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Policy Evaluation: Palivizumab Prior Authorization

In August 2012, The Oregon Health Plan (OHP) adopted drug use criteria for palivizumab (Synagis®). Palivizumab is a respiratory syncytial virus (RSV) protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.[1] Drug use criteria was developed in response to a drug use evaluation (DUE) done in May 2011.[2] The DUE incorporated the 2009 American Academy of Pediatric (AAP) guidelines[3] and an analysis[2] of the Oregon Fee-For-Service (FFS) Medicaid program during the 2009-2010 RSV season. Previously, OHP FFS covered palivizumab without restriction. Results from the 2011 DUE suggested improper timing and exceeding the recommended five doses of palivizumab provided no health benefit and directly increased costs. The current prior authorization (PA) criteria limits use of palivizumab to high risk infants identified by the AAP, to five monthly doses and to use during the months of highest RSV activity. The PA criteria also account for variability in season onset and offset, due to geographic and population differences throughout Oregon. In 2012, the cost per member per month (PMPM) was $1.85 and in 2013 it was $1.06 PMPM. Additionally, claims decreased by 40% PMPM.[4] The purpose of this drug use evaluation is to further assess the impact of the palivizumab prior authorization on use outside of established criteria and survey for unintended harm.

A literature search of Cochrane Reviews and Medline was performed to identify changes in practice since the 2011 DUE.

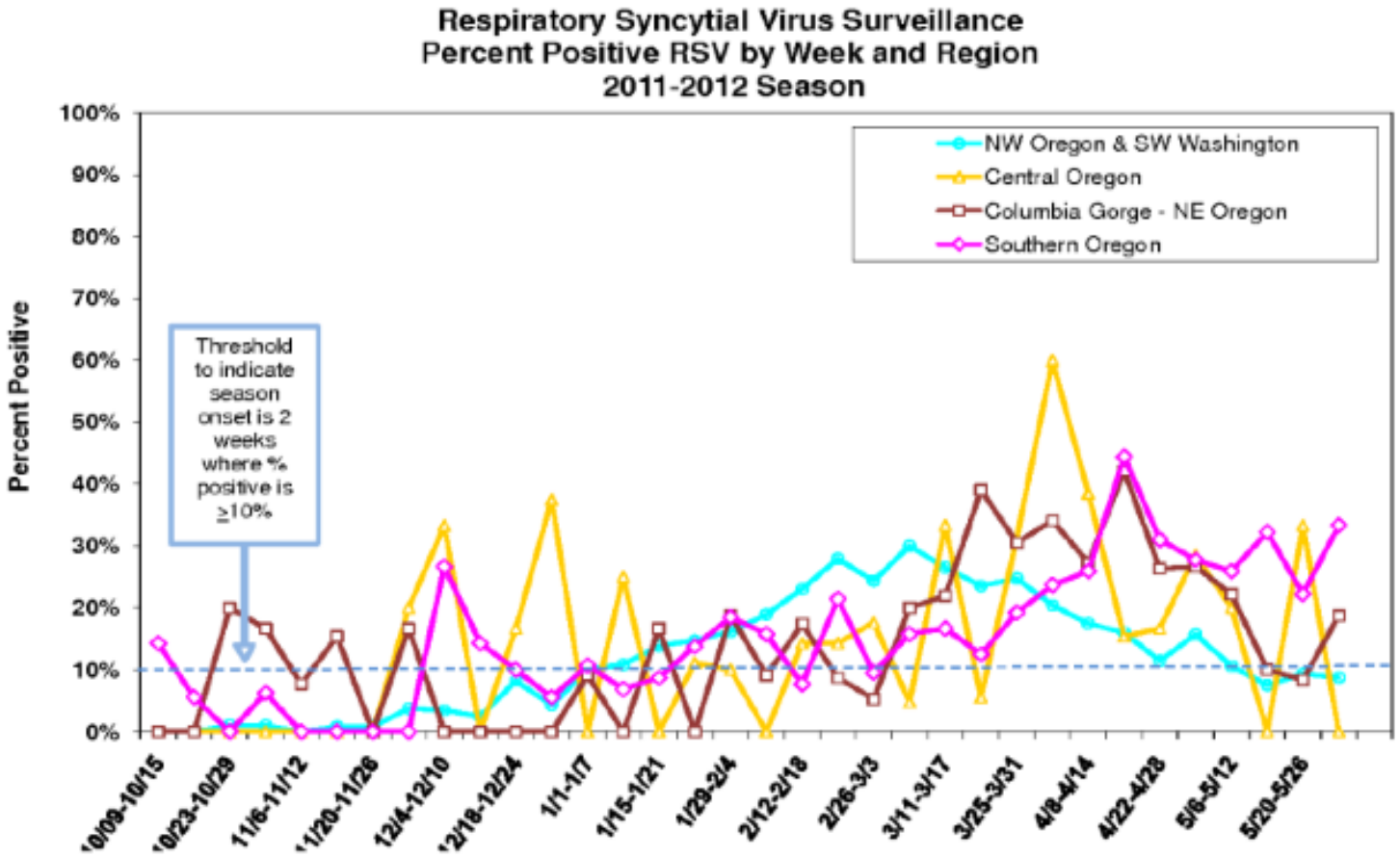
Two updated Cochrane Reviews[5,6] were identified using search term “respiratory syncytial virus.” “Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children” [5] assessed the effectiveness and safety of palivizumab prophylaxis in reducing the risk of complications in high-risk infants and children, as well, as the cost-effectiveness of prophylaxis in infants and children in different risk groups. Seven good-quality studies were included, however, it was noted most of the outcomes relied on data from two studies. High quality evidence from three studies including 2,831 participants showed a reduced risk of hospitalizations with palivizumab prophylaxis compared to placebo (RR 0.49, 95% CI 0.37-0.64), with an ARR of 5.2% (NNT 20), and a statistically non-significant reduction in all-cause mortality (RR 0.69, 95% CI 0.42-1.15). Cost-effectiveness could not be fully clarified due to the variety of methods used to perform analyses. These findings confirm current recommendations. In June 2013, a separate Cochrane Review, “Palivizumab for prophylaxis against respiratory syncytial virus in children with cystic fibrosis” was published.[6] However, their search yielded only one study, which was not enough to draw firm conclusions from.

