D. Dunn, PharmD, MBA

ABSTRACT

BACKGROUND: Respiratory syncytial virus (RSV) is the leading cause of upper and lower respiratory tract infections in infants and young children. Most children are exposed to the virus before they are 2 years old and experience such symptoms as cough, fever, and irritability. In a select population of infants, the virus can cause hypoxemia and hospitalization. To avoid hospitalization, good infection control practices should be employed, and for those infants at high risk, prophylaxis with palivizumab is indicated. Palivizumab has been shown to reduce hospitalization rates in high-risk infants by 50%. Because of the high cost of palivizumab, it is prudent to use this medication in the population in which it will be most effective. The American Academy of Pediatrics (AAP) established the criteria for those infants who would benefit the most from palivizumab prophylaxis, and these criteria were the foundation for a prior authorization (PA) program to determine coverage of palivizumab in a health plan of approximately 500,000 members.

OBJECTIVE: To (a) analyze the appropriateness of this PA program for palivizumab used prophylactically for RSV, and (b) determine the financial cost associated with the medication and disease for this health plan.

METHODS: A 3-year, retrospective study was conducted from the 2005-2006 RSV season through the 2007-2008 season. The primary endpoint outcome was the hospitalization rate associated with RSV infection. Secondary endpoints included the cost of palivizumab and RSV-related emergency room (ER) utilization. Infants were placed into 2 groups: those who received PA approval for use of palivizumab and those who were denied coverage in the PA process. Disease-related hospitalization and ER visits were identified by at least 1 administrative claim containing either a primary or secondary ICD-9-CM code for any of the following: RSV (079.6), acute bronchiolitis caused by RSV (466.11), or pneumonia caused by RSV (480.1). Drug cost was defined as the health plan’s allowed amount, which is based on a predefined fee schedule for the Current Procedural Terminology (CPT) code 90378 for palivizumab. Hospital and ER costs are the health plan allowed amounts (health plan plus member cost) based on the reimbursement rates determined by diagnosis related group (DRG) and other coding, and the plan-allowed amount based on DRGs includes all services and drugs provided in the specific encounter. Drug cost avoided was calculated as the average cost of palivizumab treatment per episode multiplied by the number of infants denied coverage of palivizumab over the 3-year study period.

RESULTS: Over 3 RSV seasons through May 2008, the PA program received 1,090 requests for coverage of palivizumab, of which 348 (31.9%) were denied. Of 742 PA-approved infants, 629 received at least 1 dose of palivizumab. The mean (SD) gestational age of the PA-denied group was 34.4 (2.5) weeks versus 32.5 (4.0) weeks for the PA-approved group (P<0.001). In the PA-denied group, 14 infants (4.0%) were subsequently hospitalized with an RSV infection, and 5 (1.4%) had an RSV-related ER visit versus 40 (6.4%) hospitalized and 14 (2.2%) with ER visits for infants in the PA-approved group (P=0.055 and P=0.019, respectively); 15 (4.3%) of the PA-denied group had either a hospitalization or an ER visit versus 42 (6.6%) in the PA-approved group (P=0.060). One patient in the palivizumab PA-approved group died. Over the 3 RSV seasons, the mean number of palivizumab doses and mean allowed palivizumab cost per treatment episode (per infant per season) were 3.64 and $6,950, respectively, and the average allowed palivizumab cost was $7,702 per utilizing infant. Total per infant costs for palivizumab, RSV hospitalizations, and RSV-related ER visits were $8,534 for infants receiving palivizumab compared with $223 for those denied palivizumab coverage (P=0.002). Drug cost avoidance associated with the PA program was estimated to be $2,418,600 (348 infants times $6,950 palivizumab cost per episode) over the 3 RSV seasons.

CONCLUSION: In a 500,000-member health plan, a PA program to restrict palivizumab use in accordance with AAP recommendations was associated with estimated palivizumab drug cost avoidance of more than $2.4 million over 3 years. There was no significant difference in the RSV-related hospitalization rate for the PA-denied versus the PA-approved groups, but the PA-denied group had a slightly lower rate of RSV-related ER visits.

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What is already known about this subject

- Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia among infants and children younger than 1 year of age.
- Palivizumab has been shown in studies to reduce the frequency of RSV-related hospitalization in high-risk infants by 50%.
- Palivizumab is an expensive medication, with wholesale acquisition cost (WAC) in 2009 of $955 per 50 mg (0.5 mL) vial and $1,802 per 100 mg (1 mL) vial.
- Joffe et al. (1999) found that the cost per avoided hospitalization associated with immunoprophylaxis with palivizumab ranged from $12,000 in the highest-risk infants to $420,000 in lower-risk infants—gestational age 33-36 weeks, used less than 28 days oxygen in the neonatal intensive care unit (NICU), and were discharged between December and August (1995 dollars).
Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia among infants and children under 1 year of age. Illness begins most frequently with fever, runny nose, cough, and wheezing. During their first RSV infection, between 25% and 40% of infants and young children have signs or symptoms of bronchiolitis or pneumonia, and 0.5% to 2% require hospitalization. Most children recover from illness in 8 to 15 days. The majority of children hospitalized for RSV infection are younger than 6 months of age. RSV also causes infections throughout life, usually associated with moderate-to-severe cold-like symptoms; however, severe lower respiratory tract disease may occur at any age, especially among the elderly or among those with compromised cardiac, pulmonary, or immune systems. In temperate climates, RSV infections usually occur during annual community outbreaks, often lasting 4 to 6 months, during the late fall, winter, or early spring months. The timing and severity of outbreaks in a community vary from year to year. The typical RSV season in Utah, where the present study was conducted, generally begins in December and lasts through April. SelectHealth, a 500,000-member integrated health system based in Salt Lake City, defines the RSV season based on local epidemiological data.

Development of an RSV vaccine is a high research priority, but one is not yet available. Current prevention options include good infection-control practices and palivizumab (Synagis), a monoclonal antibody. Palivizumab works by exhibiting neutralizing and fusion-inhibitory activity against RSV. This mechanism has been shown to inhibit RSV replication in laboratory experiments. Palivizumab can be given during the RSV outbreak season to prevent serious lower respiratory tract disease caused by RSV in pediatric patients at high risk for serious RSV disease (e.g., those with chronic lung disease [CLD], infants born prematurely with or without CLD, and those with congenital heart disease [CHD]). Palivizumab has no potential for infectious contamination, is given intramuscularly, and does not interfere with the timing of administration of vaccines. The first dose should be administered prior to commencement of the RSV season, and high-risk infants born during the RSV season may receive palivizumab prophylaxis from birth. At the time that the present study was conducted, high-risk infants received palivizumab until the end of the RSV season and thus could have received 1 to 5 injections depending on their month of birth.

The cost of RSV prophylaxis versus the cost of hospitalization continues to be debated. According to the National Institutes of Health, each year up to 125,000 infants under 1 year of age are hospitalized because of severe RSV disease. Palivizumab is a costly drug with a wholesale acquisition cost (WAC) in 2009 of $955 per 50 mg (0.5 mL) vial or $1,802 per 100 mg (1.0 mL) vial, leading to debate regarding which children should receive such prophylaxis. Lofland et al. (2000) found the incremental cost per RSV infection episode avoided ranged from $2,702 to $79,706 when the cost per course of palivizumab was $4,500. When the cost per course of palivizumab was $2,500, cost per RSV infection avoided ranged from $0 to $39,591. An analysis by Joffe et al. (1999) that explored the cost-effectiveness of palivizumab when targeting high-risk patient subgroups found that the cost per avoided RSV hospitalization was estimated at approximately $12,000 in 1995 dollars in the highest-risk patient subgroup (gestational age 23-32 weeks who received at least 28 days of oxygen in the neonatal intensive care unit [NICU] and were discharged from the NICU between September and November). However, the cost per avoided hospitalization was as high as $420,000 in the subgroup of infants whose gestational age was 33-36 weeks, who received less than 28 days oxygen in the NICU, and who were discharged between December and August, demonstrating the high cost of prophylaxis in lower-risk subgroups.

Due to the high cost of palivizumab and its special target population, palivizumab is a good candidate for prior authorization (PA). According to a survey of health plans conducted in December 2008, 81% of respondents indicated that they currently require PA for palivizumab. In order to ensure that palivizumab is used appropriately, SelectHealth has required PA for palivizumab since the time that it became commercially available. The SelectHealth PA criteria that were in place at the time of the present study were based on a high-risk population subset (Figure 1) that corresponds to the American Academy of Pediatrics (AAP) 2006 guidelines (Appendix). The objective of the present study was to analyze in a real-world setting the outcomes of application of PA criteria required by SelectHealth for palivizumab when given prophylactically for RSV, including the financial cost associated with the disease. Guidelines by the AAP define a select population for which palivizumab is recommended. Many health plans have adopted the AAP guidelines to create coverage policies for this select patient population. To our knowledge, this is the first
published analysis of the outcomes associated with a health plan’s PA criteria for coverage determination of palivizumab. The results of the present analysis were anticipated to provide assistance in refining the PA criteria for the appropriate use of palivizumab in this 500,000-member health plan.

Methods

This exploratory and descriptive study was a retrospective analysis of an administrative claims database. All members enrolled in the health plan during any of 3 RSV seasons—2005-2006, 2006-2007, or 2007-2008—were eligible for the study. Continuous enrollment was not part of the inclusion criteria because eligible infants could be born during the study period, limiting the number of months they were enrolled. Infants were included in the analysis if they had a PA request for palivizumab submitted for 1 or more of the 3 RSV seasons. PA requests are submitted to the health plan via fax by health care physicians or specialty pharmacies. These requests could be submitted prior to or during the RSV season. If approved, authorizations were entered for infants to receive up to 5 doses of palivizumab from November through April of the requested RSV season. All PA requests were reviewed by a clinical pharmacist, and benefit determination was based on the health plan’s criteria (Figure 1).

The PA-approved group was composed of infants who met the PA criteria, were approved for palivizumab coverage, and received at least 1 dose of palivizumab (Current Procedural Terminology [CPT] code 90378 [RSV immune globulin, intramuscular use]; national drug code [NDC] and Healthcare Common Procedure Coding System [HCPCS] codes are not used for reimbursement of palivizumab in this health plan). For those infants who received palivizumab, the drug was covered under the medical benefit and dispensed through a specialty pharmacy or billed through a home health provider or a physician’s office. Medical claims are reimbursed based on the submitted Health Insurance Claim Form (CMS-1500), which requires the use of either a HCPCS or CPT code, and there is no field designated for NDC numbers on the CMS-1500. Based on these limitations, SelectHealth collects NDCs when possible but chooses to reimburse based on the CPT code. The PA-denied group in this study was composed of those infants who did not meet the PA requirements and whose requests for coverage of palivizumab were denied.

Disease-related utilization was defined as any claim billed from an inpatient hospital with either a primary or secondary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for any of the following: RSV (079.6), acute bronchiolitis caused by RSV (466.11), or pneumonia caused by RSV (480.1). Inpatient visits were identified by CPT codes 99221-99239 (indicating inpatient evaluation and management). Emergency room (ER) visits were identified as services billed from an ER with corresponding CPT codes 99281-99285 (indicating ER evaluation and management). Gender, gestational age, and palivizumab utilization data were obtained from the health plan’s electronic claims database.

Outcome measures included incidence and cost of inpatient hospital stays and ER visits, the number of palivizumab doses per infant, the cost of palivizumab, and deaths. ER visits and inpatient hospitalizations were included in the analysis if they occurred during the same season that palivizumab was requested. Hospital and ER costs were expressed as total allowed amount, defined as the contracted reimbursement rate based on submitted diagnosis related group (DRG) codes per associated RSV treatment episode. Payment based on DRG includes all services and drugs provided to the infants related to the specific inpatient or ER encounter. Drug cost avoided was calculated as the average cost of palivizumab per treatment episode multiplied by the number of infants denied coverage of palivizumab over the 3-year study.
period. Deaths were verified with state vital statistics records that are exchanged electronically once per month between the state of Utah and the health plan. State-reported deaths were queried against infants included in both study groups. Mean gestational age for each infant subgroup was calculated. Between-group differences in gender, gestational age, inpatient hospitalization, and ER visit rates were assessed for statistical significance using Fisher’s Exact test for proportions and the Student’s t-test for means. The significance level was set at 0.05. Analyses were performed by an internal data analyst using Analysis ToolPak 2003. This study was approved by the Intermountain Healthcare Office of Research and Institutional Review Board.

Results

Providers submitted PA requests for palivizumab for a total of 1,090 infants over the 3 RSV seasons, of which 742 (68.1%) were approved and 348 (31.9%) were denied. Of the 742 PA approvals, 629 infants had at least 1 paid claim for palivizumab in their electronic claims record and were included in the analysis (Table 1); the 113 infants without a paid claim for palivizumab were excluded from the analysis. The cohort of PA-approved infants was 40.1% female (n=252) compared with 46.0% (n=160) in the PA-denied cohort (P=0.422). The mean (SD) gestational age was lower in the PA-approved group (32.5 [4.0] weeks) compared with the PA-denied group (34.4 [2.5] weeks, P<0.001).

Of the 348 infants who were denied coverage for palivizumab, 5 (1.4%) had a documented RSV-related ER visit, and 14 (4.0%) had an RSV-related hospital stay (Table 1). Four of the 5 infants with an ER visit had subsequent inpatient hospital claims for RSV. Of the 629 infants who met the PA criteria and received palivizumab, 14 (2.2%) had an ER visit, and 40 (6.4%) were hospitalized for an RSV infection. Of the 14 infants with an ER visit, 12 also had resulting inpatient hospitalizations. One infant who received palivizumab died of respiratory failure. There were no deaths in the PA-denied group. The mean gestational ages were not significantly different for the PA-denied group compared with the PA-approved group for the infants who had at least 1 RSV-related hospitalization or at least 1 RSV-related ER visit (Table 1).

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Drug, Hospital, and ER Utilization and Costs for PA-Approved Versus PA-Denied Infants for 3 RSV Seasons (2005-2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire sample</td>
<td>Palivizumab Approved</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Number of coverage requests</td>
<td>742</td>
</tr>
<tr>
<td>Number of infants</td>
<td>629</td>
</tr>
<tr>
<td>Number (%) female</td>
<td>252 (40.1%)</td>
</tr>
<tr>
<td>Mean [SD] gestational age</td>
<td>32.5 [4.0]</td>
</tr>
<tr>
<td>Direct drug cost of palivizumab</td>
<td>$4,844,435</td>
</tr>
<tr>
<td>Patients with at least 1 RSV hospitalizationb</td>
<td></td>
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<tr>
<td>Number (%) of infants</td>
<td>40 (6.4%)</td>
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<tr>
<td>Number (%) female</td>
<td>12 (30%)</td>
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<tr>
<td>Mean [SD] gestational age</td>
<td>33.5 [4.6]</td>
</tr>
<tr>
<td>RSV-related inpatient hospital costs</td>
<td>$517,418</td>
</tr>
<tr>
<td>Cost per hospitalized infant</td>
<td>$12,935</td>
</tr>
<tr>
<td>Patients with at least 1 RSV-related ER visitb</td>
<td></td>
</tr>
<tr>
<td>Number (%) of infants</td>
<td>14 (2.2%)</td>
</tr>
<tr>
<td>Number (%) female</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>Mean [SD] gestational age</td>
<td>34.0 [3.8]</td>
</tr>
<tr>
<td>RSV-related ER costs</td>
<td>$5,918</td>
</tr>
<tr>
<td>Mean cost per infant with ER visit</td>
<td>$423</td>
</tr>
<tr>
<td>Whole-sample costs</td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td>$5,367,771</td>
</tr>
<tr>
<td>Distinct infants with hospitalization or ER visit</td>
<td>42 (6.6%)</td>
</tr>
<tr>
<td>Per infant costs</td>
<td></td>
</tr>
<tr>
<td>Palivizumab</td>
<td>$7,701.80</td>
</tr>
<tr>
<td>Inpatient hospital</td>
<td>$822.60</td>
</tr>
<tr>
<td>ER</td>
<td>$9.41</td>
</tr>
<tr>
<td>Total costs</td>
<td>$8,533.82</td>
</tr>
</tbody>
</table>

*aStatistical tests (Fisher’s Exact for proportions and Student’s t-test for means) of between-group differences, comparing the PA-approved versus PA-denied groups. 
bUtilization and costs for hospital and ER visits with ICD-9-CM codes for RSV (079.6), acute bronchiolitis caused by RSV (466.11), or pneumonia caused by RSV (480.1). ER = emergency room; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; PA = prior authorization; RSV = respiratory syncytial virus; SD = standard deviation.
### TABLE 2  Utilization and Cost of Palivizumab by RSV Season

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infants who received palivizumab</td>
<td>239</td>
<td>229</td>
<td>229</td>
<td>629 infants</td>
</tr>
<tr>
<td>Number of doses</td>
<td>859</td>
<td>855</td>
<td>826</td>
<td>2,540</td>
</tr>
<tr>
<td>Average doses per episode (RSV season)</td>
<td>3.59</td>
<td>3.73</td>
<td>3.60</td>
<td>4.04 per infant</td>
</tr>
<tr>
<td>Total palivizumab cost</td>
<td>$1,500,040</td>
<td>$1,740,939</td>
<td>$1,603,456</td>
<td>$4,844,435</td>
</tr>
<tr>
<td>Palivizumab cost per infant</td>
<td>$6,276</td>
<td>$7,602</td>
<td>$7,002</td>
<td>$7,702 per infant</td>
</tr>
</tbody>
</table>

*The unique patient (infant) count is not equal to the total count of episodes because some infants received palivizumab in more than 1 RSV season. RSV = respiratory syncytial virus.

Between-group comparisons showed that the proportion of infants with an ER visit was significantly lower in the PA-denied group (1.4%, n = 5) than in the PA-approved group (2.2%, n = 14; P = 0.019). Additionally, of those who were denied palivizumab, per-infant inpatient hospital costs ($210.23) and total costs ($222.56) were significantly lower for the PA-denied group than for the PA-approved group ($822.60 and $8,533.82; P = 0.015 and P = 0.002, respectively). The mean gestational age of the PA-approved group (32.5 weeks) was significantly lower than the mean gestational age of the PA-denied group (34.4 weeks, P < 0.001).

The total cost of palivizumab over the 3 seasons was $4,844,435 ($7,702 per unique infant or $6,950 per treatment episode; Table 2). Among those who received palivizumab, per-infant costs for the drug increased from the 2005-2006 to the 2007-2008 season. Drug cost avoidance associated with the PA program over the 3 RSV seasons was estimated to be $2,418,600 (348 PA denials multiplied by $6,950 per palivizumab episode).

### Discussion

This study assessed the experience of a 500,000-member health plan in implementing guideline-based coverage criteria for the use of palivizumab. Of the infants who were denied palivizumab coverage, 43% were hospitalized or had an ER visit, compared with 6.6% for the infants who were approved for coverage of palivizumab (P = 0.060). The rates of RSV-related hospitalization for PA-approved infants and PA-denied infants did not significantly differ (6.4% vs. 4.0%, P = 0.055). Our RSV-related hospitalization rate of 6.4% for PA-approved infants and 4.0% for PA-denied infants compares with an average annual RSV-related hospitalization rate of 1.7% for children less than 6 months of age in the sample studied by Hall et al. (2009) that included both high-risk and low-risk children younger than 5 years of age. Hall et al. found that the RSV-related hospitalization rate was 1.7% for the youngest infants (0-5 months of age) but dropped off dramatically to 0.5% for 6 to 11 months of age, 0.3% for 12 to 23 months of age, and 0.04% for 24 to 59 months of age. Overall for children aged 0 to 59 months, 0.3% were hospitalized and 2.8% were seen in ERs for the treatment of RSV.

For patients receiving palivizumab, only 2 randomized controlled trials have investigated the efficacy of palivizumab in reducing RSV-associated hospitalizations. The IMpact-RSV clinical trial results for the 1996-1997 RSV season for children with either prematurity up to 35 weeks gestation or bronchopulmonary dysplasia/chronic lung disease (BPD/CLD) showed that the palivizumab-treated group had a 4.8% rate of RSV-related hospitalization compared with a 10.6% rate for the placebo group (P < 0.001).^{15}

Broad variability has been demonstrated in observational analyses reporting hospitalization rates associated with RSV. Estimates of RSV-related hospitalizations by the Institute of Medicine (IOM; 1985) suggested that only 55,000 U.S. infants younger than 1 year of age were hospitalized for bronchiolitis or pneumonia that might be RSV-related. Shay et al. (1999) later reported in an analysis of U.S. National Hospital Discharge Survey (NHDS) data for 1980-1996 that the rate of hospitalization for bronchiolitis for children less than 1 year of age had increased more than 2-fold over the 17-year study period, from 12.9 per 1,000 in 1980 to 31.2 per 1,000 in 1996; 57% of bronchiolitis-associated hospitalizations occurred among infants younger than 6 months of age and 81% among those younger than 1 year of age.^{17} More recently, NHDS data for 1997-2002 show that RSV-related hospitalization rates increased an additional 25% among infants less than 1 year of age. Shay et al. theorized that the burden of RSV may be increasing due to an increase in the prevalence of child care for younger children and revised criteria for hospitalization; diagnostic coding and the virulence of RSV strains were probably not factors. However, only attendance in child care was found to be a risk factor in the reported incidence of RSV-related hospitalization.

In our study, the observed RSV hospitalization rates are higher than reported in the IMpact-RSV clinical trials. One possible explanation is the demonstrated increasing rate of reported RSV-related hospitalizations since the 1980s. While national rates of RSV-related hospitalization range from 0.5% to 2%, there is significant geographical variation. Demographically, Utah residents have a higher proportion of children under the age of 5 (9.8%) and a greater number of persons per household (3.13) compared...
with national data (6.9% and 2.59, respectively). More young children in our population could contribute to higher proportion of infants with school-aged siblings, more prevalent day care attendance, or crowded living conditions. Each of these have been identified as risk factors for severe RSV disease.20,21

Our observational analysis demonstrated significantly lower costs of hospitalization for the PA-denied group compared with the PA-approved group. Common reasons for denial of PA submissions within SelectHealth include infants older than 2 years of age, no documented CHD or CLD requiring continued medical therapy, gestational age greater than 35 weeks, or gestational age 32-35 weeks without the presence of risk factors (Figure 1). Each of these characteristics imposes a greater risk for severe RSV infection. Based on the reasons for PA denial, the PA-denied group is a more healthy population. This is supported by the comparison of the gestational age, where the PA-approved group had a significantly lower gestational age than the PA-denied group. However, we found no difference in ER costs for the PA-denied group compared with the PA-approved group. We did not measure the severity of illness in the infants who had ER visits or hospitalization.

Our outcomes analysis found value in this PA program for palivizumab based on the 2006 AAP criteria. The AAP released modified recommendations for the use of palivizumab in September 2009.22 The new recommendations were updated in an effort to ensure optimal balance of benefit and cost from this expensive intervention based on additional data on risk factors for identifying children who are at increased risk of serious RSV lower respiratory tract disease. The 2009 AAP recommendations emphasize 4 main points.

1. Initiation and termination of prophylaxis have been modified to reflect RSV seasonality in different geographic locations; emphasis has been placed on the use of local epidemiologic data to define the peak outbreak months. Early initiation or continuation of therapy during months in which RSV is not widely circulating provides little benefit.

2. The dosing schedule remains unchanged for infants before 32 weeks 0 days gestation who have CHD or CLD. The recommendation for a maximum number of 5 doses is emphasized for all geographic locations for infants meeting these criteria.

3. No more than 3 doses are recommended for infants with a gestational age between 32 weeks 0 days and 34 weeks 6 days who are without hemodynamically significant CHD or CLD who otherwise qualify for prophylaxis.

