Palivizumab Utilization, Effectiveness and Cost among Florida Medicaid Recipients

EXECUTIVE SUMMARY

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*Final Report to the Agency for Health Care Administration*

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In collaboration with the University of Florida Center for Medicaid and the Uninsured.
Executive Summary

This report describes and summarizes four studies conducted for the Agency for Health Care Administration in collaboration with the University of Florida Center for Medicaid and the Uninsured. The overall study objectives were based on concerns about utilization pattern and cost-effectiveness of palivizumab (Synagis®), a monoclonal antibody used to prevent respiratory syncytial virus (RSV) infections, in Florida Medicaid infants. Considering the high expenditures of palivizumab, utilization is reserved for high-risk children during the high-risk time period (i.e., RSV seasons), but definitions of both, recipients and RSV seasons, are somewhat controversial and adherence to available recommendations in practice is unknown. Available effectiveness estimates are largely based on clinical trials of highly-selected patient groups following stringent drug administration protocols and the generalizability to current practice is unknown. Finally, even though several cost-effectiveness studies have been published, results differ vastly and the applicability to Medicaid is unknown.

We address these issues in four separate studies. In Part I we report utilization pattern and compliance with current guidelines to assess the degree of under- or overuse of palivizumab in Florida Medicaid. In Part II we compare RSV hospitalization rates and palivizumab utilization pattern to describe respective secular trends and the appropriateness of prophylaxis timing. In Part III we evaluate the effectiveness of palivizumab in real-life clinical settings, the contribution of a range of risk factors to RSV infections, and explore the impact of utilization gaps (noncompliance) on palivizumab effectiveness. Finally, in Part IV we conduct a cost-effectiveness analysis utilizing cost estimates for RSV infections and prophylaxis specific to the Florida Medicaid population and report various sensitivity analyses to facilitate optimizing palivizumab utilization.

Part I

We calculated the proportion of patients who received at least one dose of palivizumab during a given 5-months season, broken down by indication for immunization. We also report the proportion with full coverage (≥ 4 doses in one season) among palivizumab recipients, again, broken down by indication. Furthermore, we describe the number and characteristics of palivizumab recipients who received prophylaxis without meeting indications.

Our sample consisted of Medicaid recipients, aged 0-2 years between September 1998 and February 2005 with available birth certificate data. We analyzed palivizumab utilization for seven seasons, 98/99 through 04/05, each season from October 1st to the end of February. Patients had to be continuously eligible throughout an entire season. Utilizing NDC codes, we detected claims for palivizumab and categorized patients based on the number of doses received during one season. Patients were further categorized to represent the indication that put them at risk for RSV-related hospitalizations: (1): chronic lung disease (CLD); (2): premature infants born up to 32 weeks of gestational age; (3): 33-35 weeks gestational age with additional risk factors; (4D1, old guideline): CLD and asymptomatic acyanotic congenital heart disease (CHD); (4D2, new guideline): hemodynamically significant cyanotic and acyanotic CHD; (5D1): children with medication for congestive heart failure (CHF); (5D2): moderate to severe pulmonary hypertension; (5D3): cyanotic heart disease; (5D4): any of 5D1-5D3; (6): cystic fibrosis and (7): severe immunodeficiencies.

A total of 589,258 children met our seasonal eligibility criteria and were included in the seasonal analysis. These children contributed an aggregate 737,636 seasons and received 32,811 doses of
Palivizumab during the seasons 98/99 through 2004/05. The number of palivizumab users increased steadily from 409 in season 98/99 to 1970 in season 04/05. Among users, 15.4% did not meet any of the indications 1-7 in 98/99. This proportion increased throughout the observation period to 32.3% in 04/05 (637 recipients). Overall, 2,442 children received 9,510 doses without indication during the study period.

Among children with indication, Black and Hispanic infants were less likely to receive palivizumab as opposed to Whites (OR_{Black} = 0.77; OR_{Hisp} = 0.78). Findings by indication for % infants with ≥ 1 dose and % recipients with full coverage in 2004/2005 were as follows.