The New England Journal of Medicine published the multicenter, double-blind, randomized, placebo-controlled MAKI trial in May 2013.[7] This was a good-quality trial of 429 healthy preterm infants born at the gestational age of 33 to 35 weeks in Holland. The primary endpoint was number of parent reported wheezing days in the first year of life. The results were 1.8% (930/53,075 days) in the RSV-prevention group versus 4.5% (2,309/51,726 days) in the placebo group ($p<0.001$), with an ARR of 2.7% (NNT 37). The patient population was healthy preterm infants in Holland and is not representative of population indicated for RSV treatment in Oregon. Furthermore, the correlation between wheezing episodes and pulmonary damage is not well understood.

A search of the Oregon RSV surveillance and the Centers for Disease Control and Prevention surveillance identified 2011-2012 and 2012-2013 RSV season statistics. It is not mandatory to report RSV in Oregon but active surveillance is performed using volunteer laboratories. The Oregon Health Authority reports a weekly surveillance report that is a culmination of 22 laboratories in Oregon and SW Washington.[8] The National Respiratory and Enteric Virus Surveillance System (NREVSS) also report RSV regional and national trends.[9] Eight Oregon laboratories contribute to the NREVSS. Trends in RSV season onset and offset were examined to verify the current policy aligns with highest level of RSV activity.

For 2011–2012, the start of the RSV season in region 10, which includes Oregon, was late December, peaked the week of March 3, 2012, and the season lasted 18 weeks.[10] According to RSV-Oregon surveillance there were 1,428 positive RSV tests during the 2011-2012 season.[11] Figure 1 represents the 2011-2012 RSV season by region. The onset in NW Oregon/SW Washington region was later than the other regions of Oregon.