4. Infants born between 32 weeks 0 days and 34 weeks 6 days gestation qualify for prophylaxis if they have at least 1 of 2 risk factors but should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever occurs first). Risk factors have been modified to include only the following: the infant is in child care or 1 or more siblings or other children younger than age 5 live permanently in the child’s household.22

SelectHealth examined the revised AAP recommendations released online in September 2009 and incorporated the new criteria in the PA process for the 2009-2010 RSV season.23 The only modification that directly impacts the PA criteria is the recommendation for infants born between 32 weeks 0 days and 34 weeks 6 days gestation. Infants requesting coverage of palivizumab based on this criteria will be approved only if they have 1 of the following risk factors: either the infant is in child care or has siblings younger than age 5 in their household. If palivizumab is approved, coverage is limited to no more than 3 doses or until 90 days of age, whichever occurs first. The SelectHealth PA form consistent with the revised AAP recommendations was updated in September 2009 and is available via the SelectHealth Web portal at www.selecthealth.org/pharmacy.23

Limitations
First, relevant infant-specific data, such as history of underlying conditions that predispose an infant to respiratory complications (e.g., neurologic disease in very low birth weight infants, number of young siblings, child care center attendance, and exposure to tobacco smoke in the home), cannot be identified through electronic claims data and may affect the findings of this study. Second, this study is an exploratory descriptive analysis and its observational design prevents attribution of causality. Third, we did not assess compliance with the recommended number of injections or the vaccination schedule and did not require continuous eligibility for the infants; however, for SelectHealth the annual renewal rate has been 95.5%. Thus, we do not know if infants in the sample were enrolled in the health plan for the entire RSV season when palivizumab was requested. Fourth, the present study assumed that a diagnosis of RSV recorded in an administrative claim is accurate. Fifth, this study was an observational analysis that examined only the cost of RSV-related hospitalization and RSV-related ER visits, not total RSV-related costs including office visits and outpatient treatment costs.

Conclusion
RSV infections are common among young infants and can result in hospitalization for those at high risk. Palivizumab is an expensive medication that when given as prophylaxis can reduce hospitalization rates. Because of the high direct drug cost of palivizumab, PA criteria have been established to restrict coverage of the medication to the infants who would benefit most. Our 3-year retrospective analysis showed that the PA program was associated with significant palivizumab drug cost avoidance of more than $2.4 million in a 500,000-member health plan. These drug cost savings were achieved without apparent adverse clinical outcomes in the rate of RSV-related hospitalization or RSV-related ER visits. Although exploratory, these results suggest that implementation of PA criteria for palivizumab in accordance with clinical guidelines is associated with significant drug cost avoidance without an increase in the cost or the incidence of ER visits or inpatient hospitalizations associated with RSV infections.
Description of the Outcomes of Prior Authorization of Palivizumab for Prevention of Respiratory Syncytial Virus Infection in a Managed Care Organization

Authors

BRIEANA C. BUCKLEY, PharmD, is Clinical Pharmacy Coordinator; DEREK ROYLANCE, PharmD, was Pharmacy Resident at the time of this study; MATTHEW P. MITCHELL, PharmD, MBA, is Manager of Pharmacy Services; SUSHMA M. PATEL, PharmD, is Clinical Pharmacy Coordinator; H. ERIC CANNON, PharmD, is Chief of Pharmacy; and JEFFREY D. DUNN, PharmD, MBA, is Formulary and Contract Manager, SelectHealth, Salt Lake City, Utah.

AUTHOR CORRESPONDENCE: Brieana C. Buckley, PharmD, SelectHealth, 4646 W. Lake Park Blvd., Salt Lake City, UT 84120. Tel.: 801.442.7797; E-mail: Brieana.cox-buckley@selecthealth.org.

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REFERENCES


DISCLOSURES

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Buckley and Cannon were primarily responsible for the study concept and design. Roylance and Buckley were primarily responsible for data collection and interpretation with assistance from Patel and Mitchell. Roylance and Dunn were primarily responsible for writing the first version of the manuscript, and Buckley and Mitchell revised the manuscript.

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Matt Speckman, Senior Outcomes Analyst, assisted with the data analyses for this research.

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APPENDIX Palivizumab Administration Recommendations from the American Academy of Pediatrics in 2006

- Infants and children less than 24 months of age with CLD of prematurity who have required medical therapy within the past 6 months

- Infants born at greater than 28 weeks and less than 32 weeks gestation with or without CLD who are less than 6 months of age at the start of the RSV season

- Infants born at 28 weeks of gestation or less with or without CLD and who are less than 12 months of age at the start of the RSV season

- Infants born between 32 and 35 weeks gestation without CLD who are less than 6 months of age and who have 2 or more of the following risk factors: school age siblings; day-care attendance; exposure to environmental air pollutants; congenital abnormalities of the airways; severe neuromuscular disease

- Infants and children 24 months of age and younger with hemodynamically significant cyanotic and acyanotic congenital heart disease; need for prophylaxis based on degree of physiologic cardiovascular compromise

- Infants less than 24 months of age with congenital heart disease that would benefit most from palivizumab include: infants receiving medication to control congestive heart failure; infants with moderate to severe pulmonary hypertension; infants with cyanotic heart disease

- For infants and children requiring cardiopulmonary bypass and receiving palivizumab, a postoperative dose should be considered; mean decrease in palivizumab serum concentration of 58% following procedures requiring cardiopulmonary bypass

*Excerpted from the Clinical Practice Guideline. Diagnosis and Management of Bronchiolitis (2006).*

CLD = chronic lung disease; RSV = respiratory syncytial virus.
ABSTRACT

BACKGROUND: Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections and hospitalization in infants. Palivizumab is currently the only available agent for prevention of RSV infection in high-risk infants. This high-cost injectable requires monthly dosing during the RSV season. Compliance with the injection schedule is important in the prevention of RSV infection and respiratory complications. Managed care organizations have an interest in the relationship between compliance with the palivizumab dosing schedule and respiratory-related medical outcomes such as emergency room (ER) visits, physician office visits, and hospitalizations.

OBJECTIVE: To evaluate respiratory-related medical outcomes and cost for infants who were prescribed and received palivizumab in accordance with the dosing schedule recommended by the American Academy of Pediatrics (AAP) in 2006 versus those who did not.

METHODS: A retrospective claims analysis was conducted to assess the relationship between compliance with the palivizumab dosing schedule and respiratory-related medical visits and costs in a western Pennsylvania managed care organization composed of approximately 307,000 commercial and 92,000 Medicaid members. De-identified pharmacy and medical claims data were extracted for infants (0-24 months) who met prior authorization criteria and who received at least 1 dose of palivizumab during the 2006-2007 RSV season (October 15, 2006, to April 15, 2007). Patient compliance was based on (a) starting palivizumab on time, (b) receiving the expected number of injections, and (c) no more than a 37-day gap between palivizumab claims. Medical utilization (physician office visits, ER visits, and hospital admissions) was analyzed by comparing medical services (with respiratory-related ICD-9-CM codes) for compliant versus noncompliant groups. Net health plan costs (after subtraction of member cost share) were compared for compliant versus noncompliant groups. What is already known about this subject

• Respiratory syncytial virus (RSV) infection is the leading cause of lower respiratory tract infections, and each year accounts for approximately 75,000 to 125,000 hospitalizations in infants younger than 1 year of age. Palivizumab is currently the only available FDA-approved agent to prevent RSV infection in neonates but is very costly and requires monthly injections during the RSV season.
• Children at highest risk of complications from RSV infection include premature infants, children less than 2 years of age with congenital heart or chronic lung disease, and children with immune systems that are compromised by a medical condition or medical treatment.
• Because of the frequent dosing schedule for palivizumab, noncompliance is common and may be the most controllable barrier to pharmacologic prevention of RSV infection and its potentially severe sequelae in high-risk infants. Several previous studies have yielded mixed results regarding the relationship between palivizumab compliance and improved infant respiratory health.

RESULTS: Of the 245 infants who received palivizumab during the 2006-2007 RSV season, 151 (61.6%) were first-season recipients of palivizumab, and 131 (53.5%) were male; 145 (59.2%) belonged to a Medicaid benefit plan, and 100 (40.8%) belonged to a commercial benefit plan; and 73 (29.8%) were deemed to be compliant with the 2006 AAP recommended palivizumab dosing schedule. Fourteen (19.2%) of compliant infants had at least 1 respiratory-related hospital admission compared with 37 (21.5%) of noncompliant infants ($P = 0.734). The proportions of infants with at least 1 respiratory-related physician office visit were also similar for the 2 groups, 60.3% (n = 44) for compliant infants versus 64.5% (n = 111) for noncompliant infants ($P = 0.564). There was a significant difference in the proportion of infants with at least 1 respiratory-related ER visit, 15.1% (n = 11) of compliant infants versus 28.5% (n = 49) of noncompliant infants ($P = 0.034), but there were no RSV-related ER visits in either group and no significant differences between the groups in the proportion with at least 1 RSV-related office visit (9.6% for compliant infants vs. 5.8% for noncompliant infants, $P = 0.284). RSV-related hospitalization occurred in 0 (0.0%) compliant and 2 (1.2%) noncompliant infants ($P = 1.000). Compliance had significantly higher median per patient palivizumab pharmacy costs ($10,416) compared with noncompliant infants ($7,605, $P = 0.011). However, median total (palivizumab and respiratory-related medical) costs for the 2 groups did not significantly differ ($P = 0.189).

CONCLUSION: About 30% of the infants who received palivizumab during the 2006-2007 RSV season were compliant with dosing recommendations. Compliance was associated with a lower proportion of infants with at least 1 respiratory-related ER visit but not with any other study outcome, including the proportion of infants with at least 1 hospital admission or physician visit or any measure of RSV-related use. Median palivizumab per patient costs were higher for the compliant group, but there was no significant between-group difference in total median per patient cost (palivizumab drug plus respiratory-related medical cost).

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Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections and the leading cause of hospitalization in infants, accounting for approximately 75,000 to 125,000 pediatric hospitalizations in children less than 1 year of age in the United States each year. It is estimated that approximately two-thirds of all infants are infected with RSV within their first year of life and nearly all are infected by 2 years of age. RSV infections typically occur from November through March in most communities throughout the United States. Similar to the common cold, there is no standard treatment protocol for RSV infection and the virus will typically run its course in 8 to 15 days. Risk factors such as premature birth or chronic lung or heart conditions increase the chance for more severe and potentially life-threatening RSV infection.

Palivizumab (Synagis), a humanized monoclonal antibody, is approved by the U.S. Food and Drug Administration (FDA) for the prevention of serious respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease. The recommended dose is 15 milligrams per kilogram intramuscularly every 28-30 days, beginning prior to the start of RSV season, to maintain adequate antibody trough levels during the season. In the initial IMPACT-RSV randomized controlled trial (1996-1997 RSV season), palivizumab was shown to reduce RSV hospitalizations by 55% in high-risk patients compliant with the monthly dosing schedule. However, patient compliance with the dosing schedule is not optimal, as documented in the Palivizumab Outcomes Registry Study, which found only 59.3% compliance based on appropriate number of doses and timing. Potential factors associated with poor compliance with the dosing schedule include Medicaid insurance coverage, family tobacco smoking, and parental perception of drug efficacy.

Managed care efforts to improve compliance with the palivizumab dosing schedule could potentially offset the increased palivizumab costs by decreasing emergency room (ER) visits, physician office visits, and hospitalizations. One such effort, tested by Gentiva Health Services, involved a national in-home RSV prophylaxis program, which was associated with high compliance and potential cost savings. Analysis of data in the Palivizumab Outcomes Registry reported by Frogel et al. (2008) produced a contrary finding of no significant association between compliance and RSV hospitalizations when compliance was defined as the number of expected injections. However, Frogel et al. did find that when compliance was defined as receiving all doses on time (within 35 days of the previous injection), compliant infants had significantly lower odds of RSV hospitalizations than noncompliant infants (odds ratio [OR] = 0.702, 95% confidence interval [CI] = 0.54-0.91). Additionally, a cost-effectiveness analysis by Joffe et al. (1999) found that the cost-effectiveness of palivizumab varied widely depending on the infant’s baseline level of risk and “in general the cost of prophylaxis against RSV infection appeared high, relative to the benefits realized.”

Given the conflicting results of previous studies of palivizumab compliance and cost-effectiveness, the purpose of this study was to further evaluate the relationship of palivizumab compliance with respiratory-related utilization and costs.

# Methods

## Design

A retrospective analysis of an administrative claims database was conducted to determine the impact of noncompliance with the 2006 American Academy of Pediatrics (AAP) recommended palivizumab dosing schedule on respiratory-related medical services and costs from the perspective of a western Pennsylvania managed care organization (MCO) covering approximately 500,000 members (307,000 commercial plan members, 92,000 Medicaid plan members, and 108,000 Medicare plan members) during the study period. For the purpose of this analysis, data were evaluated from the commercial and Medicaid groups only. This analysis was approved as a quality improvement (QI) study under the auspices of the QI review subcommittee of the MCO.

## Inclusion/Exclusion Criteria

De-identified pharmacy and medical claims data were extracted for infants meeting the following inclusion criteria: (a) continuous enrollment during the 2006-2007 RSV season (October 15, 2006, to April 15, 2007); (b) 0-24 months of age as of the start of the RSV season; (c) pharmacy claims approved via the plan’s prior authorization process for palivizumab (Table 1); and (d) at least 1 paid claim for palivizumab during the 2006-2007 RSV season. Compliance was defined as meeting all 3 of the following criteria: (a) starting palivizumab on time; (b) refilling palivizumab on time; and (c) receiving no more than 6 injections per RSV season, pursuant to the health plan’s quantity limit which was less restrictive than the 2006 AAP guidelines that advised, “changes from this recommendation of 5 monthly doses require careful consideration of the benefits and costs.” Specifically, members born

### What this study adds

- Only 29.8% of 245 infants who received palivizumab during the 2006-2007 RSV season were determined to be compliant with the number of recommended doses and no more than 37 days between doses.
- Compared with patients who were noncompliant with palivizumab dosing, compliance was associated with a lower proportion of patients with at least 1 respiratory-related ER visit (11 of 73 [15.1%] vs. 49 of 172 [28.5%], P = 0.034) but similar proportions of patients with at least 1 respiratory-related hospital stay (P = 0.734) or physician office visit (P = 0.564). There were no RSV-related hospitalizations among compliant infants compared with 2 (1.2%) for noncompliant infants (P = 1.000), and no RSV-related ER visits occurred in either group.
- Compared with patients who were noncompliant with palivizumab dosing, the compliant group had higher median palivizumab costs per patient ($10,416 vs. $7,605, P = 0.011), but similar median total cost (palivizumab cost plus respiratory-related medical cost) per patient (P = 0.189).
prior to the season were required to have a first pharmacy claim for palivizumab on or before November 30, 2006, and subsequent claims had to occur within 37 days of the previous claim. Members born during the RSV season were assumed to receive their first dose as an inpatient and were required to have their first outpatient palivizumab pharmacy claim within 37 days of hospital discharge. Each subsequent claim had to occur within 37 days of the previous claim.

Patient compliance with the individualized palivizumab administration schedule was evaluated by comparing the number of injections identified in pharmacy claims with the expected number of injections based on date of birth and the recommended monthly dosing frequency. Infants who received an injection on or after March 15, 2007, were not required to receive an injection in April to be considered compliant, since their titer levels should have been sustainable up to 30 days post-injection, thereby carrying them through the remainder of the RSV season ending April 15, 2007. A 37-day allowable gap between claims was chosen as the measure of compliance to allow the patient time to receive the drug from the specialty pharmacy provider and make a physician office visit for administration.

Palivizumab claims were identified via pharmacy claims; Current Procedural Terminology (CPT) code 90378; and Healthcare Common Procedure Coding System (HCPCS) codes C9003, J1565, and S9562. Of note, this particular MCO has code C9003 blocked at place of service number 11 (physician office) and also uses physician mailings to encourage parents to fill prescriptions for palivizumab through the MCO's specialty pharmacy provider. Therefore, nearly all palivizumab claims in this study were under the pharmacy benefit. Medical claims for palivizumab with a dollar amount less than $500 were excluded from the study, since they are not high enough to have included the cost of the drug, and it was assumed these were miscoded claims or claims for drug administration fees.

Medical services were captured from the MCO's medical claims data warehouse and included all claims with a respiratory diagnosis coded in any field on the claim based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (Table 2). Diagnosis codes selected were reviewed with physicians to ensure relevance. Visits were classified as ER, hospital, or physician office using 2 methods. First, some claims were classified using CPT codes for evaluation and management services. For office visits, these codes included 99201-99205 for new patients; 99211-99215 for established patients; 99241-99245 for consultations; 99381, 99382, 99391, and 99392 for preventive care; and 99431, 99432, 99433, and 99435 for newborn care. For inpatient services, a partial list of evaluation and management codes was used, including 99221-99223 for initial hospital admission visit; 99231-99233 for subsequent hospital visit; 99293-99296 for pediatric critical care and neonatal intensive care unit care; 99251-99255 for consultation; and 99231-99233 for observation. For ER visits, codes 99281-99285, indicating emergency department evaluation and management, were used. Second, for claims on which a CPT code was not billed, revenue codes were used to identify claim type. Inpatient hospital admissions were identified by room and board revenue codes 100-179 plus place of service code 21. ER visits were identified by revenue codes 450-459 plus place of service code 23. Respiratory-related services provided during the initial newborn hospital stay were excluded from respiratory-related medical service utilization and cost.

### TABLE 1
Prior Authorization Approval Criteria for Palivizumab

<table>
<thead>
<tr>
<th>Age at Start of RSV Season</th>
<th>0-6 Months</th>
<th>7-12 Months</th>
<th>13-24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤28 weeks (gestational age)</td>
<td>Approve</td>
<td>Approve</td>
<td>Approve if CLD or CHD</td>
</tr>
<tr>
<td>&gt;28 weeks but ≤32 weeks (gestational age)</td>
<td>Approve</td>
<td>Approve if CLD or CHD</td>
<td>Approve if CLD or CHD</td>
</tr>
<tr>
<td>&gt;32 weeks but ≤35 weeks (gestational age)</td>
<td>Approve if CLD or CHD or if 2 of the following risk factors:</td>
<td>Approve if CLD or CHD</td>
<td>Approve if CLD or CHD</td>
</tr>
<tr>
<td>&gt;35 weeks (gestational age)</td>
<td>Approve if CLD or CHD</td>
<td>Approve if CLD or CHD</td>
<td>Approve if CLD or CHD</td>
</tr>
</tbody>
</table>

*Prior authorization criteria were based on the 2006 American Academy of Pediatrics guidelines. Only pharmacy claims were subject to prior authorization.

CHD = hemodynamically significant congenital heart disease including congestive heart failure, severe pulmonary hypertension, or cyanotic heart disease; CLD = chronic lung disease requiring medical therapy such as supplemental oxygen, bronchodilator, diuretic, or corticosteroid therapy within 6 months before the start of RSV season; RSV = respiratory syncytial virus.


### TABLE 2

Diagnoses and Codes Used to Define Respiratory-Related and RSV-Related Services

<table>
<thead>
<tr>
<th>Respiratory-Related Diagnoses</th>
<th>ICD-9-CM Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory syncytial virusa</td>
<td>079.6X</td>
</tr>
<tr>
<td>Unspecified viral infection</td>
<td>079.99</td>
</tr>
<tr>
<td>Acute nasopharyngitis (common cold)</td>
<td>460.XX</td>
</tr>
<tr>
<td>Acute sinusitis unspecified</td>
<td>461.9X</td>
</tr>
<tr>
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Note: 

- *a* Denotes an ICD-9-CM code used to identify RSV-related services.

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; RSV = respiratory syncytial virus.

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**Analysis**

Infants were first categorized as compliant (i.e., filled prescriptions for palivizumab in accordance with the dosing schedule recommended by the 2006 AAP guidelines) or noncompliant. Baseline characteristics were then compared for compliant and noncompliant infants, including first versus second season exposure to palivizumab, gender, type of insurance coverage, and duration of follow-up. Length of follow-up was analyzed using patient months, which were calculated as the actual number of coverage months for each infant from the beginning of the season or birth to the end of the season. A maximum of 7 patient months were counted for infants born prior to the start of the RSV season. This comparison was done to account for varying lengths of follow-up due to birth date. For example, an infant born in November would have 5 months of follow-up, whereas an infant born in February would only have 2 months of follow-up. This variation in length of follow-up could account for differences in the amount of medical claims incurred.

The primary outcomes were the proportions of patients with at least 1 respiratory-related ER visit, hospital admission, and physician visit. Furthermore, medical services were more specifically assessed to determine the percent of patients with at least 1 RSV-related ER visit, hospital admission, and physician office visit. RSV-related visits were defined as those with an ICD-9-CM code of 079.6 (RSV infection), 466.11 (acute bronchiolitis caused by RSV), or 480.1 (pneumonia caused by RSV).

A descriptive analysis of cost outcomes was performed to compare health plan paid costs for compliant and noncompliant infants. Health plan paid costs (i.e., after subtraction of patient cost share) were assessed for palivizumab pharmacy costs and respiratory-related medical services during the entire RSV season from October 15, 2006, to April 15, 2007. Costs were reported as the mean and median per patient cost for the season for total respiratory-related medical services and RSV-related medical services (codes in Table 2). Additionally, mean per patient per month (PPPM) costs were calculated for total cost (palivizumab pharmacy and total respiratory-related medical).

Patient characteristics for compliant versus noncompliant infants, including first-season versus second-season exposure to palivizumab, gender, and type of insurance coverage, were analyzed using the Pearson chi-square test. The between-group difference in duration of follow-up in patient months was analyzed using the Mann-Whitney U test. Respiratory-related medical visit comparisons and cost comparisons were analyzed using the Mann-Whitney U test for nonparametric data and Fisher’s Exact test for categorical data. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). The a priori P value for statistical significance was 0.05.

**Results**

From October 15, 2006, to April 15, 2007, a total of 245 infants met the inclusion criteria, including receipt of at least 1 dose of palivizumab (Figure 1). There were 10 infants with palivizumab claims that were medical rather than pharmacy claims, and 5 of
these infants had medical claims only, which meant that these 5 infants were not subject to prior authorization for coverage of palivizumab. Of the 245 infants included in the study, 73 (29.8%) were determined to be compliant with palivizumab injections, and 172 (70.2%) were noncompliant (Table 3). A higher proportion of compliant patients (71.2%) were first-season recipients of palivizumab compared with 57.6% of noncompliant patients ($P = 0.044$; Table 3). Although the median duration of patient follow-up was 7 months in both groups, the Mann-Whitney U test result was statistically significant ($P = 0.039$) because of differences in the distribution of values.

Analysis of the number and percent of patients with at least 1 respiratory-related ER, hospital, or physician visit showed that the noncompliant group had a higher rate of patients with at least 1 respiratory-related ER visit (28.5% [n = 49]) compared with compliant patients (15.1% [n = 11], $P = 0.034$) but no significant differences in hospital admissions ($P = 0.734$) or physician visits ($P = 0.564$; Table 4). For the measure of at least 1 RSV-related medical event, there were no significant differences between the compliant versus noncompliant groups in RSV-related hospitalizations (0.0% vs. 1.2%, respectively, $P = 1.000$) or physician office visits (9.6% vs. 5.8%, respectively, $P = 0.284$), and there were no RSV-related ER visits in either group.

Cost analyses showed that although the median per patient palivizumab cost was significantly higher in the compliant group ($10,416 vs. $7,605, $P = 0.011$), the median total per patient costs (palivizumab-related pharmacy and respiratory-related medical services) for the 2 groups were not significantly different ($12,466 vs. $10,600, $P = 0.189$).

**Discussion**

During the 2006-2007 RSV season, only 29.8% of patients were compliant with receiving doses of palivizumab as recommended by the 2006 AAP guidelines. Compared with noncompliance, compliance with palivizumab therapy was associated with a significantly lower proportion of patients with at least 1 respiratory-related ER visit (28.5% [n = 49]) compared with noncompliant patients (15.1% [n = 11], $P = 0.034$) but no significant differences in hospital admissions ($P = 0.734$) or physician visits ($P = 0.564$; Table 4). For the measure of at least 1 RSV-related medical event, there were no significant differences between the compliant versus noncompliant groups in RSV-related hospitalizations (0.0% vs. 1.2%, respectively, $P = 1.000$) or physician office visits (9.6% vs. 5.8%, respectively, $P = 0.284$), and there were no RSV-related ER visits in either group.