<table>
<thead>
<tr>
<th>Indication</th>
<th>% Recipients with ≥ 1 dose in 04/05</th>
<th>% Recipients with full coverage in 04/05</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>69.2%</td>
<td>76.8%</td>
</tr>
<tr>
<td>(2)</td>
<td>45.8% ; 68.6%</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>14.1% ; 60.2%</td>
<td></td>
</tr>
<tr>
<td>(4D1)</td>
<td>59.1% ; 75.4%</td>
<td></td>
</tr>
<tr>
<td>(4D2)</td>
<td>28.4% ; 76.8%</td>
<td></td>
</tr>
<tr>
<td>(5D1)</td>
<td>69.2% ; 92.6%</td>
<td></td>
</tr>
<tr>
<td>(5D2)</td>
<td>20.2% ; 63.2%</td>
<td></td>
</tr>
<tr>
<td>(5D3)</td>
<td>21.7% ; 75.3%</td>
<td></td>
</tr>
<tr>
<td>(5D4)</td>
<td>23.3% ; 76.3%</td>
<td></td>
</tr>
<tr>
<td>(6)</td>
<td>9.52% ; 61.5%</td>
<td></td>
</tr>
<tr>
<td>(7)</td>
<td>17.5% ; 72.7%</td>
<td></td>
</tr>
</tbody>
</table>

The low utilization rates for indications 6 and 7 are likely associated with lack of strong evidence for effectiveness. For indication 3, lack of data to appropriately define infants at risk resulted in the need for a conservative estimate of their number. Consequently, an overestimated denominator has contributed to the seemingly low utilization rate.

The analysis of palivizumab utilization and compliance revealed both over- and underutilization in certain areas. On one hand, room for increasing utilization was seen especially for premature children (2) and children with hemodynamically significant CHD (4D2). On the other hand, the proportion of 32.3% of palivizumab recipients without any indication according to current recommendations indicates room for resource optimization. Of note is that 69.2% of recipients without indication were premature children who received palivizumab after they exceeded the recommended age range. This proportion represents 1,689 infants who received 6,578 doses between the season 98/99 and 04/05. At approximately $1,000 per dose or more, the impact of this immunization practice on the Medicaid budget is significant. Finally, an encouraging observation is the consistently high proportion of palivizumab recipients with indication who received a full course of immunization (≥ 4 doses in one season), but it is unclear how a lower degree of compliance would affect protection against the virus and the risk for RSV-related hospitalization.

Part II

We conducted an ecologic time series study using 10 years (July 1995 to June 2005) to compare monthly palivizumab utilization rates with RSV hospitalization rates including all infants between the ages of 30 days to 2 years with at least 2 months Medicaid eligibility. Hospitalized children had to be discharged at least 30 days before a given month to assure up-to-date information on palivizumab use. In order to assess spatial pattern of monthly hospitalization rates we developed maps of all Florida counties for the fiscal year July 2003 to June 2004 utilizing the same study population.
From its market introduction, palivizumab use peaked between January and March and was lowest between June and July. RSV-related hospitalizations peaked in November/December and were lowest between June and August. Palivizumab utilization increased steadily since Sept 1998 with 1182 immunized infants per 100,000 eligible Medicaid recipients during the peak month January 2005. Growth varied with an average increase of 126.2 [95% CI: 108.8, 143.6] children per 100,000 for each consecutive annual peak month and 60.9 [44.6, 77.2] for each consecutive trough.

Monthly hospitalization rates were fairly steady prior to palivizumab introduction with an average of 363 admissions per 100,000. After that, the average annual decrease in the monthly hospitalization rate varied between -31.5 [-42.5, -20.6] per 100,000 across peaks and -11.4 [-20.9, -2.00] across troughs with an overall average HA rate of 294/100,000.