Figure 1.[11] 2011-2012 RSV Surveillance from RSV-Oregon by region



The start of the 2012-2013 RSV season in Oregon was the week ending December 8, 2012, which was 3 weeks earlier than the previous season.[9] Figure 2 shows no distinct regional differences in season onset. The season lasted 19 weeks, ending the week of May 5, 2013. Figure 3 shows a graphical representation of the 2012-2013 RSV season.[9] There were 2,437 positive RSV tests during this season represented in Figure 3.

Figure 2.[8] 2012-2013 RSV Surveillance from RSV-Oregon by region

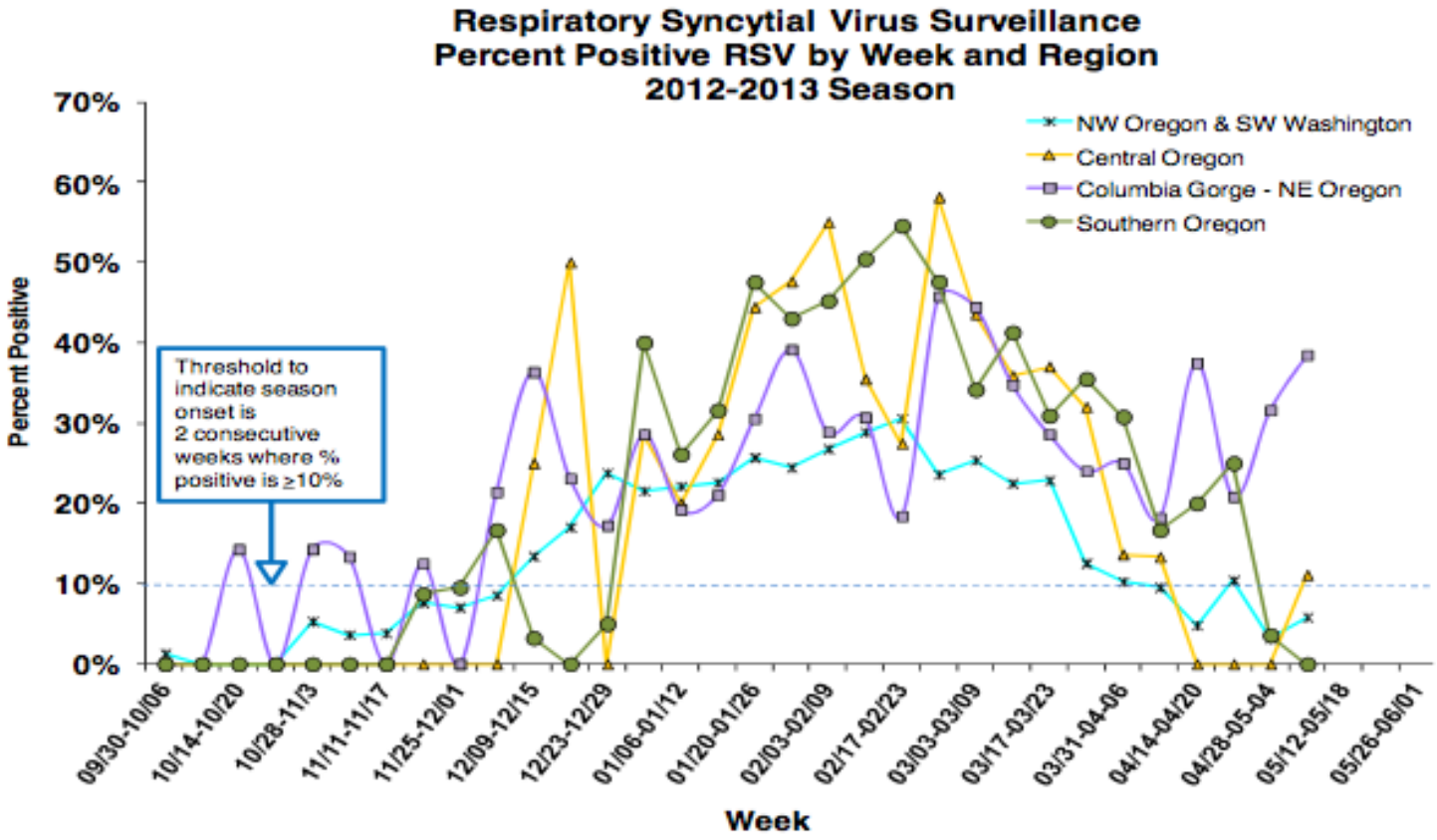
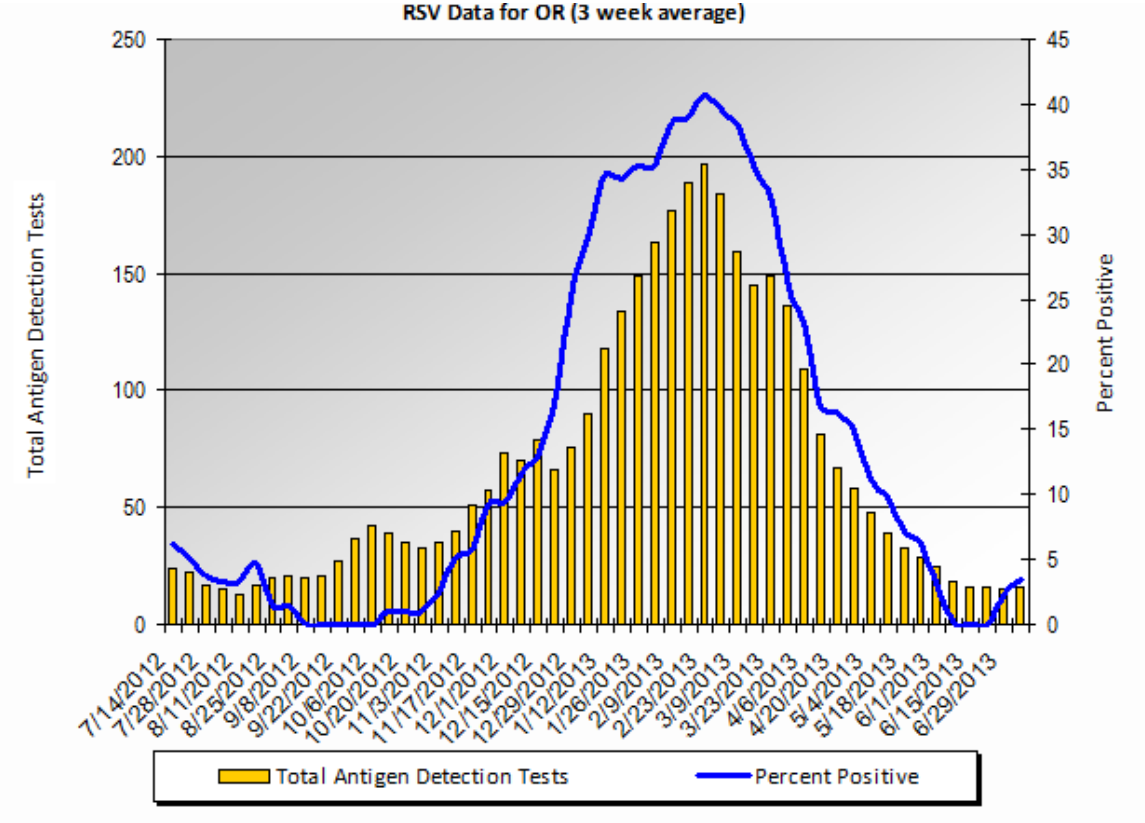