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Asthma has been evaluated in several studies, and asthma development later in life. The link between RSV and hospitalization during infancy that found 30% of children with a history of RSV had developed asthma compared with 3% of children in the control group (P < 0.001). However, this link remains to be proven and was not considered in the present short-term study for the 2006-2007 RSV season.

Several previously published studies regarding the impact of palivizumab compliance on medical outcomes have shown mixed results. The IMPact-RSV Study (n = 1,502), a randomized controlled trial, found a 93% compliance rate with a monthly dosing schedule of 5 palivizumab injections, resulting in a 55% reduction in RSV hospitalization compared with placebo. However, the IMPact-RSV Study had a long list of exclusion criteria, including hemodynamically significant coronary heart disease, prior hospitalization, prior use of palivizumab, mechanical ventilation, active or recent RSV infection, hepatic or renal impairment, and seizure disorder. Differences between the results of IMPact-RSV and the present study could be partly attributable to the more stringent exclusion criteria used in IMPact-RSV. Additionally, the IMPact-RSV Study is more than a decade old and was sponsored by the manufacturer of palivizumab as 1 of the clinical trials used in the drug approval process.

Another study, conducted by the Palivizumab Outcomes Registry Study Group (2008), was a prospective, observational registry that collected data on infant palivizumab prophylaxis and outcomes for 19,548 enrollees from 2000 to 2004. That study found a 59.3% compliance rate with palivizumab based upon infants receiving the appropriate number of doses on time (within 35 days of the previous injection). There was no association found between compliance, defined as receiving appropriate number of doses, and RSV hospitalizations. However, compliance, when defined as receiving all doses on time, was associated with a significantly lower odds of RSV hospitalization. Further potential reasons for differences in results compared with the present study include the larger patient sample size, the prospective design, and the way in which compliance was defined. The Palivizumab Outcomes Registry Study Group gathered specific information on exact date and dose of each injection, whereas the present study assumed injection date as the date of the paid palivizumab claim, which could have resulted in an inaccurate determination of compliance. Additionally, the Palivizumab Outcomes Registry Study Group considered compliance as receiving the expected total number of injections for the season based on the month the first injection was given with no more than a 35-day gap. The present study considered 3 factors in defining compliance: receipt of the first dose after hospital discharge on time, the appropriate

### TABLE 3 Patient Characteristics (N = 245)

| Characteristic          | Compliant (n = 73) | Noncompliant (n = 172) | Total (N = 245) | P Value
|-------------------------|-------------------|------------------------|-----------------|--------
| Palivizumab experience  |                   |                        |                 |        |
| First season recipient  | 52 (71.2)         | 99 (57.6)              | 151 (61.6)      | 0.044  |
| Second season recipient | 21 (28.8)         | 73 (42.4)              | 94 (38.4)       |        |
| Gender                  |                   |                        |                 |        |
| Male                    | 44 (60.3)         | 87 (50.6)              | 131 (53.5)      | 0.164  |
| Female                  | 29 (39.7)         | 85 (49.4)              | 114 (46.5)      |        |
| Type of insurance coverage |               |                        |                 |        |
| Commercial              | 35 (45.2)         | 67 (39.0)              | 102 (40.8)      | 0.362  |
| Medicaid                | 40 (54.8)         | 105 (61.0)             | 145 (59.2)      |        |
| Patient months          |                   |                        |                 |        |
| Range 1-7               | Mean 5.8          | Mean 6.4               | Mean 6.2        | 0.039  |
| Range 2-7               | Median 7.0        | Median 7.0             | Median 7.0      |        |
| Median 7.0              |                   |                        |                 |        |
| SD 1.88                 |                   |                        |                 |        |
| Range 1-7               | Range 2-7         | Range 2-7              |                 |        |
| SD 1.88                 |                   |                        |                 |        |

*Statistical analyses were performed to test the difference between the compliant and noncompliant groups. Tests included the Pearson chi-square test for palivizumab experience, gender, and type of insurance coverage and the Mann-Whitney U test for patient length of membership.

*bThere were no Medicare recipients of palivizumab during the defined study period.

The number of patient months was calculated as the actual number of coverage months from the beginning of the season or birth to the end of the season. A maximum of 7 patient months were counted for infants born prior to the start of the RSV season.

RSV = respiratory syncytial virus; SD = standard deviation.
was also sponsored by the manufacturer of palivizumab and was initiated in the 2000-2001 RSV season. The present study provides a retrospective review independent of the manufacturer and offers a more current evaluation of a sample of treated infants. Given the results of the present study, as well as the mixed results of the Palivizumab Outcomes Registry Study Group, the cost-effectiveness of palivizumab prophylaxis comes into question. A cost-effectiveness analysis by Joffe et al. (1999) assessed the medical and work-loss costs per hospitalization averted in a hypothetical cohort of premature infants and estimated number of injections, and a gap of no more than 37 days between palivizumab claims. Furthermore, the Palivizumab Outcomes Registry Study Group collected data specific to RSV admission any time a study participant was hospitalized with primary or secondary RSV infection. The present study assessed retrospectively any hospital admission (excluding the initial newborn hospital stay), ER visit, or office visit in which a respiratory diagnosis or a diagnosis of RSV was made but did not have available specific RSV laboratory testing to confirm RSV as the reason for the utilization. Finally, the Palivizumab Outcomes Registry Study Group

| TABLE 4 | Respiratory-Related Medical Claims and Costs |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|                       | Compliant Patients (n = 73) | Noncompliant Patients (n = 172) | Total Patients (N = 245) |
|                       | Number | Mean PPPM | Number | Mean PPPM | Number | Mean PPPM |
| Respiratory-related servicesb | | | | | | |
| ER visit n (%)b,c | 11 (15.1%) | — | 49 (28.5%) | — | 60 (24.5%) | — | 0.034 |
| Hospital admission n (%)b,d | 14 (19.2%) | — | 37 (21.5%) | — | 51 (20.8%) | — | 0.734 |
| Office visit n (%)b,e | 44 (60.3%) | — | 111 (64.5%) | — | 155 (63.3%) | — | 0.564 |
| Total costs for respiratory-related medical servicesf | $323,652.27 | $764.41 | $1,968,721.73 | $1,788.45 | $2,292,374.00 | $1,509.13 | NA |
| Mean (median) per patient costs for respiratory-related medical servicesf,g | $4,433.59 ($233.12) | $11,446.06 ($205.25) | $9,356.63 ($225.00) |
| RSV-related servicesb | | | | | | |
| ER visit n (%)b,c | 0 (0.0%) | — | 0 (0.0%) | — | 0 (0.0%) | — | 1.000 |
| Hospital admission n (%)b,d | 0 (0.0%) | — | 2 (1.2%) | — | 2 (0.8%) | — | 1.000 |
| Office visit n (%)b,e | 7 (9.6%) | — | 10 (5.8%) | — | 17 (6.9%) | — | 0.284 |
| Total costs for RSV-related medical servicesb | $582.22 | $1.37 | $27,164.86 | $24.67 | $27,747.08 | $18.19 | NA |
| Mean (median) per patient costs for RSV-related medical servicesb | $7.98 ($0.00) | $157.94 ($0.00) | $113.25 ($0.00) | 0.306 |
| Palivizumab cost | | | | | |
| Total palivizumab drug cost | $679,482.54 | $1,602.55 | $1,315,353.09 | $1,194.69 | $1,994,835.63 | $1,308.09 | NA |
| Mean (median) per patient palivizumab cost | $9,307.98 ($10,415.83) | $7,647.40 ($7,605.30) | $1,142.19 ($8,316.26) | 0.011 |
| Totals | | | | | |
| Total respiratory-related and palivizumab costi | $1,003,134.81 | $2,369.24 | $3,284,074.82 | $2,983.35 | $4,287,209.63 | $2,822.39 | NA |
| Mean (median) total cost per patienti | $13,741.57 ($12,466.09) | $19,093.46 ($15,999.91) | $17,498.81 ($11,009.27) | 0.189 |

aP values were derived from the Mann-Whitney U test for nonparametric data and the Fisher’s Exact test for categorical data, comparing compliant with noncompliant infants. 
bCounts indicate number of unique patients with at least 1 claim in the categories shown. Respiratory-related diagnoses are shown in Table 2. RSV diagnoses are 079.6 (RSV infection), 466.11 (acute bronchiolitis caused by RSV), and 480.1 (pneumonia caused by RSV). 
cIndicates an administrative claim for ER services, defined as a CPT code for emergency department evaluation and management services or revenue codes 450-459 plus place of service code 23. 
dIndicates an administrative claim for inpatient services, defined as a CPT code for inpatient evaluation and management or revenue codes 100-179 plus place of service code 21. 
eIndicates an administrative claim for in-office services, defined as a CPT code for office visit evaluation and management. 
fSummed costs for all claims with a respiratory-related diagnosis in any field on the claim. 
gSummed costs for all claims with an RSV diagnosis in any field on the claim. 
hSummed costs for all claims with a respiratory-related medical cost. 
iSum of palivizumab cost plus respiratory-related cost. 
CPT = Current Procedural Terminology; ER = emergency room; NA = not applicable; PPPM = per patient per month; RSV = respiratory syncytial virus.
that palivizumab prophylaxis costs anywhere from $12,000 to $420,000 per hospitalization averted, depending upon the risk and gestational age category of the infant. While cost-effectiveness varied widely among different subgroups of infants, the study authors concluded that “in general the cost of prophylaxis against RSV infection appeared high, relative to the benefits realized.” The investigators went on to say that this cost-ineffectiveness called for more stringent recommendations for palivizumab.27

An article in the April 16, 2008, issue of the Wall Street Journal, “Weighing Which Babies Get a Costly Drug,” suggested that the few infants who benefit from palivizumab may not justify the high cost of the preventive therapy.20 Perhaps the key to cost-effective treatment is in utilization management of these drugs. The need for utilization management increases with the anticipated approval by the FDA of motavizumab, another RSV preventive treatment.21

The present study’s MCO has updated its prior authorization criteria to further refine criteria for access to palivizumab treatment based on the 2009 guidelines set forth by the AAP.22 This 2009 update further restricts access by redefining the gestational age categories and (a) specifically restricts the maximum number of doses to the lesser of 3 doses or coverage up to 90 days of age for the group of patients born at gestational ages from 32 weeks, 0 days through 34 weeks, 6 days and born within 3 months before the start of the RSV season or any time throughout the RSV season; and (b) considers this group eligible only if they have 1 of 2 risk factors (previously several risk factors were considered). Additionally, the 2009 AAP guidelines also make clear that the maximum number of palivizumab injections is 5 per season regardless of the start date in a given geographic region. These recommendations imply that palivizumab was given in an overly broad patient population in prior years and may explain mixed results in assessments of outcomes and cost-effectiveness of palivizumab. Further studies are needed to assess the outcomes in this newly defined and more restricted population for recommended use of palivizumab.

Limitations

First, this was an exploratory and descriptive study of a small sample of infants. The results do not constitute a definitive test of either the effectiveness of palivizumab or the cost-effectiveness of compliance. Second, the method used to categorize compliance was somewhat subjective. This MCO chose to use palivizumab claims data (including pharmacy, medical, and home health administrative claims using appropriate C, J, CPT, and S codes) for determining compliance, permitting 37 days between claims to allow time for the parent to either inject or obtain injection of the drug. A more accurate analysis might have been achieved by querying the data for physician claims for drug administration to augment the fill dates for palivizumab pharmacy claims. However, we believe that the permitted gap of up to 37 days between fill dates of palivizumab at the specialty pharmacy avoided an overestimate of noncompliance.

Third, patients whose palivizumab claims were billed only through medical codes were not subject to prior authorization, since this requirement applies only to the pharmacy benefit. Therefore, we do not know if these patients met the 2006 AAP guideline requirements for palivizumab use. However, palivizumab was billed through medical claims for only 5 infants, 2% of our sample. Finally, the short duration of follow-up would not capture potentially favorable longer-term outcomes associated with healthier infants with fewer chronic respiratory problems.

Conclusions

Palivizumab compliance was suboptimal. Compliance with the palivizumab dosing schedule based on 2006 AAP criteria, compared with noncompliance, was associated with higher palivizumab drug costs but similar overall total costs (palivizumab plus respiratory-related medical costs). Compliance was associated with a lower proportion of patients with at least 1 respiratory-related ER visit but similar proportions of patients with at least 1 respiratory-related physician office visit or hospitalization and similar proportions of patients with any RSV-related service. Ten percent of compliant infants had at least 1 RSV-related office visit during the study period. Further studies are needed to assess the long-term respiratory health and associated medical cost differential between infants who are compliant and noncompliant with palivizumab.

Authors

JOCELYN L. DIEHL, PharmD, is Clinical Pharmacy Specialist, and JESSICA R. DAW, PharmD, is Manager, Clinical Pharmacy, University of Pittsburgh Medical Center Health Plan, Pittsburgh, Pennsylvania. KIM C. COLEY, PharmD, is Professor of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, Pittsburgh, Pennsylvania. RENEE RAYBURG, RPh, is Director, Clinical Services, Bioscrip Inc., Venetia, Pennsylvania.

AUTHOR CORRESPONDENCE: Jocelyn L. Diehl, PharmD, University of Pittsburgh Medical Center Health Plan, Two Chatham Center, 112 Washington Pl. Pittsburgh, PA 15219. Tel.: 412.454.5661; Fax: 412.454.5295; E-mail: diehjl@upmc.edu.

DISCLOSURES

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Diehl, Daw, and Rayburg developed the study concept and design. Diehl assisted Huber in data collection. The data were interpreted primarily by Coley and Diehl, with the assistance of Huber. Diehl wrote the first version of the manuscript and made most of the revisions with the assistance of Daw and Coley.
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Economic Evaluation of Childhood 7-Valent Pneumococcal Conjugate Vaccination in Korea

Hyun Soon Sohn, PhD; Dong-Churl Suh, MBA, PhD; Eunjin Jang, PhD; and Jin-Won Kwon, PhD

ABSTRACT
BACKGROUND: Streptococcus pneumoniae (sp) is a leading cause of invasive and noninvasive bacterial disease in children. 7-valent pneumococcal conjugate vaccine (PCV-7) has been shown to significantly reduce the incidence of pneumococcal diseases, such as meningitis, bacteremia, pneumonia, and otitis media. Although PCV-7 was introduced in Korea in 2003, it is not yet included in the universal immunization program.

OBJECTIVE: To evaluate the health outcomes, costs, and cost-effectiveness of universal vaccination with PCV-7 in Korean infants and to estimate the break-even price for PCV-7 from a societal perspective.

METHODS: A decision analytic model was used to evaluate the cost-effectiveness of immunization with PCV-7 in a birth cohort of Korean infants born in 2006. A universal vaccination strategy was compared with no vaccination in terms of costs and life years gained (LYG) over a 5-year time horizon. The birth cohort size, incidence of disease, resource utilization, and associated costs were obtained from the Korea National Statistical Office, the Korean Centers for Disease Control and Prevention, the Korean National Health and Nutrition Examination Survey, and the Korean Ministry of Health and Welfare. Inputs on the probabilities of clinical treatment pathways (e.g., tympanostomy) were derived from international literature if data specific to Korea did not exist. To estimate the benefits of universal immunization, the serotype-specific efficacy of PCV-7 was derived from studies conducted by Northern California Kaiser Permanente and by the Finnish Otitis Media Vaccine Study and applied to the serotypes isolated in Korean children with sp infections. The effects of vaccination on quality of life, herd immunity, benefits after the first 5 years of life, and patient copayments were not considered. A 3-dose schedule was used in the base-case analysis. A 3-dose schedule was also evaluated. The assumed price per dose was Korean won (KW) 70,000 (approximately US$54; 2009 exchange rate US$1 = KW1,300). Univariate and probabilistic sensitivity analyses were performed.

RESULTS: Implementing a 4-dose universal PCV-7 vaccination strategy in a birth cohort of 451,514 infants in Korea would prevent 96,728 cases of pneumococcal-related infections (591 meningitis, 1,379 bacteremia, 43,950 pneumonia, and 50,808 otitis media cases) and 216 deaths (199 discounted deaths averted, 575 discounted LYG over 5 years). The medical and nonmedical cost burden of pneumococcal diseases offset with vaccination was KW44,033 million (US$33.87 million). The incremental discounted cost of universal vaccination was estimated to be KW86,384 million (US$66.45 million). The incremental cost per LYG was KW150.2 million (US$115.549 million) for the 4-dose schedule and KW103.9 million (US$79,955 million) for the 3-dose schedule. The break-even costs were KW22,100 and KW28,100 per dose for the 4- and 3-dose schedules, respectively.

CONCLUSIONS: Universal PCV-7 vaccination of infants in Korea could substantially reduce pneumococcal disease morbidity, mortality, and related costs by preventing pneumococcal infections. However, at current market prices for the vaccine, a universal vaccination strategy is not cost-effective. The literature suggests that factors not considered in this analysis, including vaccine price reduction and indirect effects on public health (e.g., herd immunity), have the potential to make the public health impact and cost-effectiveness of universal PCV-7 vaccination in Korea more favorable.

What is already known about this subject
• The best way to prevent pneumococcal diseases is through vaccination. 7-valent pneumococcal conjugate vaccine (PCV-7) significantly reduced the incidence of pneumococcal diseases in large-scale studies conducted in the United States and Europe. PCV-7 is used in 74 countries worldwide and is incorporated into the national childhood immunization schedules in 16 countries. The World Health Organization recommends including PCV in infant vaccination programs.
• PCV-7 was introduced to Korea in 2003 but is not included in the universal immunization program mandated by the Korean Centers for Disease Control and Prevention. Only 15.3% of infants were administered at least 1 dose of PCV-7 in 2006. Although cost and perceptions of cost-effectiveness may affect public health vaccine recommendations, to date no study has estimated the cost effectiveness of PCV-7 immunization in Korea.
• In many countries, vaccine cost was an important variable affecting the cost-effectiveness of including PCV-7 in nationwide immunization programs. Studies that evaluated benefits and costs of PCV-7 in the United States and Canada suggested that vaccine cost would need to be lower than the manufacturer’s list price to achieve cost savings. More recent studies have also shown PCV-7 to be highly cost-effective when indirect effects on public health (e.g., herd immunity) are taken into account.

What this study adds
• This is the first health economic evaluation of universal PCV-7 immunization in Korean infants. A decision analytic model estimated that PCV-7 immunization with a 4-dose schedule in a 2006 birth cohort of 451,514 infants in Korea could prevent 96,728 cases of pneumococcal diseases and 218 deaths (199 discounted deaths averted; 995 discounted life years gained [LYG]) during the first 5 years of life.
• A universal PCV-7 vaccination program would initially cost Korean won (KW) 126,424 million (US$97.3 million) to purchase the vaccine (KW70,000 [US$54] per dose for 4 doses). Over a 5-year time horizon, PCV-7 vaccination could reduce medical and nonmedical costs by KW44,033 million (US$33.9 million), resulting in net program costs of KW82,391 million undiscounted (KW86,384 million discounted). The incremental costs per LYG were KW150.2 million (US$115.549 million) and KW103.9 million (US$79,955 million) for the 4- and 3-dose strategy, respectively.
• A PCV-7 vaccination program would result in cost savings if the vaccine price per dose was KW22,100 and KW28,100 or less for the 4- and 3-dose schedules, respectively. As in other countries, vaccine price is just 1 determinant of cost-effectiveness for a PCV-7 universal immunization strategy in Korea. The attractiveness of a PCV-7 program depends both on vaccine price and on the potential indirect effects that vaccination has on public health.

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**S**treptococcus pneumoniae (sp) is a leading cause of invasive and noninvasive bacterial disease in children throughout the world, including Korea.1,2 Pneumococcal diseases are treated primarily with penicillin, but penicillin resistance in nasopharyngeal sp is high in healthy Korean children, with rates of 82% reported in recent years.3 The high rate of drug resistance makes treatment of pneumococcal infection difficult, possibly resulting in longer hospitalizations, use of more expensive alternative antibiotic therapy, higher mortality, and consequently increased medical costs.4 Because sp is associated with bacterial meningitis, a disease with high mortality rates, careful selection of antibiotics and prevention strategies for these organisms is important. In Korea in 2006, the cost of pneumococcal diseases in children younger than 15 years of age was estimated to be Korean won (KW) 201 billion (US$154.6 million; 2009 exchange rate US$1 = KRW1,300). Across all age groups in Korea, the economic burden of pneumococcal diseases was estimated at KW790 billion (US$607.7 million), including KW148 billion for otitis media, KW550 billion for pneumonia, and KW92 billion for both meningitis and bacteremia.1

The best way to prevent sp diseases is through early vaccination. The 7-valent pneumococcal conjugate vaccine (PCV-7) has been available since 2000 to provide protection against pneumococcal diseases in children younger than 2 years of age. PCV-7 is considered clinically effective and safe and has shown significant reductions in the incidence rates of invasive pneumococcal disease, pneumonia, and otitis media in several large-scale studies conducted in the United States and Europe in infants and children.5-10 In the United States, where PCV-7 is used routinely to vaccinate children younger than 5 years of age, surveillance data from 2003 through 2003 documented substantial declines in invasive pneumococcal disease compared with pre-vaccine years.11 PCV-7 is currently available in 74 countries worldwide with 16 having incorporated PCV-7 into their national childhood immunization schedules.12 The World Health Organization (WHO) recently reported that pneumococcal disease is the foremost infectious disease among causes of death preventable by vaccination in children 5 years or younger worldwide and, as a result, has recommended including PCV in infant vaccination programs.13

Pneumococcal nasal carriage was found in 9.3% of the healthy children aged 9 years or younger and in 30%-34% of outpatient and hospitalized children aged 5 years or younger in Korea. Among the isolated sp serotypes identified in these nasal carriages, 84% are covered by PCV-7.14-17 This finding suggests that PCV-7 vaccination may reduce nasal carriage of sp and subsequent related pneumococcal infections. PCV-7 was introduced to Korea in late 2003. Because PCV-7 is an optional vaccination as recommended by the Korean Pediatric Society and is not part of the essential universal immunization program mandated by the Korean Centers for Disease Control and Prevention (KCDC), it is not covered by national health insurance. Lee et al. reported in 2006 that only 15.3% of all Korean infants were administered at least 1 dose of PCV-7 within 7 years after birth.1

Many factors can affect public health vaccine recommendations and vaccination rates. One possible limiting factor may be cost and perceptions of cost-effectiveness. The price of PCV-7 per dose makes PCV-7 the most expensive component of the routine immunization schedule.18 In a decision analytic model of the cost-effectiveness of PCV-7, a universal vaccination program in the United States was estimated to save $342 million in medical and $415 million in nonmedical costs, such as lost work time, before accounting for the vaccine acquisition cost.19 At the manufacturer’s current list price of $58 per dose, infant vaccination would cost society $80,000 per life-year saved. It was estimated that vaccination of healthy infants would result in net savings for society if the vaccine cost less than $46 per dose and net savings for the payer if the vaccine cost less than $18 per dose.19

The objectives of the present study were to estimate the projected health benefits, costs, and cost-effectiveness of universal routine vaccination in infants considered as the primary target group for PCV-7 in Korea. An additional aim was to determine the vaccine price at which the PCV-7 immunization program would break even.

### Methods

#### Decision Analytic Model Overview

A decision analytic model was used to estimate the public health and economic impact of a universal PCV-7 strategy compared with no vaccination on a static birth cohort. This model assumed as a starting point that all Korean infants born in 2006 were vaccinated with PCV-7 following a 4-dose schedule. The cohort size (451,514 infants) was defined based on birth statistics (Korean Life Table) provided by the Korean National Statistical Office.20 The cohort was assumed to change annually on the basis of death rate at each age band reported on the Korean Life Table. A decision tree (Figure 1) was constructed to project the impact of infant vaccination on the incidence of invasive pneumococcal diseases including meningitis, bacteremia, pneumonia, and otitis media. The conceptual framework for this decision tree has been extensively reported in the literature.19,21-23

The analyses were performed primarily from a societal perspective over a 5-year time horizon. Approximately 75% of invasive pneumococcal diseases in children occur before the age of 5 years.1 The efficacy of the vaccine for more than 5 years after immunization has not yet been determined.21 With uncertainty relating to the duration of vaccine protection, this model was designed to project the impact of PCV-7 on pneumococcal disease burden, associated costs, and life years gained (LYG) during the first 5 years of life. Costs and benefits were discounted at 5%. Microsoft Excel 2000 (Microsoft Corp., Redmond, WA) was used to project health outcomes and costs, producing cost-effectiveness analyses for 3- and 4-dose schedules, including univariate and probabilistic sensitivity analyses based on Monte Carlo simulation. In addition, break-even cost simulations were performed for 3- and 4-dose schedules.