Our spatial and temporal analysis of a single season illustrates (1) the seasonal character of RSV infections with most hospitalizations occurring between September and March, and (2) that season onset is earlier in the South compared to the North of Florida. However, hospitalization rates were low during summer months for all counties including those in South Florida. The comparison between palivizumab utilization and RSV-related hospital admissions shows that peaks of drug utilization consistently trail after HA peaks. Within the limitations of the study design, this suggests less than optimal immunization coverage at the period of highest risk. If regional differences are taken into account, the discrepancies between season onset and initiation of prophylaxis are likely even more pronounced.

We further observe an ecologic association of an increase in palivizumab utilization since its introduction with a decrease in RSV-related hospitalizations. This decrease is especially pronounced during season (peaks) where we observe the highest increase in drug utilization. Conversely, a smaller but still substantial increase in utilization has resulted in a smaller decrease in hospitalizations off-season (troughs). This finding indicates that the effectiveness of palivizumab prophylaxis outside of the seasons may be less and deserves further research.

In summary, palivizumab utilization trails after the peak of hospitalizations, suggesting room for improvement in timing of immunizations and the need for further studies defining seasonality in Florida. Spatial differences exist, but may not be as pronounced as proponents of all-year-round prophylaxis for Southern Florida argue. This is even more important as, across off-season troughs, a steady and substantial increase in palivizumab utilization was related to a smaller decrease in hospitalizations than observed during on-season periods. Thus, the effectiveness and cost-effectiveness of off-season immunizations should be further examined.

Part III

Clinical trial data on palivizumab efficacy are scarce and limited to a number of selected high-risk populations. With rigorous treatment protocols and often hand-selected subjects it is unclear whether efficacy estimates are generalizable to real-life situations. Guidelines have furthermore expanded their recommendations beyond those populations described in clinical trials and provider and patient decisions in clinical practice have further diluted the originally narrowly defined population of prophylaxis candidates. Treatment protocols rigorously implemented in clinical trials may not be followed in practice and noncompliance with administration schedules may decrease palivizumab
effectiveness. Considering the significant cost associated with palivizumab prophylaxis it is critical to examine its effectiveness under real life conditions.

We utilized a cohort study design to compare hospitalization rates for RSV-infections between infants who received or did not receive palivizumab. The cohort was established from the Florida Medicaid fee-for-service program which provides monthly updated information on eligibility and beneficiary demographics as well as claims detail for all pharmacy, and in- and outpatient encounters. Infants with at least three months eligibility between August and March of 1998/1999 to 2004/2005 were included in the analysis. Only infants with records in the Medicaid claims database as well as with available Vital Statistics birth certificates were included. At least one month of eligibility had to occur during the RSV season, which was defined as October to March. Infants could enter the study at the beginning of the season or any time thereafter throughout the season (index date) after they had spent a minimum of 60 days in ambulatory care. Infants were censored at the end of the season, when they turned 2 years old, when they died, or when they were admitted to the hospital for any reason, whichever came first.

The primary study endpoint was the first hospitalization for RSV-related pneumonia (ICD9-CM code 480.1), RSV bronchiolitis (466.11), or other admissions with codes for RSV infections (0.79.6). Exposure to palivizumab was defined based on pharmacy claims with drug-specific NDC code or physician office visits claims with procedure codes for palivizumab administration. Each claim was assumed to be active for a 30 day period. In order to account for potential delays between the pharmacy charge (indicating palivizumab delivery to the physician office or clinic) and the actual patient visit, we lagged the follow-up period attributed to palivizumab by seven days. Exposure was consequently defined as (1) first dose including day 7 to 37 after the first palivizumab claim, (2) subsequent dose, including day 7 to 37 after any claim following the first claim, (3) former use including day 38 to 67 after any palivizumab claim, and (4) no use, including days before the first palivizumab dose and 68 days after any palivizumab claim. Time-dependent Cox regression was used to adjust the analysis for patient-specific risk factors, geographic and seasonal parameters.