Figure 3.[8] RSV detection data from NREVSS for Oregon



Methods:

Paid FFS drug and professional claims from October 1, 2011 through June 30, 2013 were examined. Patients with dual eligibility for Medicare as identified by a benefit indicator of BMM or BMD were excluded. Patients of interest were identified if they had a claim for palivizumab. Palivizumab drug claims were identified using all National Drug Codes (NDCs) with a First DataBank Generic Sequence Number of 59245 or 59246. Palivizumab professional claims included procedure code of C9003 or 90378. No minimum enrollment restrictions were applied.

The control group included patients with an index claim (none in previous 90 days) for palivizumab in the 2011-12 RSV season (10/1/2011 – 9/30/2012). The study group included patients with an index denied claim for palivizumab in the 2012 – 13 RSV season (10/1/2012 – 9/30/2013) with an Explanation of Benefit (EOB) code equal to "1056-Prior Authorization Required", without a concurrent EOB of "2017 - Patient enrolled in MCO" and without a prior paid or rejected claim for an palivizumab in the 90 days. The study group was further categorized according to prior authorization (PA) disposition at 14 days and palivizumab therapy at 30 days: a) those who requested a PA, were approved and received palivizumab, b) those who requested a PA and were denied, c) those not requesting PA but still receiving palivizumab and those not requesting a PA and with no claim for palivizumab.

Demographics were determined from the Medicaid enrollment record at the time of the index event. Co-morbidity was determined from International Classification Diagnosis (ICD-9) codes on professional claims from birth until six months after the index event.

The primary outcomes were: 1) proportion of patients over 24 months old at initial dose, 2) proportion of patients treated outside the RSV season (before November or after April), and 3) proportion of patients exceeding treatment over 5 months. The length of therapy was estimated for the pharmacy claims assuming each patient to have one treatment, and the length was simply the sum of all the day's supply for their palivizumab claims for that year (pharmacy claims only). Where a patient had two claims on the same day to accommodate dosing, the claims were counted as one and day's supply was also counted once.

Secondary outcomes included the change in palivizumab costs and utilization, which were quantified as a monthly per member per month (PMPM) value. Costs were defined as the paid amount per claim and do not include any subsequent manufacturer rebate. Utilization was defined as the number of claims paid. Finally, the database was queried for the proportion of patients with a hospital or emergency department claim associated with active RSV infection (ICD-9 = 079.6) from the time of the index event and six months following the index event.

Results:

In the control group, 89 patients received palivizumab, with 84 accessing via FFS pharmacy claims and 5 via FFS professional claims. In the study group, 28 patients encountered the PA intervention, 12 (42.9%) had a PA approved, 1 (3.6%) did not submit a PA request, but received palivizumab, and 15 (53.6%) did not submit a PA nor receive palivizumab (see Table 1). There were no PA denials. Demographics were similar for the control and study group (see Table 1).

Table 1. Demographics*

		Control		Study Group							
				Total Study		*PA Approved*		*No PA w/ Drug*		*No PA, No Drug*	
Total	**n=**	**89**	**(%)**	**28**	**(%)**	**12**	**(%)**	**1**	**(%)**	**15**	**(%)**
Age in Months											
	Mean (months)	8.2		8.3		7.3		2		9.5	
	Range	1-44		1-22		1-18		2		4-22	
	>24	2	2.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	>12 and ≤ 24	20	22.5%	8	28.6%	3	25.0%	0	0.0%	5	33.3%
	>6 and ≤ 12	16	18.0%	6	21.4%	4	33.3%	0	0.0%	2	13.3%
	≤ 6	51	57.3%	14	50.0%	5	41.7%	1	100.0%	8	53.3%
Female		44	49.4%	12	42.9%	3	25.0%	0	0.0%	9	60.0%
Non-White		24	27.0%	7	25.0%	3	25.0%	1	100.0%	3	20.0%

*Note: Age shown is age in months as of first palivizumab claim

The control group had a greater proportion of patients meeting the criteria with <28 weeks gestation (11.2%) compared to the study group (3.6%). All other co-morbidities were similar at baseline (see Table 2). There were 15 patients that did not submit a PA and did not receive treatment. Of particular interest were the 7 patients in this group who had qualifying co-morbidities: 5 patients had patent ductus arteriosus (PDA), which puts them in group B, 2 were 31-32 weeks gestation, which puts them in group E and 1 had 25-26 weeks of gestation which puts them in group C.