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1 Economic Evaluation of Childhood 7-Valent Pneumococcal Conjugate Vaccination in Korea

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Epidemiology of Pneumococcal Diseases
The clinical and laboratory criteria used to establish estimates of pneumococcal disease incidence in this study varied according to the disease. Bacterial meningitis was based on WHO criteria, defined as having 1 or more clinical signs or symptoms of meningitis lacking an identifiable bacterial pathogen and 1 of the following: a cerebrospinal fluid (CSF) appearing turbid; reports of protein >100 milligrams per deciliter (mg per dL), glucose <40 mg per dL; or white blood cell (WBC)/100 cells per cubic millimeter with >80% neutrophils. For estimation of invasive pneumococcal disease incidence, we considered probable bacterial meningitis that was treated medically and resulted in medical costs based on a study conducted by Kim et al. (2004). Bacteremia was defined if the pathogen was isolated only in the blood without an identified focal lesion and with no symptoms other than those associated with bacteremia or sepsis.

The long-term clinical sequelae associated with pneumococcal diseases were considered in this model. Meningitis can cause severe nervous system damage, such as hearing loss and paralysis. Neurosensory hearing loss is a common severe consequence of childhood bacterial meningitis. It can be a barrier to a child’s normal speech, language, educational, and social development. Survival with deafness was assumed to require cochlear implants. Cochlear implantation has become the standard treatment for young children with severe to profound neurosensory hearing loss in Korea. We assumed tympanostomy tube insertion for 5.9% of patients with acute otitis media to allow drainage of the middle ear to improve hearing and reduce the pain caused by the pressure of the purulent effusion. Meningitis, bacteremia, and pneumonia could also result in death. However, we did not assume any mortality from otitis media.

Pneumococcal disease-related probabilities were derived from published data sources that included primarily Korean-specific epidemiology data and clinical studies supplemented by national health statistic sources in Korea (Table 1). We used pneumococcal disease incidence rates primarily from reliable Korean-specific reports and National Health Insurance (NHI) claims data reported by the Korean Health Insurance Review & Assessment Service Agency (HIRA). Data from other countries were used when Korean data were not available. For example, the probability of a child receiving a tympanostomy as a consequence of otitis media came from non-Korean sources, such as the United States and Finland. The probabilities of the remaining clinical sequelae occurring from pneumococcal diseases and disease-related mortality were based on clinical studies of Korean children.

AOM = acute otitis media; PCV-7 = 7-valent pneumococcal conjugate vaccine.
Disease Incidence Rates. The incidence of meningitis was based on a large prospective, population-based surveillance study of invasive bacterial diseases in Korean children aged less than 5 years.24 Many of the infectious disease cases in Korea have negative culture results because antibiotics are often started empirically prior to obtaining cultures. In a 1998 Korean study of hospitalized children diagnosed with meningitis, only 18.0% of the cases were confirmed by both clinical symptoms and CSF tests.50 This problem has implications for our study because the true incidence of meningitis could be greater than the 91.0 per 100,000 we used in our calculations to estimate disease burden; sensitivity analyses were performed to address this issue. We assumed that the bacterial meningitis cases that met the WHO definition would receive clinical treatment. The incidence of bacteremia was calculated based on the proportions of bacteremia and meningitis cases among invasive pneumococcal disease cases reported in a recent large observational study.16 The incidence rates of pneumonia and otitis media were estimated from NHI claims data.37 We estimated otitis media incidence on a per patient basis rather than a per episode basis.37

Causative sp Rates. Determination of sp as the underlying cause of pneumococcal disease was based on 3 Korean studies.1,38-39 In these studies, sp was the underlying cause of 43.5% of meningitis, 42.9% of bacteremia, 26.8% of pneumonia, and 29.2% of otitis media cases.

Case Estimates of Morbidity and Mortality in an Unvaccinated Population. The numbers of cases of specific pneumococcal diseases were calculated by multiplying the specific disease incidence by the cohort size at each age-band and the rate of causative

| TABLE 1 | Model Inputs: Pneumococcal Disease-Associated and Vaccine Efficacy-Associated Variables in Korean Children Younger Than 5 Years of Age |
| --- | --- | --- |
| Birth cohort size | 451,514 | Korea Statistical Information Service20 |
| Annual incidence (per 100,000) | | |
| Meningitis | 91.0 | 75.3-110.0 | Kim et al. 200424 |
| Bacteremia | 3.58 | 178.3-260.5 | Kim et al. 2004,24 Choi and Lee 199836 |
| Pneumonia | 11,988.2 | Base ± 25% | HIRA 200637 |
| Otitis media | 20,951.8 | Base ± 25% | HIRA 200637 |
| Rate of sp | | |
| Meningitis | 0.435 | | Lee et al. 20061 |
| Bacteremia | 0.429 | | Lee et al. 20061 |
| Pneumonia | 0.268 | | Lee and Woo 200738 |
| Otitis media | 0.292 | | Jung et al. 200039 |
| Annual probabilities of clinical sequelae | | |
| Disability from meningitis | 0.031 | | Kim et al. 200424 |
| Severe hearing impairment from meningitis | 0.018 | | Lee et al. 2006,1 Lee et al. 200732 |
| Cochlear implant among patients with severe hearing | 0.217 | | Ahn et al. 200731 |
| Tympanostomy from otitis media | 0.059 | | Fireman et al. 2003,8 Palmu et al. 200431 |
| Annual mortality | | |
| Meningitis | 0.046 | | Lee et al. 2006,1 Kim et al. 2004,24 Park et al. 200034 |
| Bacteremia | 0.043 | | Lee et al. 2006,1 Kim et al. 200535 |
| Pneumonia | 0.003 | | Lee et al. 20061 |
| Serotype coverage rates of PCV-7 | | |
| Meningitis and bacteremia | 0.682 | | Lee et al. 2006,1 Kim et al. 2004,3 Choi 2008,41 Lee et al. 200352 |
| Pneumonia | 0.676 | | Choi 200841 |
| Otitis media | 0.648 | | Kim et al. 2004,3 Kim et al. 2002,15 Choi 2008,41 Lee et al. 2003,52 Choi et al. 200643 |
| Vaccine efficacy (reduction of diseases) in 4–dose scenario | | |
| VT meningitis and bacteremia | 97.4% | | Black et al. 20009 |
| VT pneumonia | 90.0% | | Black et al. 20009 |
| VT otitis media | 57.0% | | Black et al. 20009 |
| Vaccine efficacy in 3-dose scenario | 95% of 4 doses | | Whitney et al. 200649 |
| Discount rate for outcomes (%) | 5 | 3, 7 | HIRA recommendation |

HIRA = Health Insurance Review & Assessment Service Agency; PCV-7 = 7-valent pneumococcal conjugate vaccine; VT = vaccine type.

a(0.45*91.0)/0.19
serum antibody concentrations in patients treated with a 3-dose schedule were comparable to those with a 4-dose schedule.\textsuperscript{45-46} Vaccinations are scheduled as 4 doses in the United States, Canada, and Netherlands, whereas many European countries, such as Sweden, Denmark, Norway, Italy, and Finland, and countries in other regions, such as Australia, primarily have a 3-dose vaccination schedule at 3, 5, and 12 months on the basis of immunogenicity studies.\textsuperscript{2,47} An immunogenicity study for PCV-7 in Korean infants reported that 97%-100% with a 3-dose vaccination showed a serum antibody concentration level greater than 0.35 micrograms per mL (the WHO-recommended minimum level to prevent invasive pneumococcal infections). Because post-vaccination mean serum antibody concentration levels were found to be higher in Korean infants than in the United States and European countries,\textsuperscript{48} we assumed that a 3-dose vaccination schedule would provide preventive effects comparable to those of the 4-dose strategy. Thus, the immunogenicity studies and regulatory agencies appear to support a 3-dose vaccination schedule as an alternative to a 4-dose schedule.

The incidence of pneumococcal infections in vaccinated infants was assumed to be reduced in proportion to the demonstrated vaccine efficacy against infections. Serotype-specific efficacy rates were applied because vaccine efficacy against pneumococcal diseases is specific to 7 serotypes. No studies to our knowledge have evaluated PCV-7 vaccine efficacy in Korean children. There is, however, no evidence of ethnic variation in PCV-7 effectiveness.\textsuperscript{7} Therefore, assumptions about vaccine efficacy were derived from the largest studies currently available, including the U.S. Northern California Kaiser Permanente (NCKP)\textsuperscript{5} and the Finnish Otitis Media Vaccine (Finnish OM)\textsuperscript{6} studies. The NCKP study evaluated the efficacy, safety, and immunogenicity of PCV-7 vaccination at 2, 4, 6, and 12-15 months in a prospective double-blind study among 37,830 children in a health maintenance organization.\textsuperscript{5} The Finnish study was a prospective, randomized, double-blind cohort design to evaluate PCV for the prevention of pneumococcal acute otitis media.\textsuperscript{6}

We estimated pneumococcal disease cases that were averted by PCV-7 during the study period (Table 1).\textsuperscript{1,3-5,15,41-43,49} First, we estimated the number of \( sp \)-pneumococcal disease cases in Korea with serotypes covered by PCV-7. The serotype coverage rates ranged from 64.8\% of otitis media to 68.2\% of meningitis/bacteremia cases. Next, we multiplied the cases with PCV-7 serotype coverage by the vaccine's efficacy for pneumococcal diseases, assumed to be 97.4\% for meningitis and bacteremia, 90.0\% for pneumonia, and 57.0\% for otitis media, using the 4-dose schedule. The estimated number of cases prevented by vaccination was equal to the serotype coverage rate times the efficacy rate times the estimated number of cases attributable to \( sp \). For example, the estimated number of meningitis cases prevented by vaccination was 0.682 × 0.974 × 890 = 591. The 3-dose schedule was assumed to have 95\% of the efficacy of the 4-dose schedule. Mean values across studies were used for the probability of tympanostomy.
TABLE 2  Medical and Nonmedical Cost-Associated Variables in Korean Children Younger Than 5 Years of Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Value</th>
<th>Ranges for Sensitivity Analysis</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine cost per dose (KW + 000)</td>
<td>70</td>
<td>10-70</td>
<td>Market price52</td>
</tr>
<tr>
<td>Direct medical cost (annual average per patient) (KW + 000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>357</td>
<td>Base ± 25%</td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>337</td>
<td>Base ± 25%</td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>190</td>
<td>Base ± 25%</td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Otitis media</td>
<td>74</td>
<td>Base ± 25%</td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Hospitalized meningitis</td>
<td>861</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized bacteremia</td>
<td>746</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized pneumonia</td>
<td>690</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>320</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td>1,698</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cochlear implant</td>
<td>705</td>
<td></td>
<td>Korea NHI reimbursement price list53</td>
</tr>
<tr>
<td>Tympanostomy</td>
<td>149</td>
<td></td>
<td>Korea NHI reimbursement price list53</td>
</tr>
<tr>
<td>Hospitalization rate</td>
<td>0.391</td>
<td></td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Average annual physician visit frequency per outpatient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>2.0</td>
<td></td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>2.5</td>
<td></td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4.0</td>
<td></td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Otitis media</td>
<td>6.5</td>
<td></td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Average length of stay per hospitalized patient (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>6.7</td>
<td></td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>6.7</td>
<td></td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7.7</td>
<td></td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Otitis media</td>
<td>4.5</td>
<td></td>
<td>HIRA 200637</td>
</tr>
<tr>
<td>Transportation cost for hospitalized patient (1-way) (KW)</td>
<td>11,019</td>
<td></td>
<td>Korea NHANES54</td>
</tr>
<tr>
<td>Transportation cost for outpatient (1-way) (KW)</td>
<td>8,891</td>
<td></td>
<td>Korea NHANES54</td>
</tr>
<tr>
<td>Hourly average wage for women aged 30-39 years (KW)</td>
<td>8,946</td>
<td></td>
<td>Korea Statistical Information Service22</td>
</tr>
<tr>
<td>Discount rate for cost (%)</td>
<td>5</td>
<td>3, 7</td>
<td>HIRA recommendation</td>
</tr>
</tbody>
</table>

HIRA = Health Insurance Review & Assessment Service Agency; KW = Korean won; NHANES = National Health and Nutrition Examination Survey; NHI = national health insurance.

Annual mortality for meningitis and bacteremia, and serotype coverage rates because these parameters were based on 2 or more studies.

Vaccine efficacy was assumed to be the same throughout 5 years and applied during the analysis period. In a recent economic study, PCV-7 was assumed to elicit a long-lasting immune response in young children, based on immunologic studies indicating that PCV-7 would stimulate a long-lasting antibody response and provide an extended duration of protection. However, vaccine effectiveness was not reported for each age group, and duration of protection afforded by the vaccine still remains uncertain. Thus, we assumed that protection efficacy would last at the same level during the 5 years.

Costs

The medical and nonmedical cost parameters used in this analysis are reported in Table 2. The average unit costs reported for medical and nonmedical cost items were based on Korean-specific data sources. Direct medical costs included the cost of vaccine and treatment for pneumococcal diseases. Direct nonmedical costs included transportation costs for medical care due to pneumococcal diseases. Indirect medical costs (not shown) included the costs associated with economic productivity loss (i.e., time spent caring for infected children by caregivers) owing to pneumococcal disease morbidity. Productivity loss due to premature death in nonvaccinated infants and productivity gains owing to prevention of premature death in vaccinated infants were not considered. These factors were not included to avoid double-counting the vaccination benefit and because children younger than 5 years of age are not old enough to participate in the labor force. In the vaccinated group, it was assumed that direct medical and nonmedical costs would be reduced to the same degree as vaccine-attributable prevention of diseases. All costs are reported
in 2006 KW currency. Prices were adjusted using the Korean Consumer Price Index.\textsuperscript{20} Vaccination Program Costs. The cost of PCV-7 is the only input cost for a vaccination program included in this model. We assumed that PCV-7 uptake was 100\% for all vaccination schedules in the 2006 birth cohort during the first year. The vaccine was assumed to be administered concurrently with other vaccines on the same day based on convenience and because there is no evidence of interactions between PCV-7 and other vaccines.\textsuperscript{12,55} The market price of PCV-7 vaccine per dose in Korea is KW100,000.\textsuperscript{52} Based on the Yearbook of Imported Pharmaceutical Goods\textsuperscript{56} and the importer's profit margin, we assumed a wholesale price of KW70,000 (approximately $US54) per dose. We used the wholesale price in our base-case analysis because it better reflects actual cost in Korea than does the market price. Vaccination-related costs, such as administration, supplies, and medical staff time, were not considered because we assumed that PCV-7 was injected at the same office visit with other vaccines. Because vaccination safety data indicate that no local infusion-related reaction or side-effect was severe enough to require significant medical attention or treatment,\textsuperscript{48} these costs were not included in the model.

Medical Costs for Pneumococcal-Associated Diseases. Direct medical costs for individual pneumococcal diseases and clinical sequelae, such as hearing loss and disability, were derived from the 2006 NHI Yearbook.\textsuperscript{37} Average annual costs per patient were calculated as total NHI costs, excluding payments made by patients, divided by the total number of patients. Direct medical costs included medical resources, such as prescribed medications, medical procedures, and diagnostic tests, used by patients diagnosed and treated for pneumococcal diseases in inpatient, ambulatory, or emergency room settings. The costs for cochlear implants and tympanostomy tube insertions were based on the NHI Reimbursement Price List\textsuperscript{53} and multiplied by a defined weighted price factor of 1.25 because these procedures are typically administered in the hospital. We assumed that the cost for neurological disability in survivors of meningitis was similar to that of paralysis. The costs of disability and severe hearing loss from meningitis and cochlear implants and tympanostomy tube insertions were added to average annual disease cost.

Nonmedical Costs Including Transportation and Work Loss. Transportation costs for a medical institution visit were based on 2005 Korean National Health and Nutrition Examination Survey (NHANES III) data.\textsuperscript{54} The one-way costs for transportation for an outpatient and a hospitalized patient were reported to be KW8,891 and KW11,019, respectively. Time lost at work by the parent of a child with pneumococcal disease was valued using the human capital method. The average gross hourly wage for Korean women laborers aged 30-39 years (assumed to be the age group with children younger than 5 years of age) was reported to be KW8,946 per hour based on national data provided by the Korea National Statistical Office.\textsuperscript{20} We assumed 4 hours of work loss for an outpatient visit and 8 hours of work loss for an inpatient admission. The rates of hospitalization, frequency of outpatient visits, and length of stay for hospitalized patients were based on the NHI Yearbook.\textsuperscript{37} Transportation and time costs related to physician visits for vaccine administration were not included because we assumed that this vaccine was administered concurrently with other vaccines in the same visit.

**Analyses**

Pneumococcal disease cases and deaths for vaccination and no-vaccination strategies were compared to determine cases of pneumococcal disease and deaths prevented over a 5-year period from vaccination. The incremental cost and benefits of a direct vaccine-induced protection effect compared with no vaccination were calculated by adding costs and benefits for each of the 2 strategies. Incremental cost-effectiveness ratios (ICERs), expressed as cost per death averted and cost per LYD, were calculated for vaccination versus no vaccination. Differences in overall cost and outcomes between the vaccination and no vaccination scenarios, respectively, were calculated for the denominator and numerator of the ICER. A 5\% discount rate was applied to cost and benefits in the cost-effectiveness analyses.

**Sensitivity Analyses.** We evaluated how the model's results changed when key assumptions were varied over plausible ranges using univariate and probabilistic sensitivity analysis primarily around the cost per discounted death estimates. We performed sensitivity analyses for the following parameters: pneumococcal disease incidence rates, disease-associated medical costs, discount rate, and vaccine price per dose. The ranges of variables used in sensitivity analyses for the annual incidence of meningitis and bacteremia were based on the 95\% confidence intervals reported in published sources. A plus/minus (\pm) 25\% range around the base-case value was applied for all other variables considered in the sensitivity analyses. We varied vaccine costs from KW10,000 up to KW70,000 (the base-case price) per dose. Additionally, a break-even cost, defined as the per dose vaccine price that results in a total cost of vaccination equivalent to the total resulting discounted cost savings for avoided pneumococcal disease, was calculated.

A probabilistic sensitivity analysis was performed using a 10,000-replication Monte Carlo simulation. We assumed that (a) incidence rates of pneumococcal diseases, such as bacteremia, meningitis, pneumonia, and otitis media, had beta-distributions; and (b) medical costs for bacteremia, meningitis, pneumonia, and otitis media and clinical sequelae, such as hearing loss and disability, had gamma-distributions,\textsuperscript{57} with standard errors that were the same as the mean values derived from the NHI Yearbook. We calculated 95\% confidence intervals (CI) for ICERs using the percentile method. Cost-effectiveness acceptability curves were calculated to identify the probability of vaccination.
Economic Evaluation of Childhood 7-Valent Pneumococcal Conjugate Vaccination in Korea

### TABLE 3 Estimated Pneumococcal Disease Outcomes and Costs in a Cohort of Korean Infants During the First 5 Years of Life with No Vaccination and Vaccination, and ICER in a Base-Case Analysis

<table>
<thead>
<tr>
<th>Pneumococcal Disease Outcomes and Costs</th>
<th>No Vaccination (NV)</th>
<th>Vaccination (V)</th>
<th>Difference (NV-V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases(a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal meningitis</td>
<td>890</td>
<td>299</td>
<td>-591</td>
</tr>
<tr>
<td>Pneumococcal bacteremia</td>
<td>2,076</td>
<td>697</td>
<td>-1,379</td>
</tr>
<tr>
<td>Pneumococcal pneumonia</td>
<td>72,238</td>
<td>28,289</td>
<td>-43,950</td>
</tr>
<tr>
<td>Pneumococcal otitis media</td>
<td>137,558</td>
<td>86,749</td>
<td>-50,808</td>
</tr>
<tr>
<td>Subtotal</td>
<td>212,762</td>
<td>116,034</td>
<td>-96,728</td>
</tr>
<tr>
<td>Disability from pneumococcal meningitis</td>
<td>28</td>
<td>9</td>
<td>-19</td>
</tr>
<tr>
<td>Hearing loss from pneumococcal meningitis</td>
<td>16</td>
<td>5</td>
<td>-11</td>
</tr>
<tr>
<td>Cochlear implant from pneumococcal meningitis</td>
<td>3</td>
<td>1</td>
<td>-2</td>
</tr>
<tr>
<td>Typanostomy from pneumococcal otitis media</td>
<td>8,116</td>
<td>5,118</td>
<td>-2,998</td>
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<tr>
<td>Death from pneumococcal meningitis</td>
<td>41</td>
<td>14</td>
<td>-27</td>
</tr>
<tr>
<td>Death from pneumococcal bacteremia</td>
<td>89</td>
<td>30</td>
<td>-59</td>
</tr>
<tr>
<td>Death from pneumococcal pneumonia</td>
<td>217</td>
<td>85</td>
<td>-132</td>
</tr>
<tr>
<td>Subtotal</td>
<td>347</td>
<td>129</td>
<td>-218</td>
</tr>
<tr>
<td>Discounted total life years in birth cohort</td>
<td>2,044,180</td>
<td>2,044,378</td>
<td>199(b)</td>
</tr>
<tr>
<td>Costs (KW million)(a)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vaccine cost</td>
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<tr>
<td>Medical cost</td>
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<td>-13,372</td>
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<tr>
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<td>69,134</td>
<td>38,473</td>
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<tr>
<td>Subtotal</td>
<td>95,484</td>
<td>177,875</td>
<td>82,391</td>
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<tr>
<td>Discounted total net cost</td>
<td>86,823</td>
<td>173,207</td>
<td>86,384</td>
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<td>Base-case analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(at a vaccine price KW70,000 per dose)</td>
<td>ICER (KW million per LYG)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-dose schedule</td>
<td>435 per death averted; 150.2 per LYG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-dose schedule</td>
<td>301 per death averted; 103.9 per LYG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(a\)Vaccination scenario figures represent a 4-dose schedule.
\(b\)Life years gained with vaccination.

ICER = incremental cost-effectiveness ratio, KW = Korean won; LYG = life years gained.

being cost-effective at various levels of willingness to pay (WTP) for an additional discounted death averted.

### Results

#### Base Case Analysis

The health outcomes and costs for the no-vaccination and universal vaccination strategies are presented in Table 3. Over a 5-year time horizon, the estimated numbers of cases of pneumococcal disease attributed to sp in the 2006 birth cohort were 212,762 in the no-vaccination strategy and 116,034 under a universal 4-dose vaccination program. Permanent disability from meningitis was estimated to occur in 28 children without vaccination and 9 children with vaccination. Without vaccination, hearing loss from meningitis was estimated to occur in 16 children without vaccination and 5 children with vaccination. With vaccination, hearing loss and cochlear implant cases would be reduced to 5 and 1, respectively. Typanostomy was estimated to be performed in 8,116 children without vaccination and 5,118 with vaccination. The estimated numbers of deaths due to sp-related meningitis, bacteremia, and pneumonia were 347 in the no-vaccination strategy and 129 in a universal vaccination program. Thus, a 4-dose PCV7 immunization program could prevent 96,728 cases of pneumococcal diseases (591 meningitis, 1,379 bacteremia, 43,950 pneumonia, and 50,808 otitis media) and 218 deaths, resulting in 575 discounted LYGs for the first 5 years from birth.