The analysis included a total of 898,054 infants representing 1,429,486 infant-RSV-seasons with the predominant portion of infants (975,137) starting the cohort at the beginning of the season. Infants who received palivizumab were less likely to be Hispanic and on average younger than infants who did not receive palivizumab. Consistent with guidelines, palivizumab users were more likely to have RSV prophylaxis indications such as chronic lung disease or low gestational age as well as other measures of morbidity such as disability, diagnosis of Down syndrome, and history of respiratory problems and of extensive healthcare utilization.

Repeated prophylaxis with palivizumab showed a 21% reduction in the risk for RSV hospitalizations. The first dose of palivizumab did not exhibit effectiveness, which may be due to suboptimal plasma levels or the fact that palivizumab may have been initiated in some instances to treat beginning RSV infections, thus, merely indicating existing infections that were acquired prior to administration of prophylaxis. Former use of palivizumab maintained some reduction in RSV hospitalization risk, but confidence intervals were wide and limit conclusions. However, it cannot be concluded that short gaps of noncompliance severely affect a patient’s coverage, but further analysis is needed to quantify how much a deviation of the recommended immunization schedule can be tolerated without consequences for effectiveness.

Part IV
Immunoprophylaxis of respiratory syncytial virus is limited by the high cost of the prophylactic agent, palivizumab. Cost for a single dose can range from $651 over $1,226 to $2,448 depending on an infant’s weight. Furthermore, the need for monthly injections during high-risk periods with a minimum duration of five months amplifies the financial burden of RSV prophylaxis. An array of cost-effectiveness analyses on palivizumab have been published, however using rather low drug cost estimates. Furthermore, disease characteristics including RSV incidence can differ between different populations and result in different cost-effectiveness estimates. This study uses Florida Medicaid claims data to maximize applicability of its findings to infant Florida Medicaid recipients.

In this cost-effectiveness analysis, we calculated the dollar-amount necessary to allocate to immunoprophylaxis with palivizumab in order to save one RSV-related hospitalization expressed as incremental cost effectiveness ratio (ICER). We created economic models for 8 categories of patients, including infants 0 to 2 years of age, according to palivizumab guidelines: presence of chronic lung disease (CLD) and no other indication; congenital heart disease (CHD) only; CLD and prematurity (less or equal 32 weeks gestation); CHD and prematurity; CHD and CLD; any of CHD, CLD or prematurity; and none of these indications. Furthermore, we created a premature category for infants up to 6 months of age who were born at ≤ 32 weeks gestation to incorporate guideline-defined age restrictions.

We utilized a decision tree with the alternatives immunoprophylaxis with palivizumab and no immunoprophylaxis. We obtained the model input parameters cost for palivizumab, as well as cost and incidence of RSV-hospitalizations, from Florida Medicaid claims data. Our dataset was based on the RSV season from October 2004 to March 2005 and included 1,121,212 subject months from 247,686 infants. Input parameters in the model included palivizumab cost, cost of RSV related hospitalizations and the pseudo-incidence of RSV in the absence of prophylaxis. These parameters were extracted from Medicaid claims data. We used effectiveness estimates for the decrease in RSV hospitalization risk from clinical trials and varied these in a sensitivity analysis to include our own observed effectiveness estimates.

Among a total of 1,121,212 infant-months 10,761 had claims indicating palivizumab utilization. Claims ranged from $1.16 to $3,067.40, however most claims were clustered around 4 values: $651.45 corresponding to a 50mg dose, $1,226.35 for a 100mg dose, $1,877.8 for a 150mg dose and $2,448.47 for a 200mg dose. Higher doses were associated with increasing patient age. The mean cost for a RSV-related hospital admission ranged between $4,025.10 [95% confidence interval: 3,812, 4,238] for infants without indication for prophylaxis to $9,244.21 [5,165, 13,323] for premature infants with CLD.