Table 2. Co-morbidities – ICD9 present from date of birth to 6 months after Index Claim (age is age at index claim)*

Criteria Group	Age in months	Diagnosis (ICD9 code) n=	Control		Study Group							
					Total Study		*PA Approved*		*No PA w/ Drug*		*No PA, No Drug*	
			89	(%)	28	(%)	1	(%)	1	(%)	1	(%)
Group A or B	**<24**	**CHD or CLD** (746xx, 747xx, 748xx)	29	32.6%	10	35.7%	5	41.7%	0	0.0%	5	33.3%
Group C	**<12**	**<28 wks gestation** (76521, 76522, 76523, 76524)	10	11.2%	1	3.6%	0	0.0%	0	0.0%	1	6.7%
Group D	**<12**	**Neuromuscular diagnosis** (358xx)	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Group E	**< 6**	**29 to ≤32 wks gestation** (76525 or 76526)	8	9.0%	2	7.1%	0	0.0%	0	0.0%	2	13.3%
Group F	**<3**	**33 to 34 wks gestation** (76527 or 76528)	4	4.5%	0	0.0%	1	0.0%	0	0.0%	0	0.0%
None of the above			42	47.2%	16	57.1%	7	58.3%	1	100.0%	8	53.3%
Any of the above			47	52.8%	12	42.9%	5	41.7%	0	0.0%	7	46.7%

No patients over the age of 24 months received initial treatment with palivizumab in the study group vs. 2 (2.2%) in the control group (see Table 3). Similarly, patients did not receive drug therapy outside the RSV season in the study group compared to 13 (15.5%) before November and 7 (8.3%) after April in the control group (see Table 3). Furthermore, there were no patients receiving treatment for longer than 5 months in the study group vs. 14 patients (16.7%) in the control group (see Table 3).

Table 3. Primary Outcomes

Outcome	**Control n= 89 (%)**		**Total Study n=28 (%)**	
Patient > 24 months old	2	2.2%	0	0.0%
	n=84* (%)		**n=12* (%)**	
Claims before November	13	15.5%	0	0%
Claims after April	7	8.3%	0	0%
Therapy > 5 months	14	16.7%	0	0%
*pharmacy claims only				

Secondary outcomes included utilization, costs, and hospitalizations. There was decreased utilization PMPM and cost PMPM (see Figure 4 and 5) in the study group. The average seasonal PMPM decreased from $2.03 in control group to $1.31 in study group (see Figure 5). This is an estimated $105,000 per year cost avoidance. No patients in the control or the study group were hospitalized or had emergency department visits within 6 months of the index claim.