The medical and nonmedical cost burden of sp pneumococcal disease in an unvaccinated birth cohort aged 5 years or younger was KW95,484 million. An estimated total of KW44,033 million in medical (KW13,372) and nonmedical (KW30,661) cost reductions would occur because of the 4-dose vaccine program. The 3-dose vaccine regimen would be expected to provide 95% of the health and economic benefit of the 4-dose regimen based on our assumption of vaccine efficacy. The costs of acquiring vaccine for the 451,514 infants in the 2006 birth cohort were estimated to be KW126,424 million for the 4-dose regimen and KW94,818 million for the 3-dose regimen. The undiscounted incremental program costs were estimated to be KW82,391 million (discounted KW86,385 million) for the 4-dose regimen and KW52,986 million (discounted KW56,781 million) for the 3-dose regimen. For the 4-dose schedule, the cost per discounted death averted was KW435.2 million ($334,787), and per discounted LYG was KW150.2 million ($115,549). For the 3-dose schedule, the cost per discounted death averted was KW301 million ($231,538) and per discounted LYG was KW103.9 million ($79,995).
Sensitivity Analyses

Results of the univariate sensitivity analyses are shown in Figure 2. The ICER was decreased by reducing the vaccine cost and increasing disease incidence rates in the sensitivity analyses. The annual incidence of pneumonia appeared to be the disease parameter to which the ICERs were most sensitive. As expected, the ICERs were more favorable when the cost of vaccine was lower. At vaccine prices of KW30,000 and KW20,000 per dose, the corresponding ICERs per discounted death averted were KW71 million and KW20 million, respectively. The break-even costs at which the acquisition cost of vaccine equals the discounted cost offsets from vaccine were KW22,100 and KW28,100 for the 4- and 3-dose schedules, respectively (Figure 3). In probabilistic sensitivity analyses, mean ICERs were KW495 million (95% CI = 392-550) and KW324 million (95% CI = 222-373) in the 4- and 3-dose scenarios, respectively (data not shown).

The acceptability curves for a universal vaccination program at various vaccine price cut-offs and dosing schedules are shown in Figure 4. With a 4-dose schedule and 50% probability of vaccination being cost-effective, values for WTP for an additional LYG were KW18 million, KW116 million, and KW310 million at vaccine prices per dose of KW20,000, KW30,000, and KW50,000, respectively. As expected, the probabilities of vaccination being cost-effective in the 3-dose schedule were higher than in the 4-dose schedule at the same WTP.

Discussion

Although decisions about universal introduction of a vaccine to a national child immunization program are strongly influenced by the vaccine’s acquisition price, an overall evaluation of both the costs and benefits of a program is necessary for an informed decision. In this study, a decision analytic model estimated that a universal PCV-7 program would significantly reduce pneumococcal disease incidence and mortality for 5 years after birth. The study also demonstrated the potential to offset some medical and nonmedical costs with vaccination. Study results may be helpful for decision makers to determine whether or not to introduce PCV-7 to the universal vaccination program in Korea. As the KCDC continues to evaluate immunization programs, a cost-effectiveness study of PCV-7 may provide a useful framework for assessing the health and economic impact in Korea.

Decision analytic models similar to that reported in the present study were used in economic evaluations for PCV-7 in the United States,19 Australia,22 Finland,23 and the Netherlands,58 and for the Haemophilus influenzae type B (Hib) vaccine in Korea.59 This type of model can be used to compare the cost-effectiveness of a vaccination with no vaccination option as newer vaccines are introduced.

The economic benefits of PCV-7 vaccination have been evaluated in a number of countries. The results have been used to inform vaccine policy change decisions, sometimes to include PCV-7 in the country’s national immunization program. These studies are diverse in their assumptions about vaccine efficacy, incidence rates, and reported results. In a 2000 study of the projected cost savings associated with PCV-7 in the United States, it was estimated that vaccination of infants would result in net savings for society and health care payers if the vaccine cost per dose was less than $46 and $18 respectively.59 In a 2004 cost-effectiveness study conducted in England and Wales, the universal vaccination program was not expected to be cost-effective from
the National Health Service perspective at the current price of the vaccine (assumed 30 pounds (£) per dose, 3-dose program); however, researchers estimated that a 50% reduction in vaccine cost would bring the cost per quality-adjusted life year (QALY) gained to within normal acceptable ranges. In a 2003 Canadian study, it was estimated that the societal benefit-to-cost ratio would be 0.57 at the vaccine price of $58 per dose, and vaccination would result in net savings for society if the vaccine price was less than $30 per dose. In the Netherlands, it was reported that the baseline cost-effectiveness ratio of a PCV-7 vaccination program at a vaccine price of 40 euros (€) per dose would be relatively unfavorable when compared with other interventions that have been implemented in the country. However, after adjustment for the incidence rates of meningitis and bacteremia and inclusion of the herd protection effect (i.e., reduction in the disease incidence rate from reduced transmission of pneumococci after infant vaccination to nonvaccinated individuals), the ICER was reduced by one-fourth. In these studies, vaccine purchasing cost was found to be the most important variable that affects the decision whether to include PCV-7 in the national immunization program in individual countries. Several factors other than those assessed in the present study have the potential to affect the cost-effectiveness of a vaccination program. A review of recently published economic evaluation studies for PCV-7 programs conducted during 2002-2006 showed that cost-effectiveness of PCV-7 vaccination programs would be viewed as attractive in developed countries if the net long-term impact remains beneficial, determined by a mixture of effects related to herd immunity, serotype replacement (i.e., change in serotype distribution occurring after infant vaccination), and antibiotic resistance. Cost-effectiveness of PCV-7 vaccination would also be enhanced if a 3-dose schedule confers near-equivalent protection to a 4-dose schedule. The cost-effectiveness of PCV-7 has recently been updated to include the indirect effects of herd immunity on incidence of invasive pneumococcal disease, pneumonia requiring hospitalization, and otitis media after 7 years of use in the United States. The ICER dropped from US$201,000 per life year saved to US$10,400 per life year saved after accounting for herd immunity. In summary, the benefits of vaccine programs are difficult to evaluate precisely because of uncertainties about the current pneumococcal disease burden, period of vaccine efficacy, and the long-term effect of vaccines on pneumococcal disease epidemiology. Some assumptions of our model should be verified using clinical data in the future to reduce uncertainties. PCV-7 vaccination may have other benefits, such as reducing...
antibiotic-resistant sp organisms. Korea is an area with serious antibiotic resistance problems. There is some evidence to suggest that sp isolates resistant to antibiotics were reduced by PCV-7 vaccination. As antibacterial resistance is a risk factor for sp causative infections, reduction of antibiotic-resistant pathogens could have additional positive effects not measured in the current analysis. On the other hand, PCV-7 has preventive effects for only about 90 sp specific serotypes, but these can be replaced by other serotypes not included in a vaccine after introduction of vaccination. Invasive pneumococcal diseases caused by serotypes other than those found in PCV-7 were found to be increased during the vaccine period (2002-2006) compared with the pre-vaccine period (1997-2001) in Spain. Serotype replacement has emerged as a limitation of PCV-7 but is still controversial. Furthermore, if serotype replacement caused a reduction in the carriage of vaccine serotypes, herd immunity would be of less interest. Also, there are some variations in common pneumococcal serotypes in different parts of the world and in transmission of the pathogen in different socio-cultural circumstances. These variations mean that overall and long-term effectiveness of widespread use of PCV-7 is difficult to predict at the population level. In addition, as there were no data in Korea to estimate the potential effects of herd immunity and a lack of reliable information on the changes of vaccine efficacy from decreased antibacterial resistance, we analyzed only direct vaccine effectiveness for the first 5 years in a birth cohort without modeling the possibility of serotype replacement or herd immunity.

The main health outcomes measured in this analysis were deaths averted and LYG on the basis of reduced mortality. We did not capture quality of life (QOL) gains attributable to the reduced short- and long-term morbidity associated with pneumococcal disease because we had no available QOL data in Korean children for the individual health states considered in this model. It is not possible to quantify the impact of this omission on the resulting ICERs and their apparent attractiveness. In a study by Butler et al. (2004), the ICER for PCV-7 was AUS$230,130 per LYG, while the cost per disability-adjusted life year (DALY) averted was AUS$121,100. In a study by Hubben et al. (2007), the ICER for
PCV-7 was €15,600 per LYG and €14,000 per QALY gained. In both cases the ICER was more attractive when a QOL adjustment was made to the health outcome in the ratio.

An economic evaluation of a Hib vaccination program by Shin et al. (2008) conducted in Korea can be used as a reference to compare with the present study’s results. Shin et al. found that the benefit-cost ratio for Hib vaccination was 0.77 at the assumed vaccination cost of KW26,000, but the ratio would be increased to 1.0 if the vaccination cost was less than KW20,000, one-half the current price of KW40,000 per dose of vaccine. Shin et al. suggested that the low economic benefit was attributable to the low incidence rate of Hib infection and the high price of the Hib vaccine.

Our study results show that a nationwide PCV-7 vaccination program would produce a net savings if the vaccine prices per dose were no more than KW22,100 (US$17) for a 4-dose or 28,100 (US$22) for a 3-dose regimen, suggesting that similar price levels for both Hib and PCV-7 are appropriate for integration into a universal immunization program. The public health rationale should be clearly based on clinical outcomes, benefits, and costs. A decision about PCV-7 introduction into immunization programs would depend on vaccine price as a major determinant of cost-effectiveness.

**Limitations**

First, we used a simplified decision analytic model to avoid too many assumptions. For the disease sequelae, some events may occur in combination, or more rare events may occur that were not captured in the model.

Second, vaccine efficacy was followed for only 5 years after birth even though the duration of efficacy may be longer. Longer follow-up would produce much better clinical outcomes and cost savings because input cost would not increase while outcomes, including reduced productivity loss and disease incidence for the extended period, would be counted. This limitation might make the results of our analysis conservative. Also, only confirmed cases proven from culture were assumed in this study, potentially resulting in underestimation of actual pneumococcal disease incidence.

Third, there are uncertainties and potential biases in the disease incidence rates and vaccine efficacy rates used in this model. In some instances, we used data from other countries because Korean epidemiology data were not available. We estimated otitis media incidence on a per patient basis from NHI data rather than a per episode basis, resulting in an underestimation of disease burden and efficacy. The study by Lee et al. (2006) that was used to estimate disease-related morbidities and mortalities was a 10-year retrospective study conducted in university hospitals. This setting is highly selective, and high-risk patients are usually referred to teaching hospitals, many of which are in a localized geographic area. In spite of these shortcomings, our use of Korea-specific data for most key parameters provided a reasonably accurate assessment of invasive pneumococcal diseases in Korean children. For vaccine efficacy, data from other countries were used when Korean data were not available. However, we adjusted assumptions about PCV-7 vaccine efficacy to reflect the distribution of serotypes most prevalent in Korea.

Fourth, because assumptions about pneumococcal disease-related direct medical costs were derived from NHI data, they did not include costs paid by patients, resulting in an underestimation of the cost of disease. The break-even costs for vaccine would have been higher if patient out-of-pocket expenditures were included in the cost offsets of a vaccination program. In order to better understand the impact that these uncertainties may have on outcomes, sensitivity analyses were performed for varied ranges of pneumococcal disease incidence rates and cost of disease. The ICERs were most sensitive to the incidence of pneumonia and the cost of vaccine.

Finally, we did not consider some factors that affect vaccine efficacy and the magnitude of its benefits on a population basis. These include the indirect effect or herd immunity protection inferred on unvaccinated individuals of all ages, the potential to reduce antibiotic resistance due to decreased use of antibiotics, and replacement of PCV-7 serotypes with nonvaccine serotypes. No reliable Korean data were available on these factors. PCV-7 has been reported to have the potential to reduce nasopharyngeal colonization and transmission of vaccine-type pneumococcal pathogens from vaccinated children to the unvaccinated population. This herd immunity effect could also have an impact on the cost-effectiveness of the PCV-7 strategies. There is some evidence that pneumococcal disease incidence is lower in both children and adults since universal PCV-7 vaccination was introduced in children.

**Conclusion**

In this analysis, we predicted that universal PCV-7 vaccination of infants in Korea can significantly reduce the economic burden, morbidity, and mortality of pneumococcal disease by preventing pneumococcal infections. However, the cost-effectiveness of either a 4- or 3-dose vaccination strategy based on deaths averted or LYGs appears to be unattractive at current vaccine prices. The literature suggests that factors not considered in this analysis have the potential to make the public health impact and cost-effectiveness of universal PCV-7 vaccination in Korea more favorable. The impact of herd immunity, improved quality of life among nonfatal pneumococcal disease patients, reduced antibiotic resistance, longer than assumed duration of efficacy, and potential confounding of the true incidence rate because of empiric antibiotic therapy could improve the ICERs and net costs. Future research is needed to improve knowledge about these parameters in Korea and better inform future cost-effectiveness modeling.
Economic Evaluation of Childhood 7-Valent Pneumococcal Conjugate Vaccination in Korea

Authors

HYUN SOON SOHN, PhD, is Lecturer, College of Pharmacy, Sookmyung Women’s University, Seoul, South Korea. EUNJIN JANG, PhD, is Principal Researcher, Outcomes Research Team, National Evidence-Based Healthcare Collaborating Agency, Seoul, South Korea. DONG-CHURL SUH, MBA, PhD, is Professor, and JIN-WON Kwon, PhD, is Research Fellow, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey.

AUTHOR CORRESPONDENCE: Dong-Churl Suh, MBA, PhD, Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 160 Frelinghuysen Rd., Piscataway, NJ 08854-8020. Tel: 732.445.5215, Ext. 402; Fax: 732.445.2533; Email: dsuh@rci.rutgers.edu.

DISCLOSURES

This research was performed in a university setting without external funding. Study concept and design were contributed primarily by Sohn and Kwon with the assistance of Suh. Data collection was performed primarily by Sohn with the assistance of Kwon. Data interpretation and writing of the manuscript were performed primarily by Sohn and Jang. Sohn and Suh made most of the manuscript revisions.

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ABSTRACT

BACKGROUND: Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infection (LRTI) in infants and young children, accounting for approximately 75,000-125,000 hospitalizations per year. It is estimated that in 2000, RSV infection accounted for 1.7 million office visits, 402,000 emergency room visits, and 236,000 hospital outpatient visits per year for children younger than 5 years of age. Palivizumab, a humanized monoclonal antibody directed against RSV, is the only immunoprophylaxis therapy approved by the FDA for prevention of serious lower respiratory tract disease caused by RSV in infants (up to 2 years of age) who meet 1 or more of the following criteria for high risk: (a) gestational age up to 35 weeks; (b) diagnosis of chronic lung disease (CLD, formerly bronchopulmonary dysplasia [BPD]); or (c) diagnosis of cyanotic or complex congenital heart disease. The RSV season typically occurs between November and March but may vary by region. During the period of our review, depending on local duration of the RSV season, infants usually required 5 monthly (every 28-30 days) intramuscular injections of palivizumab. Infants born in the middle of the season received their palivizumab doses from the time of birth to the end of the season and, therefore, may have required less than 5 doses. It is unclear if compliance with monthly doses is a problem and whether noncompliance increases the risk of RSV hospitalizations in routine clinical practice.

OBJECTIVES: To (a) identify and describe compliance rates and the factors that influence parental compliance with immunoprophylaxis regimens, (b) review intervention programs and describe those that have been associated with increased compliance, and (c) summarize the association of compliance with RSV hospitalization rates.

METHODS: An electronic literature search was conducted using journal databases, including Ovid, Current Contents, Embase, Medline In-Process & Other Non-Indexed Citations; Ovid Medline, PubMed, and Web of Science; and an abstract database, Medical Intelligence Solution, for citations through April 2008. Specific search terms used were palivizumab with patient compliance, patient adherence, or patient persistence.

RESULTS: Twenty-five articles and abstracts met the inclusion criteria. Available studies were mostly retrospective or observational prospective. Compliance, defined in various ways across the studies, varied between 25% and 100%, and 12 studies identified some of the factors related to noncompliance. Compliance generally was lower among Medicaid patients, African American patients, and other minorities. Ten studies (3 manuscripts and 7 abstracts) investigated the association of administration of prophylaxis through monthly home visits by a health professional with parental compliance with therapy. Most of the home-based programs were associated with higher compliance rates compared with clinic or office programs. Rates as high as 94% and 64% were achieved when Medicaid infants and infants of minority descent, respectively, received their doses through a home health program. When these infants received their doses at a clinic or office, depending on the definition of compliance, rates were 61%-100% for Medicaid infants and 44% for infants of minority descent. Reminder telephone calls to parents or caregivers, comprehensive multidisciplinary programs that included extensive counseling of parents, calendars with sticker reminders, and education in the language native to parents also were associated with increased compliance, although statistical significance was reported in only 1 study. Several studies recommended educating parents on the benefits of RSV prophylaxis, alleviating transportation and language difficulties, recognizing cultural differences and biases, and clarifying misperception of RSV illness severity. Home health programs had lower rates of RSV hospitalizations than office-based programs in 3 analyses conducted in 2 studies. In 4 other abstracts, the rates of RSV hospitalization for home health programs and office-based administration did not significantly differ. In a large, 4-season, prospective outcome study, compliant infants had lower RSV hospitalization rates than those who were not compliant under one definition of compliance (doses within 35-day intervals). RSV hospitalization rates were not significantly different using another definition of compliance (receipt of anticipated doses, expected vs. observed rates). In a large survey of 10,390 infants identified from pharmacy dispensing records, RSV hospitalization rates were 1.4% in the compliant group versus 3.1% in the noncompliant group (OR = 2.2, 95% CI = 1.4-3.5, P < 0.001). Adjustment for confounding was not reported in these studies.

CONCLUSION: Medicaid and minority infants were less likely to receive scheduled palivizumab doses. Home-based programs for the administration of palivizumab have been investigated more than other interventions and are associated with improved compliance compared with office-based administration. Compliance with dosing, in general, was associated with lower RSV hospitalization rates. However, these strategies should be further investigated using well-designed studies.

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What is already known about this subject

- Respiratory syncytial virus (RSV) is a leading cause of hospitalization among infants and young children accounting for approximately 75,000-125,000 hospitalizations per year. In 2000 in the United States, RSV infection accounted for an estimated 1.7 million office visits, 402,000 emergency room visits, and 236,000 hospital outpatient visits for children younger than 5 years. Although the mortality rate in patients with RSV LRTI hospitalization is less than 1% overall, children with heart and lung disease have significantly higher mortality rates (3.4% and 3.5%, respectively).
- Palivizumab, approved by the FDA in 1998, remains the only therapy for prevention of severe RSV disease in high-risk infants.

Note: This article is the subject of an editorial that appears on pages 59-66 of this issue.
Respiratory syncytial virus (RSV) infection is a leading cause of lower respiratory tract infection (LRTI) in infants and young children. RSV-related illnesses account for approximately 75,000-125,000 hospitalizations per year. Furthermore, RSV was associated with a mortality rate of 5.3 per 100,000 person-years for infants younger than 1 year of age due to respiratory and circulatory causes from the 1990-1991 through 1998-1999 annual respiratory illness seasons (July through June). Although the mortality rate in patients hospitalized with RSV LRTIs is less than 1% overall, children with heart and lung disease have significantly higher mortality rates (3.4% and 3.5%, respectively). A study by Paramore et al. (2004) estimated that in 2000, RSV infection accounted for 1.7 million office visits, 402,000 emergency room visits, and 236,000 hospital outpatient visits per year for children younger than 5 years of age in the United States.

The economic costs of RSV LRTIs are high. Premature infants (up to 35 weeks gestational age), including those with chronic lung disease (CLD, formerly bronchopulmonary dysplasia [BPD]), infants with cyanotic or complex congenital heart disease, and those with severe neurologic or airway problems, are particularly vulnerable to developing severe LRTIs, requiring frequent hospitalizations. In Horn and Smout’s study of 304 infants hospitalized for bronchiolitis or RSV pneumonia at 9 children’s hospitals from 1995-1996, rates of intensive care unit (ICU) admission were 31.3% overall, as high as 48.4% in infants born at 33-35 weeks gestational age (n = 31), and 39.3% in those born at up to 32 weeks gestational age (n = 28). Intubation was required in 16.4% overall, 38.7% of those born at 33-35 weeks gestational age, and 21.4% of those born at up to 32 weeks gestational age. In the subgroup born at up to 35 weeks gestational age, mean ICU length of stay was 5.8-7.7 days, and mean hospital stay was 6.8-8.4 days.

Estimates of the cost of RSV-related hospitalization vary. Using data from a large managed care organization, Joffe et al. (1999) calculated the mean cost of a hospitalization for RSV as $8,502 in 1995 dollars, but Robbins et al. (1998) calculated a higher “plausible estimate” of $15,000-$25,000 per RSV hospital admission. A more recent poster abstract report estimated the mean cost of RSV hospitalization, in 2007 dollars, to be $9,014 in full-term infants (n=1,983), $13,876 in infants born at less than 33 weeks gestational age (n=46), and $18,403 in infants born at 33-36 weeks gestational age (n=149). In addition, although a significant association has been shown between RSV infection in childhood and long-term development of subsequent asthma and recurrent wheezing, a systematic review of the literature suggested that further studies are needed to confirm this association.

No completely effective treatment for RSV LRTIs exists, and attempts at developing a vaccine have proven unsuccessful thus far. Palivizumab (Synagis; MedImmune, Gaithersburg, MD), a humanized monoclonal antibody directed against the F protein of RSV, is the only immunoprophylaxis therapy available that is approved by the U.S. Food and Drug Administration (FDA) for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease. During the time of our review, palivizumab dosing usually consisted of 5 monthly (28-30 days) intramuscular injections of 15 milligrams per kilogram (mg per kg) administered during the RSV season, which typically occurs between November and March, but may vary by region. Because infants born during the RSV season receive their palivizumab doses from the time of birth, infants included in the studies covered by this review may have required less than 5 doses.

What is already known about this subject (continued)

- Two randomized controlled trials (RCTs) have investigated the efficacy of palivizumab in reducing RSV-associated hospitalizations. During the 1996-1997 RSV season, for children with either prematurity up to 35 weeks gestation or bronchopulmonary dysplasia/chronic lung disease (BPD/CLD), palivizumab compared with placebo reduced RSV-associated hospitalizations for both those without BPD/CLD (78% reduction: 8.1% vs. 1.8%, P<0.001) and those with BPD/CLD (39% reduction: 12.8% vs. 7.9%, P=0.038). In the second RCT, RSV-associated hospitalizations were reduced by 45% for palivizumab versus placebo (9.7% vs. 5.3%, P=0.003) for children aged 24 months or younger with hemodynamically significant congenital heart disease in 4 RSV seasons from 1998-1999 through 2001-2002.
- Palivizumab has a mean half-life of approximately 20 days and is dosed in monthly (28-30 days) intramuscular injections of 15 milligrams per kilogram during the RSV season.