The highest seasonal pseudo-incidence for RSV related hospital admissions without immunoprophylaxis was found for premature infants who also had CLD with a 6-month incidence of 6.81% [95% confidence interval: 3.3, 11.9] between October 2004 and March 2005. Infants without indication showed the lowest incidence with 0.6% [0.2, 1.2].

ICERs reached from $261,191 [95% confidence interval: 121,615, 833,093] for premature infants up to 6 months of age without any other indication to $3,683,667 [1,268,378, 13,717,492] for infants up to two years of age without indication.

ICERs for palivizumab were found to be high with prophylaxis cost far exceeding the financial benefit of preventing hospitalizations. We were able to identify factors that are associated with more beneficial ICERs including young age and the presence of several indications. Palivizumab cost had a large influence on the ICERs, however only at cost of less than $30 per dose would immunoprophylaxis be cost saving. The model was not sensitive to RSV related costs, indicating that even the consideration of possibly avoided long-term adverse consequences associated with RSV infections such as asthma would
not improve the ICERs by a large margin. Further work will examine the influence of age within indications and timing of prophylaxis on cost-effectiveness.

In conclusion, we were not able to identify a scenario that would offset prophylaxis cost unless drug costs were significantly decreased. Even significant increases in drug effectiveness would only marginally improve cost-effectiveness ratios. This is largely due to the fact that (1) RSV hospitalizations rates are low and corresponding numbers needed to treat high, (2) drug costs are high especially since multiple doses are needed to cover infants throughout the RSV season. Current recommendations aim to optimize the investment of resources by focusing on infants at high-risk for infections, but (a) they lack necessary detail and stringency if economic implications are considered, and (b) they are insufficiently followed. Specific prophylaxis and reimbursement guidelines that explicitly consider patient characteristics, geographic and seasonal difference, and the interplay between these three factors are needed to allocate scarce resources to the right patients at the right time and place.

**Conclusion and Key Messages**

1. We observe a growing proportion of infants who receive palivizumab but do not meet any of the guideline-defined indications. The major reason for deviation from guidelines is age, accounting for more than 6,000 doses of palivizumab during the 7-year study period. With age being one of the strongest predictors for RSV infection risk, it is recommended that older age be carefully considered in reimbursement decisions to optimize utilization of prophylaxis.

2. Infants who meet criteria for guideline-defined indications receive prophylaxis to varying degree. While utilization rates generally exceed 60% in infants with chronic lung disease and prematurity, infants with congenital heart disease appear more frequently undertreated, which may be associated with diagnostic complexity and rapid changes in risk status.

3. More than two-thirds of children exposed to palivizumab received a full course of prophylaxis. If existing claims data properly reflect true drug administration, compliance rates are encouraging.

4. Timing of prophylaxis is not optimal and appears to trail behind season onset. Better and geographically specific identification of season onset and communication to providers is needed.

5. Utilization of palivizumab during off season months is not associated with decreases in RSV infection rates of the magnitude as observed during on-season. This, and the generally low RSV hospitalization rates during off seasons, even in South Florida, does not seem to justify immunoprophylaxis outside of a core season. We will follow up on optimal timing considering patient and geographic characteristics in a subsequent study.

6. Palivizumab showed lower effectiveness rates than reported in clinical trials, but the results should be interpreted with caution. There was no evidence from the analysis that short delays in treatment affect patient coverage, significantly alleviating some of the concerns about noncompliance. However, most effective RSV protection appears to occur only after more than one dose of palivizumab has been used, which emphasizes the need to assure continued administration throughout the season.

7. RSV prophylaxis is not cost-effective to Medicaid. The small RSV incidence, the corresponding large number needed to treat, and the high drug cost result in rather unattractive cost-effectiveness ratios. Parameters with great influence on cost-effectiveness are drug cost and the RSV background incidence. Palivizumab effectiveness has an only moderate effect on cost-effectiveness indicating an only moderate effect of improved compliance on cost savings. Thus,
in optimizing palivizumab utilization, attention should be focused on the optimal selection of high-risk patients and prophylaxis periods.