Figure 4. Palivizumab Utilization July 2011 – June 2013

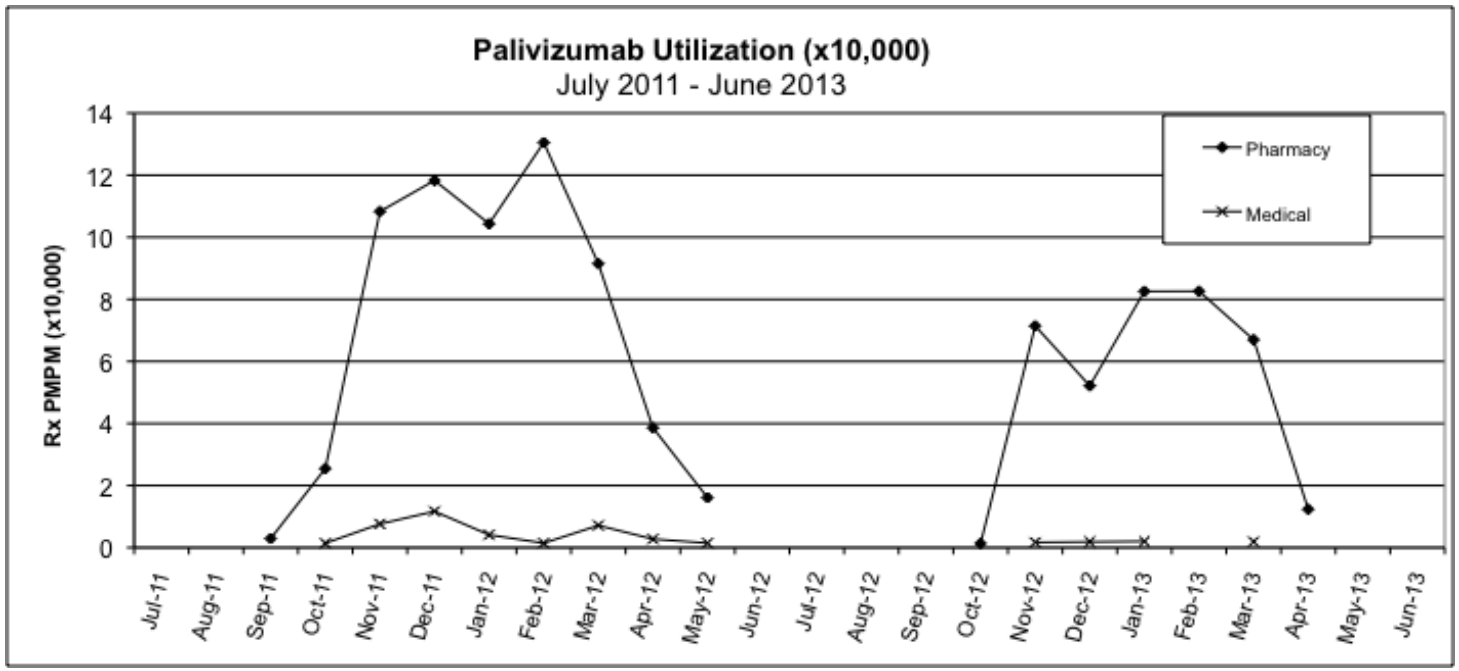
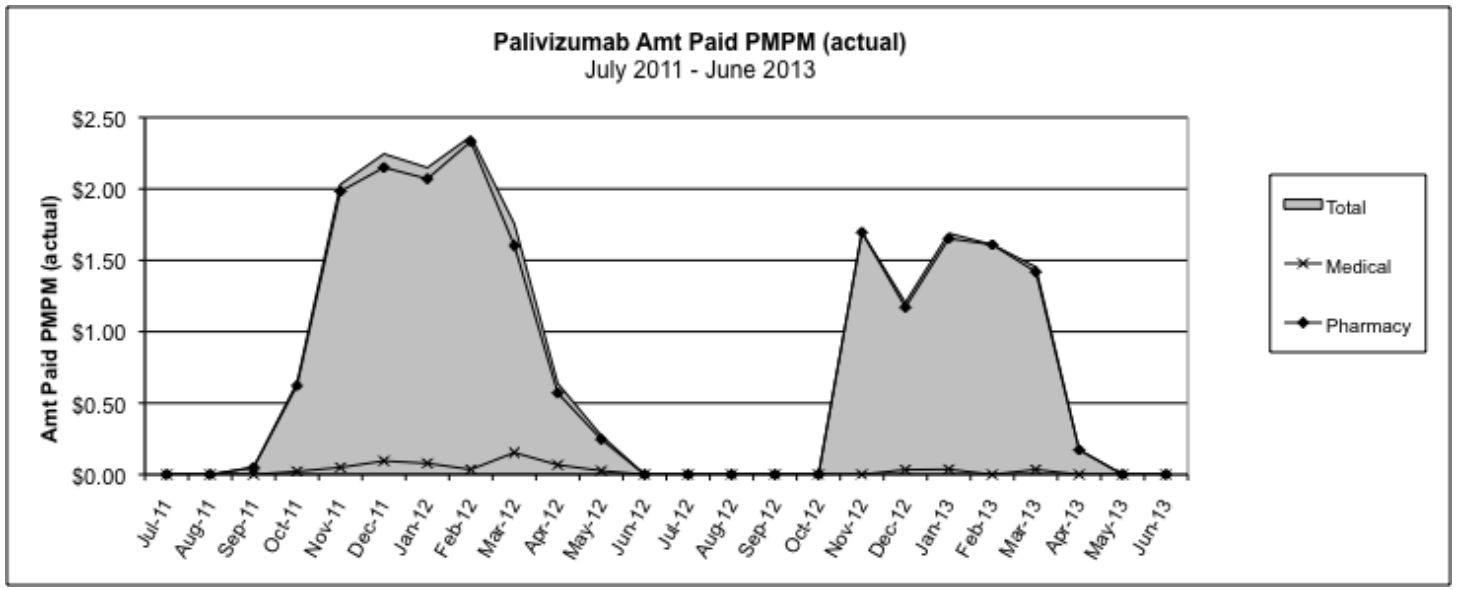