What this review adds

- Rates of compliance with RSV prophylaxis range from 25% to 100% and are more variable than those observed in clinical trials (92% and 93%).
- Compliance rates tend to be lower in infants enrolled in Medicaid and in minority groups, ranging between 44% and 100% using office- or clinic-based administration. Home health programs have been associated with better compliance rates, ranging from 64% to 94%, in these groups.
- Other factors that negatively affect compliance include limited access to care, parental perception of limited benefits with prophylaxis, transportation problems, and language difficulties. Interventions aimed at eliminating these barriers should be investigated further using well-designed studies.
- Home-based programs for the administration of palivizumab have been investigated more than other interventions and are associated with improved compliance compared with office-based administration. Compliance with dosing, in general, was associated with lower RSV hospitalization rates. However, these strategies should be further investigated using well-designed studies.
The efficacy of palivizumab in reducing the incidence of lower respiratory tract disease is well established. In clinical studies, palivizumab has been shown to reduce the overall incidence of RSV-associated hospitalizations in high-risk pre-term infants and those with CLD and congenital heart disease (CHD) compared with placebo.\textsuperscript{10,21,22} In the pivotal licensure study, significant reductions in RSV-associated hospitalizations were observed in premature children up to 35 weeks gestation in comparison with placebo, both among those without BPD/CLD (78% reduction: 8.1% vs. 1.8%, \textit{P}<0.001) and those with BPD/CLD (39% reduction: 12.8% vs. 7.9%, \textit{P}=0.038), with an overall reduction of 55% (10.6% vs. 4.8%, \textit{P}<0.001).\textsuperscript{11} The most common adverse events, occurring at least 1% more frequently in palivizumab-treated versus control patients, were upper respiratory infection, otitis media, fever, and rhinitis.\textsuperscript{10,21} In comparison with placebo, palivizumab reduced RSV-associated hospitalizations by 45% (9.7% vs. 5.3%, \textit{P}=0.003) in infants and young children with hemodynamically significant CHD.\textsuperscript{22}

The Palivizumab Outcomes Registry was a prospective observational registry designed to collect data on the demographics, clinical characteristics, and outcomes of infants who received palivizumab for prophylaxis of RSV in the United States from 2000 to 2004.\textsuperscript{23} Data collected in this registry and in several other observational post-marketing studies provided further evidence regarding the effectiveness of palivizumab in preventing serious RSV disease leading to hospitalization.\textsuperscript{24,25} Rates of RSV hospitalization were as low as 0.7% among prophylaxed infants during the most recent RSV season (2003-2004) in the Palivizumab Outcomes Registry.\textsuperscript{23}

Because of this evidence supporting the benefits of palivizumab immunoprophylaxis, 2006 recommendations by the American Academy of Pediatrics (AAP) guidelines (Red Book) for the use of palivizumab were as follows: (a) palivizumab prophylaxis should be considered for infants and children younger than 24 months of age with CLD of prematurity who required medical therapy for CLD (supplemental oxygen, bronchodilator, or diuretic or corticosteroid therapy) within 6 months before the start of the RSV season; (b) infants born at 32 weeks of gestation or earlier may benefit from RSV prophylaxis, even if they do not have CLD; (c) children who are 24 months of age or younger with hemodynamically significant cyanotic and acyanotic CHD will benefit from palivizumab prophylaxis, with the greatest likelihood of benefit in those who are receiving medication to control congestive heart failure or have either moderate to severe pulmonary hypertension or cyanotic heart disease; and (d) most experts recommend that among infants born at 32-35 weeks gestation, prophylaxis should be reserved for those at greatest risk of severe infection (i.e., 2 or more risk factors, such as child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease) and who are younger than 6 months of age at the start of the RSV season (Appendix).\textsuperscript{13} During the period of this review, the 1998, 2003, and 2006 recommendations were applicable.\textsuperscript{13,30,31} New AAP recommendations for immunoprophylaxis with palivizumab were published in September 2009.\textsuperscript{32}

A study of North Carolina Medicaid enrollees during the 2002-2003 RSV season estimated a mean per patient seasonal cost for a group of infants immunoprophylaxed with palivizumab to be $5,117, including the costs of the drug and of treatment for RSV.\textsuperscript{33} Given the high costs of palivizumab, compliance could be an important issue to payers. Frequently, managed care organizations spend significant time and effort to prior authorize requests for palivizumab to ensure that high-risk infants receive prophylaxis.\textsuperscript{34} Once prior authorization is obtained, compliance with the prescribed regimen is needed to maintain protection throughout the season. Thus, noncompliance diminishes the value of the expense already incurred for previously administered palivizumab doses and could result in hospitalization and higher costs.

Because palivizumab has a mean half-life of approximately 20 days, monthly injections are recommended during the RSV season.\textsuperscript{19} Palivizumab serum concentrations of at least 40 micrograms per milliliter (ug per mL) have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold.\textsuperscript{19} Monthly intramuscular doses of 15 mg per kg in pediatric patients younger than 24 months of age achieved mean (SD) 30-day trough serum drug concentrations of 37 (21) ug per mL after the first injection, 57 (41) ug per mL after the second injection, 68 (51) ug per mL after the third injection, and 72 (50) ug per mL after the fourth injection.\textsuperscript{19}

Understanding the characteristics of the noncompliant infant, the consequences of noncompliance, and interventions that potentially increase compliance should be useful to managed care decision makers. This literature review (a) identifies and describes compliance rates and the factors that influence parental compliance with palivizumab immunoprophylaxis regimen; (b) reviews intervention programs and describes those that have been associated with increasing compliance; and (c) summarizes the impact of compliance with the recommended regimen of palivizumab immunoprophylaxis on RSV hospitalization rates.

**Methods**

An electronic literature search was conducted using journal databases, including Ovid (BIOSIS, 1993-April 2008), Current Contents (1997-April 2008), Embase (1980-April 2008), Medline In-Process & Other Non-Indexed Citations; Ovid Medline (1950-April 2008), PubMed (1950-April 2008), Web of Science (1986-April 2008); and an abstract database, Medical Intelligence Solution (1998-April 2008). The search of abstract and journal databases combined the term palivizumab (or its synonyms) with the terms patient compliance to therapy, patient adherence to therapy, or patient persistence with therapy. For Ovid and Web of Science, the term patient cooperation was also used to make the search more comprehensive. The following inclusion criteria were
A Systematic Review of Compliance with Palivizumab Administration for RSV Immunoprophylaxis

FIGURE 1  Flowchart for Study Selection

<table>
<thead>
<tr>
<th>Journal Database</th>
<th>Abstract Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Contents (1997-April 2008)</td>
<td></td>
</tr>
<tr>
<td>Embase (1980-April 2008)</td>
<td></td>
</tr>
<tr>
<td>Medline (1950-April 2008)</td>
<td></td>
</tr>
<tr>
<td>PubMed (1950-April 2008)</td>
<td></td>
</tr>
<tr>
<td>Web of Science (1986-April 2008)</td>
<td></td>
</tr>
</tbody>
</table>

Applied to the search: focus on palivizumab use and compliance with therapy, articles uploaded until April 2008, and articles written in English. Exclusion criteria were as follows: abstracts/articles not related to palivizumab (e.g., respiratory syncytial virus immune globulin intravenous [RespiGam]), those focusing on provider compliance with guidelines or other topics, those not reporting compliance rates, and those reporting use of palivizumab primarily in populations not currently indicated for prophylaxis.

A total of 116 articles and abstracts were reviewed for topic significance (Figure 1). Initially, 67 articles and abstracts met the inclusion criteria. In the second review cycle, duplicate articles and abstracts and multiple reports of the same data were excluded; for these studies, the most recent report with the most comprehensive data was used. Of 34 articles and abstracts that met the inclusion criteria in the second review cycle, 9 were rejected because their focus was on provider compliance with guidelines or on off-label use or because they did not provide information relevant to the scope of this review (remaining articles, n = 25). All authors performed screening in each review cycle independently and met to discuss and reach final agreement on included and excluded abstracts and articles.

Data from different studies selected were summarized into the following categories to help understand the literature available: (a) characteristics of compliant versus noncompliant infants (12 studies); (b) home-based versus office or clinic care (10 studies); (c) programs to improve compliance (6 studies); and (d) impact of compliance on RSV hospitalizations (2 studies). Some studies provided information that fit more than 1 category.

Results

A total of 25 articles and abstracts were identified as relevant to compliance with palivizumab.23,35-58 Of these, 8 involved retrospective review of data,35-42 11 were prospective,23,43-52 4 involved surveys,53-56 and 2 involved a review of data retrospectively combined with a follow-up call/interview.57,58 A total of 8 studies were peer-reviewed articles,23,39-43,47,49,52,53,56 1 was a letter to the editor,23 and the remaining 16 were meeting abstracts,35-38,40,41,44,46,49-51,54,55,57,58

Compliance was defined in various ways across studies. In 11 studies,37,40,42,43,47,49,52-55 infants who received all recommended palivizumab doses were considered compliant. In 1
study, compliance was defined as receipt of at least 80% of recommended doses. In 5 studies, the definition of compliance was based on appropriate intervals (21-35 days) between doses, whereas 6 studies defined compliance as receipt of all palivizumab doses and/or as receipt of doses at appropriate intervals. In studies that used number of doses to define compliance, the actual number of injections given at the appropriate time was compared with the projected number of injections an infant should receive. Infants and young children who did not receive the projected number of doses were considered noncompliant. Some abstracts did not adequately describe their definition of compliance, presumably due to space restriction. Nevertheless, the information contained in these abstracts regarding compliance rates before and after specific interventions is included in this review. Overall compliance rates varied from as low as 25% to as high as 100%. The compliance rates of patients in clinical studies involved in palivizumab licensure were 92% and 93%. Thus, compliance in routine practice was more variable.

**Characteristics of Compliant and Noncompliant Infants**

Twelve studies explored factors positively and negatively associated with compliance to immunoprophylaxis with palivizumab. A program in which telephone interviews were conducted using a quantitative questionnaire revealed that compliance was significantly higher in nonsmoking families (79.8% vs. 47.4%, P = 0.003, odds ratio [OR] = 4.38, 95% confidence interval [CI] = 1.59-12.20) and in families that did not have an infant with previous RSV infection (75.7% vs. 33.3%, P = 0.022, OR = 6.25, 95% CI = 1.08-35.71). A retrospective review of records (n = 650) from a variety of prophylaxis administration sites reported noncompliance rates of 70% for physician offices, 26% for day health centers, 12% for pulmonologists' offices, 11% for outpatient clinics, and 9% for at-home administration of palivizumab by a visiting nurse. The authors concluded that compliance with an RSV prophylaxis program was greater in a more specialized setting.

Medicaid enrollment was associated with noncompliance with the recommended regimen. A large number of infants in the Palivizumab Outcomes Registry (47% of 19,474) were enrolled in Medicaid. When risk factors and compliance with therapy were compared in infants enrolled in Medicaid with other insurance coverage, a higher proportion of infants enrolled in Medicaid were found to be noncompliant (22% vs. 15%, P < 0.001) when the number of doses received was compared with the number of doses anticipated, irrespective of duration between doses. When the definition of noncompliance accounted for between-dose duration exceeding 35 days, the rates of noncompliance for Medicaid and other coverage, respectively, were 37% versus 24% (P < 0.001). Langkamp et al. (2001; 2002) also reported lower compliance in a subgroup of Medicaid patients compared with patients in the sample overall evaluated over 2 RSV seasons (1999-2000: overall compliance 78% vs. Medicaid subgroup 68%; 2000-2001: overall compliance 79% vs. Medicaid subgroup 68%). However, the authors reported neither the subgroup sizes nor the statistical significance of these differences.

In a study reported by Romero et al. (2004), among infants of minority descent (African American, Hispanic, Asian, Pacific Islander, Native American or other/mixed ethnicity) who constituted 45.5% (n = 2,862 of 6,291) of the Palivizumab Outcomes Registry cases observed during the 2002-2003 RSV season, 45% received their doses on average every 30 days compared with 62% of Caucasian infants (P < 0.001). During the 2002-2003 season, only 52% of the 994 African American infants enrolled in the Registry, the majority (74%) of whom were covered by Medicaid, received all palivizumab doses within an average of 30 days, according to Geflandt et al. (2004).

Parental perception of the benefits of immunoprophylaxis is an important consideration when designing interventional programs to enhance compliance. Langkamp and Hlavin (2001) reported the results of a survey mailed to 385 families (211 completed questionnaires) of high-risk infants (i.e., infants who had been discharged from a neonatal ICU or who had CLD not associated with prematurity) who were eligible to receive prophylaxis in 1998-1999. The strongest predictor of compliance was the parents' perception that palivizumab would protect their infant from RSV. A total of 78% of infants received all of their doses; 67% of parents in the compliant group answered that they believed palivizumab would protect their infant “a great deal” against RSV, compared with 48% of parents in the noncompliant group (P = 0.04). Langkamp et al. (2001; 2002) reported that parental perception continued to have an influence on compliance rates over the next 2 seasons of 1999-2000 and 2000-2001. Parents who thought that palivizumab would protect their child against RSV infection “some” or “a lot” (believers) were more likely to be compliant than those who thought it would protect “not at all” or “a little” (skeptics)—88% compliance among believers versus 53% among skeptics (P < 0.001) in 2000-2001 and 85% compliance among believers versus 18% among skeptics (P < 0.001) in 1999-2000.

Lack of transportation was also a barrier to compliance. In the 1998-1999 season, 85% of parents in the compliant group versus only 65% in the noncompliant group reported that they had no difficulty with transportation (P = 0.004). In addition, parents of Medicaid children who were worried about their infant being infected with RSV were more likely to be compliant than less worried parents (OR = 6.62, 95% CI = 1.22-35.97, P = 0.03). Langkamp and Hlavin concluded that parental education emphasizing the benefits of palivizumab immunoprophylaxis may influence compliance and that advice from primary care providers, such as the 2-page letter provided to parents in the Langkamp and Hlavin study, may play an important role in improving compliance.

Results of some studies carried out outside the United States may be applicable to some U.S. populations. In a multicenter,
prospective study involving 118 Italian pediatric centers in which 4,859 children were recruited, Macagno (2005) showed that compliance with palivizumab prophylaxis was low in children starting the program in October and November but increased over the course of the season. This finding suggests that Italians perceived the risk of RSV infection mainly during the peak of the outbreak. The number of expected doses in this study was 8,328, and the actual doses administered were 4,881, which can be estimated as an overall compliance rate of 58.6%. A similar prospective surveillance study repeated the following year revealed that compliance with immunoprophylaxis was relatively stable for a limited period of the RSV season, between December and March, with a decrease after February. Compliance progressively decreased from the first to the last dose. The overall compliance rate for this study was reported to be 66.1%. Language barriers also may influence compliance. Pignotti et al. (2006) conducted a survey among the parents of 216 infants receiving RSV prophylaxis. Over a 4-year period involving 4 cohorts of high-risk infants, the overall compliance rate with all doses was 87%, and the strongest factor affecting poor compliance was being foreign-born or a non-native speaker (P < 0.01). A palivizumab outpatient prophylaxis program was carried out in a tertiary level neonatal intensive care unit in Italy. Retrospective analysis of medical records and recorded demographic data for 156 high-risk infants, of whom 16 were foreign-born, revealed that the compliance rate with all doses during 3 respiratory seasons was 86% overall, compared with 56% among foreign parents. The strongest predictor for poor compliance was being foreign-born and speaking a non-native language (P < 0.001). Although these studies reported data collected outside the United States, the findings may be applicable to U.S. patients of minority origin.

Overall, barriers that influence or predict noncompliance with the recommended regimen of RSV prophylaxis were found to be parental smoking, Medicaid enrollment, lower parental expectations for the benefits of RSV prophylaxis, lack of transportation, and language difficulties.

Home-Based Versus Office/Clinic Care
Ten studies have assessed the impact of an at-home intervention program on compliance and outcomes from documented RSV disease. Three of these, only 1 of which assessed a large patient sample, were presented as full manuscripts and as meeting abstracts (Table 1). Home interventions consist of monthly visits by a professional from a home health care agency for administration of palivizumab at the patient’s home. However, an exact description of the program was not always provided. These studies were performed using retrospective medical record review. Exceptions were the Palivizumab Outcomes Registry analyses and the study by Golombek et al. (2004), which used prospective observational designs. All of the studies compared home health patients with clinic/office patients in the same RSV season except Hand et al. (2008), who used a pre-intervention versus post-intervention comparison. Sample size, when reported, varied from 41 to 17,641 in groups being compared. Two studies did not report the sample size for the home or the clinic/office group and compared 3 groups: outpatient clinic, home, and primary care physician office. Therefore, P values reported correspond to a 3-group comparison. Also, 1 study had a sample size of less than 50 per group. Nine of the 10 studies were single-center studies that followed infants from a particular local hospital, the geographic location of which was mentioned only in 2 reports (Newark, Delaware, and Bronx, New York). One study involved 256 pediatric sites located throughout the United States (41 states and the District of Columbia). All 10 studies reported data on primarily high-risk infants with Medicaid patients in 4 of them. Data from the Palivizumab Outcomes Registry were reported for all patients available at follow-up and for the Medicaid subgroup. One study reported data on minority infants, and 1 reported data on urban inner-city infants. Definitions of compliance were based on total number of doses, doses given on schedule, or doses within 35 days of previous dose. Compliance rates at clinic or office sites ranged from 36% to 100%, as compared with home health rates, which ranged from 64% to 96.9%. For Medicaid patients, the compliance rates for clinic or office ranged from 53% to 100%, whereas home health compliance rates ranged from 75% to 94%. In one study, minority patients had a compliance rate of 44% at the clinic/office setting and 64% at the home setting (P < 0.001). In another study, the rates for urban inner-city patients were 83.3% for clinic/office setting and 96.2% for home setting (P = 0.012, calculated using a Fisher’s exact test). Most comparisons found significantly better compliance rates with home health programs as compared with clinic/office programs except the 2001 Langkamp study in which 1 of the clinic groups had higher compliance than the home health group.

When the association between RSV hospitalization and administration site was investigated, patients who received all doses of palivizumab at home had lower RSV hospitalization rates than did clinic/office patients in the Palivizumab Outcomes Registry study (overall: 0.4% vs. 1.2%, P = 0.014; Medicaid: 0.6% vs. 1.6%, P = 0.02) and a lower mean number of all-cause hospitalizations per patient during the RSV season in a 2008 study by Hand et al. (0.35 vs. 1.01, P = 0.001). However, in 4 studies, the differences in RSV hospitalization rates for clinic/office and home health care were not significant. Note that 1 study did not specify whether the hospitalization rate reported during the RSV season was attributable to documented RSV hospitalizations. These studies did not report any multivariate analyses to control for potential confounders. Although the data from these studies suggest better compliance in home-based programs, well-designed studies would help further establish this relationship.
## TABLE 1
Compliance with Recommended Regimen of RSV Prophylaxis and Hospitalization Rates—At-Home Versus Clinic or Office Administration of Palivizumab

<table>
<thead>
<tr>
<th>Source Design</th>
<th>Definition of Compliance</th>
<th>Population</th>
<th>Clinic or Office Program</th>
<th>Home Health Program</th>
<th>Compliance Rate</th>
<th>RSV Hospitalization Rate</th>
<th>Compliance Rate</th>
<th>RSV Hospitalization Rate</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peer-reviewed studies (n = 3)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frogel et al., 2008</td>
<td>Observational prospective over 4 RSV seasons (registry)</td>
<td>All anticipated doses or more</td>
<td>Primarily high-risk infants</td>
<td>17,641</td>
<td>81</td>
<td>1.2 (overall)</td>
<td>1,226</td>
<td>88</td>
<td>0.4 (overall)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All doses within 35 days</td>
<td>Primarily high-risk infants</td>
<td>17,641</td>
<td>69</td>
<td></td>
<td>1,226</td>
<td>76</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All anticipated doses or more</td>
<td>Primarily high-risk Medicaid infants</td>
<td>8,070</td>
<td>76</td>
<td>1.6 (overall)</td>
<td>885</td>
<td>90</td>
<td>0.6 (overall)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All doses within 35 days</td>
<td>Primarily high-risk Medicaid infants</td>
<td>8,070</td>
<td>61</td>
<td></td>
<td>885</td>
<td>75</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paul et al., 2002</td>
<td>Retrospective</td>
<td>All scheduled doses administered</td>
<td>Discharged from special care nursery, met AAP criteria</td>
<td>41</td>
<td>36</td>
<td>Not reported</td>
<td>32</td>
<td>67</td>
<td>Not reported</td>
<td>0.02</td>
</tr>
<tr>
<td>Hand et al., 2008</td>
<td>Retrospective</td>
<td>Projected doses within 35 days</td>
<td>Medicaid, neonatal clinic patients, met AAP criteria</td>
<td>109</td>
<td>61.6</td>
<td>1.01</td>
<td>127</td>
<td>81.8</td>
<td>0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Poster abstracts (n = 7)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chua et al., 2008</td>
<td>Retrospective</td>
<td>Doses on schedule</td>
<td>Discharged from NICU, met AAP criteria</td>
<td>1,041</td>
<td>69</td>
<td>0.29</td>
<td>1,549</td>
<td>82</td>
<td>0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chua et al., 2007</td>
<td>Retrospective</td>
<td>Monthly doses during RSV season</td>
<td>Discharged from NICU, met AAP criteria</td>
<td>676</td>
<td>91</td>
<td>0.74</td>
<td>618</td>
<td>95</td>
<td>0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Golombek et al., 2004</td>
<td>Prospective</td>
<td>Doses given on schedule</td>
<td>Met AAP criteria</td>
<td>1,487</td>
<td>89.2</td>
<td>2.01</td>
<td>4,881</td>
<td>96.9</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Langkamp and Hlavin, 2002</td>
<td>Retrospective</td>
<td>All doses</td>
<td>High-risk Medicaid infants</td>
<td>Not reported</td>
<td>53 CCH/79 PMD</td>
<td>Not reported</td>
<td>Not reported</td>
<td>94</td>
<td>Not reported</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Langkamp et al., 2001</td>
<td>Retrospective</td>
<td>All doses</td>
<td>High-risk Medicaid infants</td>
<td>Not reported</td>
<td>62 CCH/100 PMD</td>
<td>Not reported</td>
<td>Not reported</td>
<td>80</td>
<td>Not reported</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Romero et al., 2004</td>
<td>Observational prospective (registry)</td>
<td>Doses every 30 days</td>
<td>Primarily high-risk minority infants</td>
<td>2,561</td>
<td>44</td>
<td>Not reported</td>
<td>164</td>
<td>64</td>
<td>Not reported</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Srinivasan and Srinivasan, 2007</td>
<td>Retrospective</td>
<td>80% of doses administered</td>
<td>High-risk urban inner-city infants</td>
<td>72</td>
<td>83.3</td>
<td>2.8</td>
<td>80</td>
<td>96.2</td>
<td>1.3</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*Refers to the AAP criteria for the administration of palivizumab that were in effect at the time that the present study was conducted.

*Patients in this study were from 2 different birth cohorts in 2 different RSV seasons. Hospitalization results represent mean number of all-cause hospitalizations per patient during the RSV season.

*P values were not presented in the original paper but were calculated by the authors of the present study based on a 2-sided Fisher’s exact test.

*Because these studies compared 3 groups instead of 2, this P value corresponds to a 3-group comparison.

*The study report indicates that for privately insured patients in the study sample, site of administration was not significantly associated with compliance; however, no numeric details were reported for this comparison.

AAP = American Academy of Pediatrics; CCH = outpatient clinic at children’s hospital; NICU = neonatal intensive care unit; NS = not statistically significant; PMD = primary care physician’s office; RSV = respiratory syncytial virus.
TABLE 2 Results of Interventions

<table>
<thead>
<tr>
<th>Source</th>
<th>Programs</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pignotti et al., 2004-2005</td>
<td>Letter to non-native parents and their physicians explaining risks of RSV infection and benefits of prophylaxis</td>
<td>Not reported</td>
<td>80</td>
</tr>
<tr>
<td>Awaida et al., 2005</td>
<td>Reminder telephone calls to parents or caregivers</td>
<td>89</td>
<td>64</td>
</tr>
<tr>
<td>Roberts et al., 2006-2007</td>
<td>Comprehensive multidisciplinary RSV prophylaxis program</td>
<td>24</td>
<td>25.0</td>
</tr>
<tr>
<td>Singleton et al., 2006</td>
<td>Training of community health aides for at-home administration of RSV prophylaxis in a remote region of Alaska</td>
<td>111</td>
<td>74.0</td>
</tr>
<tr>
<td>Biais et al., 2004</td>
<td>Staff outreach program</td>
<td>900</td>
<td>99.5</td>
</tr>
</tbody>
</table>

Study measuring compliance defined as mean number of doses received

<table>
<thead>
<tr>
<th>Source</th>
<th>Programs</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frogel and Nerwen, 2005</td>
<td>Coordinated neonatal/general pediatric practice program</td>
<td>61</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*aAuthors reported a total n of 16 families over 3 RSV seasons.

bP = 0.005.

RSV = respiratory syncytial virus.

Programs to Improve Compliance

Six studies reported impact of an intervention program on compliance (Table 2).40-42,49,50,52 Five of these used pre-intervention versus post-intervention comparisons,40-42,49,50,52 whereas 1 reported only post-intervention data.41 One study analyzed the association of pharmacy intervention with compliance.50 Sample sizes, when provided, ranged from 24 to 900. Studies were mostly observational with retrospective assessment of data via records or survey. None used a randomized design or contemporaneous comparison group. Interventions included simple telephone reminders to parents or caregivers,50 multidisciplinary programs involving counseling, reminder telephone calls on the day prior to the appointment, and nurses tracking charts.40 Complete definitions of interventions and compliance were not always present. All studies reported increased compliance rates but only Roberts et al. (2006) reported statistical testing.50 When a comprehensive multidisciplinary program that included counseling, tracking charts, and reminder telephone calls was implemented, the contribution of each individual approach to the overall improvement in compliance rate was not analyzed.40

Interventions to address language and socioeconomic levels were associated with improvements in compliance. When Pignotti et al. used language translators, together with a letter explaining to non-native parents and their physicians the risks of RSV infection and the benefits of prophylaxis, compliance rates increased from 80% to 88% over 2 RSV seasons.42 Pignotti et al. reported in a letter to the editor that use of nonmedical language translators in the absence of the letter was unhelpful in promoting compliance.42 In a study by Awaida et al. (2005) in a pharmacy department setting, reminder telephone calls to parents were associated with an increase in compliance from 64% to 92%.50

Another intervention was the development of a coordinated neonatal/general pediatric RSV bronchiolitis/pneumonia prevention program. A total of 493 high-risk infants were enrolled over 6 RSV seasons.49 In the first season (Fall 1998-Spring 1999), patients averaged 3.6 doses, whereas in the sixth season (Fall 2003-Spring 2004), patients averaged 5.6 doses. The percentage of patients receiving some or all doses at home increased from 5% to 58% over this time. Biais et al. (2004) reported that a unique home care-based model that included monthly skilled pediatric nurse visits, monthly assessments, and RSV prevention education resulted in a RSV hospitalization rate of 1.42%, with a compliance rate of 99.5%; however, only post-intervention results were reported.41

A new procedure involving extensive counseling of parents, reminder telephone calls, calendars with reminder stickers, and tracking charts in the nursing medication rooms was used to improve compliance in a hospital-based clinic.50 Results showed that an increased percentage of infants (71%) received the appropriate number of injections after implementation of the new interventions compared with 25% before the new interventions (P = 0.005).40

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RSV hospitalization rates among high-risk premature infants decreased after palivizumab introduction in the Yukon Kuskokwim Delta region of Alaska. However, compliance with monthly injections remained low because prophylaxis was administered at the Delta regional hospital that was not easily accessible to or from the village by patients’ families or a visiting nurse. During the 2003-2004 RSV season, a pilot project was conducted to train certified community health aides to administer palivizumab. Compliance was measured by comparing the actual number of injections administered with the projected numbers, based on mode of administration. Following implementation of the pilot project, 90.4% of projected doses were administered, compared with 74% in previous years.

Impact of Compliance on RSV Hospitalizations

In a study by Berger et al. (2003), palivizumab use was assessed in 10,390 infants based on dispensing records for a pharmacy benefits management company that provided follow-up telephone contact to ensure the prescribed dose was administered. A total of 9,675 (93.1%) of 10,390 infants were found to be compliant, defined as having no more than 35 days between shipment of doses. RSV hospitalization rates were 1.4% in the compliant group versus 3.1% in the noncompliant group (OR=2.2, 95% CI=1.4-3.5, P<0.001).

The Palivizumab Outcomes Registry provided an opportunity to characterize the patterns and scope of palivizumab administration in a cross section of infants in the United States and to correlate compliance with scheduled injections with RSV hospitalization outcomes. Over a 4-year study period, compliance as defined by number of expected doses was not significantly associated with RSV hospitalization in the registry. However, using a different definition of compliance—receipt of all doses within 35 days of the previous dose—odds of RSV hospitalization were significantly lower for those who were compliant (OR=0.70, 95% CI=0.54-0.91; RSV hospitalization rates in compliant vs. noncompliant infants were 1.16% vs. 1.65%, respectively, P=0.007).

This study also reported a significant association between RSV hospitalization and number of injections in compliant patients (i.e., those who received all doses within 35 days of the previous dose) with a greater number of hospitalizations observed among infants with a lower number of injections (P<0.001). In another analysis of this study, Medicaid patients had higher noncompliance rates defined as receipt of all anticipated doses (22% Medicaid vs. 15% non-Medicaid) and doses within 35 days (37% Medicaid vs. 24% non-Medicaid; both comparisons P<0.001) compared with non-Medicaid patients. Medicaid patients had higher RSV hospitalization rates compared with non-Medicaid patients (1.6% vs. 0.9%, P<0.001).

Discussion

Our review indicated that compliance with immunoprophylaxis is variable and is suboptimal in certain patient subgroups, such as infants with Medicaid coverage, African Americans, and other minority populations. Several factors were associated with noncompliance, including Medicaid enrollment and minority race, lower parental expectations about the benefits of RSV prophylaxis, lack of transportation, language difficulties, and socioeconomic level. Despite the progress that has been made in reducing hospitalization rates, infants whose parents are noncompliant with palivizumab continue to have hospitalization rates that are unacceptably high. A comparative analysis of the financial implications of such programs should reveal the most cost-effective and realistic program. Some of the characteristics...
of the noncompliant infant identified in the reviewed studies should be used to develop intervention strategies for each particular group of patients to promote optimal compliance. These interventions could include patient reminder telephone calls, multilingual call centers, or focused patient education efforts that target those demonstrating such a need.

Much of the literature examined in this review reported that a home care strategy for administration of palivizumab, by offering consistent delivery of medication and ongoing parent/caregiver education, was associated with better compliance with therapy. The support services provided by specialty pharmacies are now widely used to streamline the drug distribution, delivery, and management process in ways that engage patients in their care.59 Our search did not reveal any study that assessed the effect of timely delivery by specialty pharmacies on compliance. However, it is possible that some of the studies did use specialty pharmacies for drug delivery but did not report it. This should be an interesting and important avenue to explore.

Many programs described in this review involved multiple interventions, and most studies did not measure the impact of individual interventions. Therefore, individual strategies to improve compliance with therapy require further study using adequate sample sizes and research designs, predefined outcomes, and standardized definitions and methods for evaluating outcomes. In the interim, interventions such as home-based health care could be helpful to high-risk patients and especially certain subgroups with suboptimal compliance, such as Medicaid recipients. The financial implications of home-based health care represent an interesting avenue to explore but are not within the scope of this review.

Limitations

First, this review identified several important limitations in the available research literature. Different studies varied slightly in their definitions of compliance, making it difficult to compare outcomes across studies. Much of the data originated from meeting abstracts that provided limited information about each study, including details about interventions and methods. Other shortcomings in the literature include deficient study designs, non-standardized outcomes, inadequate sample sizes, and absence of statistical testing, making it difficult to draw definitive conclusions. These limitations may affect the degree to which findings are applicable in clinical situations; however, the studies described here provided information that could potentially be considered in decision making.

Second, our search was based on the keyword palivizumab together with the terms compliance, adherence, or persistence. This search may have missed some articles whose primary focus was not compliance or palivizumab; it may have also missed articles that did not use these exact terms as keywords but reported results relevant to this study. Future studies should attempt to correct these limitations.

Conclusion

This systematic literature review emphasizes that compliance with immunoprophylaxis to prevent RSV LRTI can be variable and is suboptimal in certain subgroups. A number of strategies to improve compliance have been tried. The most investigated strategy was an at-home program of palivizumab administration. By eliminating most barriers to compliance, this strategy offered consistent delivery of palivizumab and ongoing parent/caregiver education. Furthermore, it was associated with a significant decrease in hospitalization rates in 2 of 6 studies. Compliance in general is associated with decreased hospitalization rates. Early identification of infants at risk for poor compliance could help in tailoring intervention programs specifically aimed at improving compliance and ultimately patients’ outcomes.

Authors

MICHAEL P. FROGEL, MD, is Associate Professor of Pediatrics, Albert Einstein College of Medicine, and Chief of General Pediatrics, Schneider Children’s Hospital, New Hyde Park, New York. DAN L. STEWART, MD, is Professor of Pediatrics, Kosair Children’s Hospital, Louisville, Kentucky. MICHAEL HOOPES, PharmD, is Director, Medical Information; ANCILLA W. FERNANDES, PhD, is Associate Director, Health Outcomes and Pharmacoeconomics; and PARTHIV J. MAHADEVIA, MD, MPH, is Senior Director, Health Outcomes and Pharmacoeconomics, MedImmune, LLC, Gaithersburg, Maryland.

AUTHOR CORRESPONDENCE: Michael P. Frogel, MD, Schneider Children’s Hospital, Division of General Pediatrics, 410 Lakeville Rd., Ste. 108, New Hyde Park, NY 11042. Tel.: 516.465.4377; E-mail: frogel@lij.edu.

DISCLOSURES

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Summary of the 2006 AAP Guidelines for RSV Prophylaxis

| Premature, no CLD, no CHD | ≤28 weeks GA: Consider palivizumab if ≤ 12 months of ageb |
|  | 29–32 weeks GA: Consider palivizumab if ≤ 6 months of ageb |
|  | 32–35 weeks GA: Consider palivizumab if younger than 6 months of ageb with at least 2 risk factorsc |
| Hemodynamically significant CHDd | Consider palivizumab if younger than 24 months of ageb |
| CLD and receiving medical therapy within 6 months of RSV season |  |

aAAP, 2006.13 New guidelines were promulgated in September 2009.12
bAge at start of RSV season.
cRisk factors: child care attendance, school-age siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease.
dThose most likely to benefit include infants receiving medication to control congestive heart failure, with moderate to severe pulmonary hypertension, or with cyanotic heart disease.
eMedical therapy for CLD—supplemental oxygen, bronchodilator, or diuretic or corticosteroid therapy.
AAP = American Academy of Pediatrics; CHD = congenital heart disease; CLD = chronic lung disease; GA = gestational age; RSV = respiratory syncytial virus.
Utilization Management Opportunities for Palivizumab for Prophylaxis of Respiratory Syncytial Virus Complications in Infants

Frederic R. Curtiss, PhD, RPh, CEBS, and Kathleen A. Fairman, MA

A survey conducted in December 2008 of 69 health plans representing over 83 million commercial, Medicare, and managed Medicaid members found that 81% of the health plans required prior authorization (PA) for coverage of palivizumab (Synagis). Palivizumab is commonly covered under the medical benefit (73%) rather than the pharmacy benefit, and is ranked among the therapeutic areas with the highest priority for utilization management (UM). Health plans cite as the primary motivation for targeting palivizumab for UM intervention “to prevent inappropriate use,” the same motivation attributed to UM interventions for growth hormones, blood cell stimulants, and omalizumab for asthma.

Despite the importance of UM interventions and the prevalence of PA programs for the use of palivizumab in prophylaxis of respiratory syncytial virus (RSV), to date there have been no peer-reviewed analyses of the clinical, service, or cost outcomes of PA interventions for this high-cost injectable. In this issue of JMCP, Buckley et al. provide the first information in the medical literature regarding the outcomes of a PA intervention to determine coverage for palivizumab. Based on American Academy of Pediatrics (AAP) guidelines, this PA intervention was associated with similar or better clinical outcomes while saving about $2.4 million in palivizumab drug cost over 3 RSV seasons from 2005 through 2008 in a health plan of about 500,000 members. Also in this issue of JMCP, Diehl et al. report the results of an exploratory study of the association between compliance with palivizumab and respiratory-related medical utilization in a small sample of children aged 0 to 24 months who met similar AAP-based PA criteria and were immunoprophylaxed during the 2006-2007 RSV season, finding no significant relationships between palivizumab compliance and RSV-related utilization.

Indications and Recommendations for Appropriate Use of Palivizumab

Palivizumab was approved by the U.S. Food and Drug Administration (FDA) in June 1998 for “prophylaxis of serious lower respiratory tract disease, caused by respiratory syncytial virus, in pediatric patients at high risk of RSV disease.” The initial product label included the indication “for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD) and infants with a history of prematurity (=35 weeks gestational age).”

AAP guidelines initially (1998) recommended that the appropriate use of palivizumab should be based on the age of the infant at the start of the RSV season: (a) children less than 2 years old with chronic lung disease (CLD) who required medical therapy within the 6 months prior to the RSV season, (b) infants less than 1 year old born up to 28 weeks gestation, and (c) infants less than 6 months old born between 29 and 32 weeks gestation. For infants with a gestational age of 32 to 35 weeks, the AAP guidelines suggested that palivizumab “should be reserved for those infants with additional risk factors” that “predispose to respiratory complications,” including neurologic disease, young siblings, child care attendance, “exposure to tobacco smoke in the home, anticipated cardiac surgery, and distance to and availability of hospital care for severe respiratory illness.” The initial AAP guidelines in 1998 further suggested that many infants should not receive palivizumab despite “qualifying for the approved indications” because the “risk of rehospitalization for serious respiratory illness will be low, and the cost and logistical difficulties associated with prophylaxis may outweigh the potential benefits.”

The efficacy of palivizumab in prophylaxis of RSV-related hospitalization has been studied in 2 randomized controlled trials (RCTs). Palivizumab was initially approved by the FDA based on the IMpact-RSV trial (1998), which was conducted during a single RSV season (1996-1997) and randomized 1,502 children who at the start of the RSV season were either (a) aged 24 months or younger with bronchopulmonary dysplasia (BPD, now known as CLD) or (b) aged 6 months or younger with a history of premature birth (defined as 35 weeks gestation or less) to placebo or 5 monthly intramuscular (IM) injections of palivizumab 15 milligrams (mg) per kilogram (kg) administered over 150 days. In the IMpact-RSV trial, the incidence of RSV-related hospitalization was 10.6% (n=53) among 500 patients in the placebo group compared with 4.8% (n=48) among 1,002 patients in the palivizumab group (P<0.001). The numbers needed to treat (NNT) in IMpact-RSV were 17.2 for the sample overall, 20.4 for children with BPD (12.8% placebo vs. 7.9% palivizumab, P=0.038), and 15.9 for premature infants without BPD (8.1% placebo vs. 1.8% palivizumab, P<0.001).

Patients with uncorrected congenital heart disease (CHD) were excluded from the IMpact-RSV trial. There was no mention of CHD in the initial palivizumab product label, and the AAP recommendations in 1998 indicated that palivizumab was “not recommended for children with cyanotic congenital
heart disease. The palivizumab product label was revised in July 2004 to include the additional indication for “children with hemodynamically significant CHD,” based on the results of 1 clinical trial conducted over 4 consecutive RSV seasons among infants aged 2 years old or younger with hemodynamically significant CHD. This second RCT of palivizumab, conducted by Feltes et al. (2003), found a RSV-related hospitalization rate of 9.7% in the placebo group (63 of 648 patients) compared with 5.3% (34 of 639 patients) in the palivizumab group (IM 15 mg per kg) followed for 150 days after randomization. The NNT for the Feltes et al. study was 22.7. RSV-related hospitalization is the primary endpoint in clinical analysis of the effectiveness of palivizumab, because there is no evidence that palivizumab affects mortality associated with RSV infection.

Notably, both clinical trials cited on the palivizumab product label involved dosing and regimen completion rates that are implausible in the real world. Almost all patients in both RCTs completed the studies, and 92%-93% completed all 5 injections, exactly 30 days apart.

What is the True Incidence of RSV-Related Hospitalizations and ER Visits?

In an analysis of the U.S. National Hospital Discharge Survey (NHDS) data for the 17-year period from 1980 to 1996, Shay et al. found an estimated 1.65 million hospitalizations for bronchiolitis among children younger than 5 years and estimated that there were 51,240 to 81,985 annual bronchiolitis hospitalizations related to RSV infection among children younger than 1 year of age. Shay et al. noted that prior to their research only the Institute of Medicine (IOM, 1985) had estimated a national rate of RSV-related hospitalizations, about 55,000 per year for infants younger than 1 year and about 36,500 for children aged 1 to 4 years. However, the IOM estimates were based on assumptions that 0.5% of children younger than 5 years who were infected with RSV would require hospitalization, and that infants younger than 1 year would account for 60% of the RSV-related hospitalizations.

While this analysis by Shay et al. is widely referenced in the research literature as a benchmark for the incidence of RSV-related hospitalizations, these researchers reached their estimate of RSV-related hospitalizations by assuming, based on previously published viral epidemiology studies, that RSV was the etiologic agent in 50% to 80% of November through April hospitalizations for bronchiolitis in the NHDS database for 1994 to 1996. This estimation method was necessary because there were no specific International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for RSV-related disease, other than RSV pneumonia (ICD-9-CM 480.1), until October 1996. Using the NHDS database for the 2-year period from January 2000 through December 2001 to identify hospital stays with the specific ICD-9-CM codes for RSV (466.11 for RSV bronchiolitis, 480.1 for RSV pneumonia, and 079.6 for RSV infection), Holman et al. found 221,450 RSV hospitalizations for infants younger than 1 year of age, of which 196,009 (88.5%) were specific to RSV bronchiolitis. Annualized, the resulting count of approximately 111,000 RSV hospitalizations in U.S. infants in 2000-2001 suggests that Shay et al.’s figures may have been underestimates.

During the 17-year period from 1980 to 1996 studied by Shay et al., 57% of the estimated 1.65 million hospitalizations for bronchiolitis were accounted for by children younger than 6 months and 81% by children younger than 1 year. Among children younger than 1 year, annual bronchiolitis hospitalization rates increased more than 2-fold, from 1.29% in 1980 to 3.12% in 1996. If the portion of bronchiolitis hospitalizations attributed to RSV was 50% to 80% in 1996, 1.56% to 2.50% of children younger than 1 year were hospitalized with RSV-related disease in 1996. Probably representing the combined effects of change in coding methodology and a continued pattern of increasing RSV hospitalization rates, Holman et al. found in 2000-2001 that the rates of RSV hospitalizations per 1,000 live births were approximately 30.3 (3.0%) for males and 24.4 (2.4%) for females, or 27.4 (2.7%) overall (Table 1).

Hall et al. found in population-based surveillance in 3 U.S. counties (Nashville, Rochester and Cincinnati) absolute rates of RSV-related hospitalizations of 1.7% for infants 0-5 months of age, 0.5% for infants 6-11 months of age, 0.3% for children 12 to 23 months of age, 0.04% for children 24 to 59 months of age, and 0.3% overall for children 0 to 59 months of age, over 4 RSV seasons (2000-2004). RSV is the apparent cause of 1 every 334 hospitalizations and 1 of every 38 ER visits in children younger than 60 months of age.

In this issue of JMCP, Buckley et al. found RSV-related hospitalization rates of 6.4% (40 of 629) in infants who were approved by the PA process to receive palivizumab, compared with 4.0% (14 of 348) for infants who were denied PA requests for coverage of palivizumab (P=0.035), for a combined rate of 5.5% (54 infants with hospitalizations divided by 977 infants). This rate is considerably higher than the hospitalization rates for bronchiolitis estimated by Shay et al. for infants younger than 1 year of age for 1980 (1.3%) and 1996 (3.1%). The discrepancy is probably partly attributable to both the upward trend in RSV-related hospitalization suggested by the analyses of NHDS data and to the likely higher risk of the infants in Buckley et al.’s sample, whose physicians requested PA for palivizumab, compared with the U.S. infant population as a whole. There is also considerable variation in rates of RSV-related hospitalization among regions of the country. For infants under 6 months of age, Hall et al. found rates of RSV-related hospitalization of 1.3% in Nashville, 1.4% in Rochester, and 3.4% in Cincinnati. Notably, the American Southwest, where Buckley et al.’s study was conducted, had one of the highest RSV hospitalization rates in the country in 2000-2001; Holman et al. found rates of 4.8% among American Indians in the southwestern United States and 3.7% among all infants in the West.
$9,308 for 73 compliant infants versus $7,647 for 172 noncompliant infants.

In addition to the aforementioned nonsignificant difference in RSV-related inpatient hospitalizations between PA-approved and PA-denied infants, Buckley et al. found a higher rate of RSV-related ER visits in the PA-approved group (n = 14, 2.2%) compared with the PA-denied group (n = 5, 1.4%; P = 0.019), and 6.6% of the infants in the PA-approved group had either a RSV-related hospitalization or RSV-related ER visit compared with 4.3% of the infants in the group denied PA for coverage of palivizumab (P = 0.060).

### How Much Does Palivizumab Reduce the Incidence of RSV-Related Hospitalization and ER Visits?

This is the $64,000 question, or more accurately, the $7,000 per patient per RSV season question. Buckley et al. found that the real-world cost for prophylaxis of RSV in a health plan in 2005-2008 was about $6,950 per infant per season in direct drug costs. Buckley et al. assessed health plan cost plus member cost (i.e., managed care organization [MCO] allowed charge for palivizumab), whereas Diehl et al. found health plan drug cost (after subtraction of member cost share) for palivizumab to average $8,142 per infant in the 2006-2007 RSV season, or a mean of $9,308 for 73 compliant infants versus $7,647 for 172 noncompliant infants.

In addition to the aforementioned nonsignificant difference in RSV-related inpatient hospitalizations between PA-approved and PA-denied infants, Buckley et al. found a higher rate of RSV-related ER visits in the PA-approved group (n = 14, 2.2%) compared with the PA-denied group (n = 5, 1.4%; P = 0.019), and 6.6% of the infants in the PA-approved group had either a RSV-related hospitalization or RSV-related ER visit compared with 4.3% of the infants in the group denied PA for coverage of palivizumab (P = 0.060).

### TABLE 1 Rates of RSV-Related Hospitalization

<table>
<thead>
<tr>
<th>Source—Study Authors and Population</th>
<th>RSV Season</th>
<th>RSV-Related Hospitalization Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMbps-RSV7 children either (a) aged 2 years or younger who required continuing medical therapy for CLD or (b) history of premature birth (&lt;35 weeks gestation) and aged &lt;6 months at start of RSV season</td>
<td>1996-1997</td>
<td>Placebo: 10.6% PA: 8.3% Palivizumab: 7.9%</td>
</tr>
<tr>
<td>Children with CLD</td>
<td></td>
<td></td>
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<tr>
<td>Premature infants without CLD</td>
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<td></td>
</tr>
<tr>
<td>Feltes et al. (2003)10 children aged 2 years or younger with hemodynamically significant CHD</td>
<td>4 seasons: 1998-2002</td>
<td>Placebo: 9.7% PA: 5.3% Palivizumab: 5.3%</td>
</tr>
<tr>
<td>Holman et al.13 U.S. population &lt;1 year of age (NHDS database)</td>
<td>2 seasons: 2000-2001</td>
<td>Male: 3.0% Female: 2.4% Age &lt;6 mos.: 4.2% Age 6-11 mos.: 1.3% Overall: 2.7%</td>
</tr>
<tr>
<td>Holman et al.13 American Indian and Alaska Natives &lt;1 year of age</td>
<td>2 seasons: 2000-2001</td>
<td>Male: 3.7% Female: 3.2% Alaska: 7.1% Southwest: 4.8% Overall: 3.4%</td>
</tr>
<tr>
<td>Hall et al.14 3 U.S. counties (Nashville, Rochester, Cincinnati)</td>
<td>4 seasons: 2000-2004</td>
<td>Age 0-5 mos.: 1.7% Age 6-11 mos.: 0.5% Age 12-23 mos.: 0.3% Age 24-59 mos.: 0.04% Age 0-59 mos.: 0.3%</td>
</tr>
<tr>
<td>Frogel et al.15 Palivizumab Outcomes Registry—U.S. population6</td>
<td>4 seasons: 2000-2004</td>
<td>Male: 1.5% Female: 1.0% Overall: 1.3% GA &lt;32 wks.: 1.8% GA 32-35 wks.: 0.8% GA &gt;35 wks.: 1.1% CLD: 2.4% CHD: 1.9% CAA/SND: 2.1% Medicaid: 1.6% 2000-2001 RSV season: 2.9% 2001-2002 RSV season: 1.5% 2002-2003 RSV season: 1.1% 2003-2004 RSV season: 0.7%</td>
</tr>
<tr>
<td>Buckley et al.2 MCO with PA for palivizumab</td>
<td>3 seasons: 2005-2008</td>
<td>PA approved: 6.4% PA denied: 4.0%</td>
</tr>
<tr>
<td>Diehl et al.3 MCO with PA for palivizumab6</td>
<td>2006-2007</td>
<td>Compliant: 0.0% Noncompliant: 1.2%</td>
</tr>
</tbody>
</table>

*All subjects received at least 1 dose of palivizumab.