Figure 5. Palivizumab Costs July 2011 – June 2013



Discussion:

In this observational study, all of the primary outcomes were reduced to zero in the study group. The PA eliminated use of palivizumab outside of the established criteria, which correlated with decreased utilization and cost.

The results are similar to a retrospective study conducted by SelectHealth plans, which incorporated data from three RSV seasons from 2005-2008 to evaluate implementation of PA criteria for palivizumab.[12] This 500,000-member health plan used the 2006 AAP guideline to develop prior authorization criteria. Results suggested significant drug cost avoidance without an increase in the cost or incidence of ER visits or inpatient hospitalizations associated with RSV infections.

There were no hospitalizations or emergency room visits within 6 months of index claim. Prior authorizations can create a barrier to treatment due to administrative burden, which may be reflected by patients with qualifying co-morbidities not receiving treatment. Eight patients with qualifying co-morbidities did not request a PA or receive drug. Five individuals had a diagnostic code of PDA, which is group B. Group B also must have one of

the following qualifiers: receiving treatment for congestive heart failure, moderate to severe pulmonary hypertension, or cyanotic heart disease. It is possible the patients did not have one of these qualifiers but this information could not be captured by ICD-9 codes. According to the AAP, palivizumab is indicated for children who are <24 months of age with hemodynamically significant cyanotic or acyanotic CHD.[3] This definition is further classified into groups that are not at increased risk of RSV. PDA is categorized as hemodynamically insignificant heart disease, and therefore does not warrant immunoprophylaxis.[3] One patient was found with a medical diagnosis of "acute bronchiolitis due to RSV." This patient was a premature twin, in which both twins did not receive palivizumab despite having qualifying co-morbidities and were 5 months at the start of RSV season. Despite likely qualifying for immunoprophylaxis, these 3 patients had no subsequent hospital or emergency encounters.

This study is limited because it is observational and a small, disproportional sample. Selection bias is minimized by including patients in the study group who encountered the PA request rather than only patients with paid claims. Administrative claim studies are prone to follow-up bias which is a primary concern in this study. More than 90% of professional claims are submitted within 6 months of the service date. Thus patients with index events after January 2013 may have incomplete follow-up that could affect the number of hospitalizations and emergency encounters in the study group. Additional limitations to retrospective claim data are the chance for miscoding and the inability to define all criteria from the claims. For example, group F, which included patients <90 days at the start of the RSV season, gestational age of $\leq$32-34 weeks and 6 days, and at least one of the following risk factors: daycare attendance or siblings <5 years old, was not included as a primary outcome because no specific ICD-9 correlated to this group. This may account for patients who did not fit any of the pre-specified diagnostic descriptions, but had an approved PA. Finally, prior authorizations often influence patients to pay cash for treatment. However, this is a Medicaid population and palivizumab is a high cost drug so this is unlikely.

In conclusion, the palivizumab PA policy was associated with prescribing patterns that conformed to the desired criteria. The policy reduced to zero the primary outcomes of: proportion of patients over 24 months old at initial dose, proportion of patients treated outside the RSV season (before November or after April), and proportion of patients treated over 5 months. This was reflected in decreased utilization PMPM and decreased cost PMPM with an estimated gross cost avoidance of $105,000 in the last season. It did not result in increased hospitalizations and emergency room visits during 2012-2013 but there is a potential for follow-up bias in the study group.

Recommendations:

- **Continue the palivizumab PA for the 2013-2014 RSV season with no adjustments.**
- **Follow-up study needed in December or January to ensure safety indicators remain acceptable.**

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