CAA/SND = congenital airway abnormality or severe neuromuscular disease; CHD = congenital heart disease; CLD = chronic lung disease; GA = gestational age; MCO = managed care organization; mos = months; NHDS = National Hospital Discharge Survey; PA = prior authorization; RSV = respiratory syncytial virus; wks = weeks.
The rate of RSV-related hospitalization varies greatly among subgroups of infants with certain risk factors. As noted above, the initial product label for palivizumab did not specify CHD as an indication for palivizumab. The label was revised in July 2004 to include the indication for “children with hemodynamically significant CHD,” based on the RCT results reported by Feltes et al. for RSV seasons 1998-2002. In a separate analysis of data from the Palivizumab Outcomes Registry for 19,548 children who received at least 1 dose of palivizumab during 1 or more of 4 RSV seasons (2000-2004), 7.7% (n = 1,500) had a medical history of CHD. Frogel et al. found a 1.2% hospitalization rate for infants without CHD versus a 1.9% hospitalization rate among 1,490 infants with CHD (P = 0.03); within the CHD subgroup, the rate declined sharply from 4.3% in the 2000-2001 season and 2.8% in the 2001-2002 season to 1.4%-1.5% in the 2 consecutive seasons from 2002-2004.

Of the risk factors, the highest rates of RSV-related hospitalization for children in the Palivizumab Outcomes Registry from 2000 to 2004 were found for children with CLD (2.4% of 4,329), versus 2.1% of 1,122 children with congenital airway abnormality or severe neuromuscular disease, 1.8% of 7,786 children with gestational age less than 32 weeks, 1.6% of 9,228 children with Medicaid coverage, 1.6% of 7,260 children born into families with 3 or more children, and 1.5% for 10,481 males. Univariate logistic regression analysis showed that gestational age of 32-35 weeks was not a predictor of RSV-related hospitalization, with an absolute rate of 0.8% compared with 1.1% for gestational age greater than 35 weeks (P = 0.16), but there was a higher rate of RSV-related hospitalization for single births (1.4%) versus multiple births (1.0%, P = 0.03).

In the study by Hall et al. of 5,067 children less than 5 years of age who were either hospitalized from 2000-2004 or seen as outpatients from 2002-2004 for acute respiratory infection in 3 U.S. counties during the RSV season, 18% (n = 919) had RSV infections. The RSV infection rate was 20% in hospital inpatients, 18% in the ER, and 15% in office visits. Palivizumab was found to have been administered to 174 of 1,765 (9.9%) high-risk children (defined as chronic pulmonary, cardiac, kidney or immunodeficiency disease; cancer; or sickle cell anemia); and to 140 of 657 (21.3%) of premature infants (gestational age less than 36 weeks). Particularly important to the subject of the effectiveness of palivizumab in real-world practice, 9.8% (n = 17) of 174 high-risk patients who had received palivizumab and 11.4% (n = 16) of 140 premature births who had received palivizumab were hospitalized with RSV infection.

**Does Compliance with the Monthly Regimen for Palivizumab Matter?**

In this issue of *JMCP*, Diehl et al. found in real-world analysis of palivizumab utilization in an MCO with approximately 400,000 Medicaid and commercially insured members that RSV-related hospitalizations occurred in none of 73 infants determined to be compliant with palivizumab versus 2 of 172 (1.2%) noncompliant infants (P = 1.00). Diehl et al. defined compliance as meeting all 3 of the following criteria: (a) fill date for the first palivizumab pharmacy claim within 37 days of the newborn hospitalization discharge date; (b) fill dates for all subsequent palivizumab pharmacy claims within 37 days of the previous fill date; and (c) up to 6 palivizumab pharmacy claims for babies born prior to the RSV season, or sequential claims from birth through the end of the season for babies born during the season.

Finding comparative data for the results reported by Diehl et al. is not straightforward. When compliance is defined as receipt of all palivizumab doses within a mean of 35 days of the previous dose, Frogel et al. in this issue of *JMCP* cite RSV-related hospitalization rates of 1.4% for children compliant with the palivizumab regimen compared with 3.1% in children determined to be noncompliant (P < 0.001). However, these are unpublished data that were collected via telephone survey and reported only in a poster abstract presented by Berger et al. in 2003, with no control for confounding variables. Using data derived from the Palivizumab Outcomes Registry, Frogel et al. found no association between RSV-related hospitalizations and compliance defined as the number of expected palivizumab injections. However, by the alternate measure of compliance defined as receipt of each dose within 35 days of the previous dose among patients with at least 2 doses, the rate of RSV-related hospitalization was 1.7% for noncompliant children versus 1.2% for compliant children (P = 0.007).

Although this latter definition comes close to that used by Diehl et al., critically important methodological differences make comparing the results of the studies problematic. First, the Palivizumab Outcomes Registry Study measured compliance beginning with the month that the first injection was administered. In contrast, Diehl et al. defined infants whose injections did not begin within 37 days of the initial newborn discharge as noncompliant. Thus, an infant whose physician chose to initiate palivizumab immunoprophylaxis more than 37 days after birth but who maintained regular injections after that point was defined as compliant by the Palivizumab Outcomes Registry Study authors but noncompliant by Diehl et al. Second, RSV hospitalizations were measured using virology testing in the Palivizumab Outcomes Registry Study but using diagnoses recorded in claims data in the Diehl et al. study. Third, as often happens in real-world analyses of MCO outcomes, the Diehl et al. study was underpowered. Diehl et al.’s cohort sizes of 73 compliant and 172 noncompliant infants fall far short of the 310 cases in each group that would have been necessary for 80% power (2-tailed test, alpha 0.05) to detect a difference in RSV hospitalization rates of 11% versus 5%, the results obtained in the IMPact-RSV trial for placebo- and palivizumab-treated infants, respectively.
Does Administration of Palivizumab by a Home Health Nurse Improve Clinical Outcomes?

A primary message in the subject review by Frogel et al. in this issue of *JMCP* has to do with the potential value of palivizumab administered by home health care as “a key component in ensuring compliance during the RSV season.” Frogel et al. summarize what is known about RSV-related hospitalizations and other outcomes associated with compliance with the palivizumab once-monthly regimen based on 3 peer-reviewed studies and 7 poster abstracts that compared administration of the drug in the clinic or office versus home health care. Not surprisingly, in most studies the home care method of administration was associated with increased compliance with palivizumab immunoprophylaxis. However, whether improved clinical outcomes might accrue from home health administration of palivizumab is doubtful based on currently available evidence.

Of the 10 studies of home health administration included in Frogel et al.’s review, 6 compared hospitalization rates for palivizumab administration by home health versus clinic or office settings. Of those, only 2 found significant differences between home health and clinic/office administration, 1 of which assessed all-cause hospitalizations. Of the 5 studies to assess the percentage of babies with a hospitalization attributable to RSV, only 1, the Palivizumab Outcomes Registry Study, found significantly lower RSV hospitalization rates in home health care as compared with clinic/office (0.4% versus 1.2% for the sample overall, \( P = 0.014 \); 0.6% vs. 1.6% for a subgroup of Medicaid-enrolled infants, \( P = 0.02 \)).

Thus, absent consistent evidence of clinical benefit, Frogel et al. base their advocacy of home health administration in part on a theory that “a home-based delivery system might offer some additional benefit of decreasing exposure of the infant to pathogens, including RSV, in the clinic or office setting.” Frogel et al. provide support for this assertion by citing Hand et al.’s brief report of a study that did not measure exposure to pathogens but in which the authors wrote that they “speculate that the decreased number of medical visits and hospitalizations may be a function of decreased exposure of the high-risk infant to the clinic environment.” This is a curious citation by Frogel et al. because they acknowledge earlier in their review article that the report by Hand et al. suffers from the shortcoming that the research did not assess whether the hospitalizations reported during the RSV season (defined as October 1, through April 30) were actually attributable to RSV.

Actually, there are a number of shortcomings in the report by Hand et al., which bring into question the “evidence” produced from research on the subject of clinic/office versus home health nurse administration of palivizumab. First, Hand et al. compared RSV hospitalization rates across 2 RSV seasons, clinic-based administration for the 2000-2001 RSV season versus home-based administration in the 2001-2002 RSV season. Second, the authors do not report important methodological details, such as the number of patients lost to follow-up. Third, the authors mention a subgroup analysis of patients 100% compliant with palivizumab but present no data or counts to support the claim that hospitalizations were lower in the home-based arm, and the number of patients cited (n = 155) does not match the count of 171 patients 100% compliant across the 2 RSV seasons that is shown in the sole data table in their brief report. Fourth, the study by Hand et al. is not generalizable because all infants were Medicaid eligible (and Medicaid covered the service for home administration of palivizumab). Fifth, the cost of home-based services was not addressed; and sixth, there is no disclosure of funding or financial conflicts of interest in this brief report published in 2008 from data collected 6-7 years earlier. In short, the study by Hand et al. fails the test of quality of evidence, and the mean per patient number of hospitalizations reported by Hand et al., 1.01 in the clinic-based group versus 0.35 in the home-based group, are all-cause, not documented as RSV-related.

At a more basic level for MCOs, the practical value of using home health care to prevent exposure to pathogens in physician offices is markedly unclear in a patient population targeted to receive therapy in part because of exposure to pathogens in child care, an AAP risk criterion for palivizumab use. Notably, the proportion of Palivizumab Outcomes Registry Study patients who were either enrolled in child care themselves or were living with an enrolled sibling more than doubled from 22.5% in 2000-2001 to 51.4% in 2003-2004.

AAP Guidance in 2009 Narrowed the Scope of Appropriate Use of Palivizumab

In September 2009, the Committee on Infectious Diseases of the AAP modified its 2003 and 2006 clinical practice guidelines and 2006 *Red Book* recommendations for the use of palivizumab for the prevention of RSV infections. The 2009 AAP policy statement narrowed significantly the target population for receipt of palivizumab prophylaxis, particularly for infants with a gestational age of 32 weeks to 35 weeks (Table 2). By far the most dramatic change is limitation of palivizumab to the lesser of 3 doses or 90 days of age, in premature infants born between 32 weeks 0 days and 34 weeks 6 days who do not have CHD, CLD, neuromuscular disease, or congenital abnormalities of the airways. Previously, a maximum of 5 doses was recommended for all high-risk infants. Second, the gestational age eligible for recommended prophylaxis was reduced by 1 day, from 35 weeks 0 days in the 2006 *Red Book* to 34 weeks 6 days in the AAP 2009 policy statement; this change means that the AAP 2009 policy statement deviates slightly from the FDA-approved labeling that defines prematurity as gestational age 35 weeks or less.

The third important change that effectively reduces the target population is reduction in the scope and definition of risk factors that qualify for palivizumab prophylaxis in the subgroup of infants born from 32 weeks 0 days through 34 weeks 6 days gestational age. In addition to gestational age and age younger than 6 months at the start of the RSV season, the 2006 *Red Book*...
suggested that at least 2 of 5 risk factors (“child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease”) be present before considering the administration of palivizumab. Although the 2006 guidelines recognized that passive exposure to household smoke should not normally be considered as a risk factor, exposure to environmental air pollutants, which was included in the 2006 guidance, has been removed altogether as a risk factor from the 2009 guidance. Now, 2 risk factors are recognized for consideration of the use of...
palivizumab in infants born between 32 weeks 0 days and 34 weeks 6 days and less than 90 days of age: (a) “infant attends child care;” or (b) “1 or more siblings or other children younger than 5 years live permanently in the child’s household.”

Therefore, only 1 of the 5 former risk factors (day care attendance) survives into the 2009 policy statement in its previous form, and having school-aged siblings has been replaced by living with siblings or other children less than 5 years of age. The 2009 AAP policy statement attributes this change to “inconsistencies among studies that attempted to define risk factors identifying children at greatest risk of serious RSV lower respiratory tract disease” and an intent to better target the children at “highest risk of severe disease” by focusing on the 2 factors that most consistently predict risk of developing serious RSV lower respiratory tract disease.

The 2009 AAP policy statement for the use of palivizumab to prevent RSV infections remains unchanged for infants with hemodynamically significant CHD, birth before 32 weeks 0 days, and CLD associated with prematurity. For these 3 groups, a maximum of 5 doses of palivizumab is still recommended. But, the 2009 AAP policy statement is also clear that when palivizumab prophylaxis is initiated after the start of the RSV season in these infants and children, all 5 doses will not be necessary. Table 1 in the 2009 policy statement also specifies the earliest start date for initiation of a maximum 5 monthly doses in infants or young children with CLD or CHD as July 1 in southeast Florida, September 15 in north-central and southwest Florida, or young children with CLD or CHD as July 1 in southeast Florida, September 15 in north-central and southwest Florida, and November 1 in “most other areas of the United States.”

One does not have to make a careful reading of the 2009 AAP policy statement on the use of palivizumab for the purpose of reducing RSV-related hospitalization to determine that the Committee on Infectious Diseases was (a) attentive to the high cost of the drug and the inconsistency in the medical literature regarding the risk factors that truly predict RSV-related hospitalization, and (b) more definitive than in previous guidelines in specifying groups of infants who will most likely not benefit from immunoprophylaxis. The 2009 AAP policy statement is clear that premature infants with gestational age from 32 weeks 0 days to 34 weeks 6 days are at higher risk of RSV-related hospitalization if born during the RSV season or if they are younger than 3 months of age at the start of the RSV season. Among the groups of infants who should not receive palivizumab because of insufficiently increased risk of RSV or lack of evidence of benefit are the following: (a) infants with hemodynamically insignificant heart disease; (b) infants with lesions that can corrected by surgery, “unless they continue to require medication for congestive heart failure;” (c) “infants with mild cardiomyopathy who are not receiving medical therapy for the condition;” (d) immunocompromised children (except those with severe immunodeficiency or advanced acquired immune deficiency syndrome); and (e) patients with cystic fibrosis.

How Much is a PA Program for Palivizumab Really Worth?

Questions about the relative value of treatments are unimportant in an environment of unlimited resources. However, managed care interventions assume that resources are not unlimited, and Buckley et al. found palivizumab drug cost savings of about $2.4 million over 3 RSV seasons (2005-2008), without adverse clinical outcomes as measured by RSV-related ER visits and RSV-related hospitalizations. While the direct administrative costs for operation of this program are not reported, it is reasonable to estimate that a clinical pharmacist with convenient access to electronic medical records in an integrated health system might require 15 minutes on average to review each PA request to make a coverage determination based on explicit criteria. Therefore, the 1,090 PA requests processed by the health plan studied by Buckley et al. would require 272.5 hours or total administrative payroll costs of about $20,450 over 3 RSV seasons to save $2.4 million, assuming a 2,000 hour work-year and annual salary and fringe benefit costs of $150,000. Not a bad return on investment, $100 savings for $0.80 administrative cost.

From another perspective, the PA program for palivizumab described by Buckley et al. saved their health plan of 500,000 members about $0.13 per member per month (PMPM). Annual drug cost savings of $800,000 may not seem so large when expressed as PMPM costs. On the other hand, if these PMPM savings are applied to the entire U.S. population of approximately 300 million people, the research by Buckley et al. suggests that there is nearly $500 million in potentially avoidable palivizumab drug costs each year in the United States, some of which may be realized in the operation of existing PA programs. Palivizumab might be the perfect poster child for PA interventions in managed care that are evidenced-based and result in quality improvement by delivering equivalent or better clinical outcomes at lower cost.

Authors

FREDERIC R. CURTISS, PhD, RPh, CEBS, is Editor-in-Chief, and KATHLEEN A. FAIRMAN, MA, is Associate Editor and Senior Methodology Reviewer of the Journal of Managed Care Pharmacy.

AUTHOR CORRESPONDENCE: Frederic R. Curtiss, PhD, RPh, CEBS, Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314. Tel.: 830.935.4319; E-mail: jcurtiss@amcp.org

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Medication Therapy Management and Collaborative Drug Therapy Management

With the current push for health care reform, many are asking how ongoing government programs like Medicare Part D are performing. The Medicare Modernization Act of 2003 established the requirement that Medicare Part D prescription drug plans (PDPs) and Medicare Advantage prescription drug plans (MA-PDs) provide medication therapy management programs (MTMP) using pharmacists or other qualified health care providers as part of their benefits. In general, medication management services encompass care beyond traditional medication counseling. MTM services are designed to maximize the benefits of prescribed medication regimens, increase medication adherence, and reduce the risk of adverse drug events and drug interactions.

In an article by Spooner (2007), he suggested that at the 1-year mark, it was time to start evaluating MTMP services. Spooner recommended that evaluations focus on the following 2 questions: “are we correctly identifying patients who would benefit the most and has the MTM been successful in achieving established goals.” According to the Medication Therapy Management in Pharmacy Practice: Core Elements of an MTM Service Model Version 2.0, MTM programs should also be designed “to improve collaboration among pharmacists, physicians, and other health care professionals, enhance communication between patients and their health care team; and optimize medication use for improved patient outcomes.”

In a recently published article in JMCP, Cook and Mburia-Mwalili discussed Medicare Part D policy changes that have affected pharmacists working in MTMP. They described how the availability of the National Provider Identification (NPI) numbers and pharmacy-specific Current Procedural Terminology (CPT) codes have facilitated the implementation of MTMP by allowing pharmacists to seek reimbursement for their services. The authors suggest that with a wide range of services being provided including mailed information, telephone consultations, as well as in-person appointments, large chain community pharmacies may be the best settings for the provision of MTM because of previously developed billing infrastructure and in-store clinics with prior trained clinical staff. However, Cook and Mburia-Mwalili acknowledge that even with a collaborative approach of pharmacist and prescriber, community pharmacy chains would not likely manage more serious chronic conditions. We foresee collaborative drug therapy management programs as a way to gather data for outcomes of improvements of these chronic conditions.

Collaborative Drug Therapy Management

CDTM refers to collaborative practice agreements between pharmacists and prescribers in which pharmacists are enabled to initiate, modify, or continue drug therapy for specific patients as defined in a written guideline or protocol. CDTM is being used in the following areas: immunizations, asthma therapy, dyslipidemia therapy, warfarin anticoagulation therapy, diabetic therapy, smoking cessation therapy, and flu/antiviral therapy. Currently, 46 states in the U.S. have authorized CDTM agreements between pharmacists and physicians, including most recently Massachusetts and Rhode Island. Of the 4 states that do not have CDTM programs (Alabama, Oklahoma, Maine, and New York), pharmacists in New York are lobbying to implement a CDTM bill (S.3292/A.6448).10

Kaiser Permanente of Georgia (KPGA) health plan is a non-profit health maintenance organization that provides integrated health care services to more than 250,000 members at 15 medical offices in the Atlanta metropolitan area. At KPGA, clinical pharmacists are part of a collaborative team that provides CDTM and MTM for patients diagnosed with dyslipidemia, diabetes, hypertension, or coronary artery disease as defined in protocols developed by clinical pharmacists and primary care physicians (PCPs). A patient-specific protocol is valid for 2 years unless the patient changes physicians or disenrolls from the KPGA health plan. The CDTM protocols include algorithms for specific drug therapy modifications, dosing ranges, and monitoring information for insulin management, hypertension management, diabetes management, lipid management, lab monitoring, and aspirin therapy initiation.

Patients are enrolled into these programs through direct referral by PCPs or via administrative queries of a Web-based electronic database. When a protocol is signed by a PCP, all current patients of that PCP are authorized to be managed under the protocol as well as future patients that are individually referred to clinical pharmacists by that PCP. The collaborative protocols with KPGA PCPs allow the clinical pharmacists to confer with patients and other members of the health care team to initiate medications, order laboratory tests, and adjust dosages on the basis of lab results or reported side effects, as well as make formulary conversions.

In addition to the use of collaborative protocols, KPGA providers, patients, and staff also rely heavily upon electronic medical records (EMRs). The database used for referrals is integrated with the KPGA EMR and the collective data are used to identify patients who are due for laboratory tests, those who are diagnosed with specific chronic diseases and have not met their goals, have not seen their PCPs in more than 1 year and Medicare Part D patients eligible for enrollment in the MTMP. EMRs offer access to a complete patient history, including, but not limited to procedures, medication recommendations, and existing medical conditions. At KPGA, the clinical pharmacists and the health care team use EMRs to coordinate patient care at each point of service, including office visits, laboratory services, prescription services, hospitalizations, phone consultations, and online services. Patients enrolled in the KPGA health plan have access to view online portions of their medical record and information about their office visits. The Web-based portal also allows...
patients to safely and securely send messages to their providers, view lab results, schedule appointments, and order medications for pick-up or delivery. The use of this innovative information technology may potentially reduce fragmentation of medical care as it increases collaboration among providers.

**MTMP at KPGA**

In 2009, the Centers for Medicare and Medicaid Services (CMS) reported that in 2008 there were 712 active Part D approved MTM programs, 609 MA-PD and 103 PDP. Criteria for these programs vary, however, targeted beneficiaries must have multiple chronic diseases to be enrolled. The top 4 chronic conditions frequently targeted by MTMPs in 2008 were diabetes, heart failure, hypertension, and dyslipidemia. Enrollees must also be taking multiple Medicare Part D drugs which are likely to incur annual costs of $4,000 or greater. The minimum number of covered Medicare Part D drugs to determine MTMP eligibility varied among MTMPs in 2008, ranging from as few as 2 to as many as 15; most programs required a minimum of 5 to 8 medications (62.4%) per beneficiary for MTMP eligibility.

In the second quarter of 2009, the clinical pharmacists at KPGA began monitoring MTM patients under the collaborative protocol. The KPGA MTMP identifies and invites patients that are likely to incur annual drug costs greater than or equal to $4000, are taking at least 5 chronic or maintenance medications covered by Medicare Part D, and have at least 2 of the 5 following chronic conditions: asthma, diabetes, chronic kidney disease, hypertension, and coronary artery disease. Patient participation in the KPGA MTMP is voluntary, and MTM clinical pharmacists attempt to provide services to all MTM-eligible members. Initially, welcome letters are mailed, and patients are later contacted by telephone and invited to participate in the MTMP. If a patient is unable to be reached by telephone after 3 attempts, a letter is mailed requesting his/her response by a specified date to become enrolled in the program. Failure of the patient to respond by the specified date will indicate the member’s decision not to participate in the MTMP. Eligible members may opt out at any time by contacting their MTM clinical pharmacists. MTM enrollment has grown from 101 patients in 2009 Q1 to 270 patients in 2009 Q3, and currently 330 (44%) of 750 MTM-eligible members are enrolled in the KPGA MTMP.

After enrollment, MTM clinical pharmacists perform an initial assessment to validate the complete medication profile and the following target areas: patient compliance, drug therapy duplication, potential drug interactions, potential cost-effective alternatives, and drug therapy appropriateness. Next, MTM patients have their individualized therapeutic goals defined. After the initial patient assessment, the MTM pharmacist will conduct follow-up telephone encounters with the patient at least quarterly or more frequently if necessary, to assess progress toward treatment goals. Patient-specific education and instruction regarding medication use is provided, as appropriate, during each encounter.

Going forward, CDTM protocols may be used to define outcome measures such as low-density lipoprotein (LDL) goals and hemoglobin A1c goals, and identify the patients who are due for laboratory monitoring. Currently, preliminary outcomes data are being collected on the use of high-risk medications in the elderly to monitor for safety.

**Conclusion**

Pharmacists play a central role in management of medication therapy, particularly for patients with chronic conditions, and CDTM can enhance that role. The EMR in our health system allows for seamless collaboration and the sharing of information among providers and their patients. With the use of a Web portal for access to the electronic database and the list of patients enrolled in CDTM protocols, we are able to identify Medicare patients who are monitored by clinical pharmacists at KPGA. The CDTM protocols and agreements between clinical pharmacists and PCPs facilitate the delivery of MTMP services in our health system.

**Stephanie Roberts, PharmD, BCPS**  
Clinical Pharmacy Specialist  
Kaiser Permanente  
Stephanie.Roberts@kp.org

**Rachel Gainsbrugh, PharmD**  
Clinical Pharmacy Specialist  
Kaiser Permanente  
Rachel.D.Gainsbrugh@kp.org

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