PHARMACEUTICAL INNOVATION AND INFANT HEALTH:
PALIVIZUMAB AND RSV IN CALIFORNIA

BY

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Abstract

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The respiratory syncytial virus (RSV) is the leading cause of bronchiolitis and other lower respiratory diseases in infants and is also the foremost cause of hospitalizations of infants younger than one year of age. In 1998 palivizumab was approved, a drug designed to provide passive immunity against the virus for infants who have risk factors making them especially susceptible to severe RSV infections. Although the drug can never increase the likelihood of a severe RSV infection, infants who are born with well developed respiratory and immune systems receive no additional benefit from the drug, and because of the high price of the drug, with a full treatment regimen costing over $5,000 per infant, the American Academy of Pediatrics (AAP) releases policy statements outlining which risk factors should be considered when determining if an infant will benefit from the application of palivizumab.

This analysis uses the California Linked Birth and Inpatient Database to identify infants who are at risk for a severe RSV infection and who will benefit from the use of palivizumab, and examines subsequent admission records for the presence of RSV admissions. The empirical models used are based on the difference-in-differences framework and rely on the identification of specific risk factors that are present at birth.

It is found that there were likely minimal improvements of infant health outcomes immediately after the introduction of the drug, although in 2002 and thereafter there are reductions in the RSV admission rate that can be attributed to the use of palivizumab. The results also show that there were little if any reductions in inpatient charges. Analysis is also conducted to establish how total RSV related spending, which includes both inpatient charges associated with RSV admissions and spending on palivizumab, varies with compliance rates. It is shown that high compliance rates result in utility maximizing outcomes when AAP guidelines are closely followed.

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Table of Contents

List of Tables

PHARMACEUTICAL INNOVATION AND INFANT HEALTH: PALIVIZUMAB AND RSV IN CALIFORNIA

List of Figures

PHARMACEUTICAL INNOVATION AND INFANT HEALTH: PALIVIZUMAB AND RSV IN CALIFORNIA

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1 Introduction

1.1 Motivation

Access to new medical technologies is both a blessing and a curse on the American health care market. The utilization of these high cost medical technologies is expected to improve health outcomes, but it is often the case that older and less expensive technologies lead to very similar health outcomes but at a fraction of the cost of their modern substitutes (CBO, 2008). Relative to other developed nations the US has much higher per capita health spending but outcomes are not necessarily improved (Reinhardt et al., 2004). One aspect of this apparent conundrum is the potential for inefficient allocation of this expensive medical technology, to the point where the marginal health benefits gained from these new technologies are much smaller than the marginal costs that are spent providing them.

This research will study the effectiveness of a single drug, palivizumab, and how the drug's availability has potentially improved infant health outcomes in a real-world, non-clinical setting among a large population. A single drug designed for infants does not represent all of the economic issues occurring the US health care market, but this single drug does represent a microcosm in which many of the issues at play in the ongoing health care debate are present: A high priced drug is designed to protect infants from a very prevalent and potentially severe condition; there is no consensus as to which infants should receive the drug as it benefits some more than others; parents want the best care for their children; doctors want to improve patients' health; and pharmaceutical companies are expected to behave as rational, profit maximizing firms.

1.2 Background

The respiratory syncytial virus (RSV) is the leading cause of bronchiolitis and other lower respiratory diseases among American infants (Welliver, 2003). By two years of age nearly all children will have been infected with the virus, with most of these infections presenting themselves with relatively minor symptoms similar to the common cold, such as nasal congestion or a cough (Glezen et al., 1986). However, it is not uncommon for RSV infections among infants to be severe enough to require a hospitalization – in fact RSV is the leading cause of hospitalization for infants in the US (Joffe et al., 1999; Boyce et al., 2000). Each year the virus is responsible for approximately 120,000 hospitalizations of young children nationwide, most of whom are in their first year of life (Leader and Kohlhase, 2003). These RSV related hospitalizations represent about 2.5% of all newborn children, and nearly a quarter of the total number of all non-birth inpatient admissions to infants under one year old (Hall et al., 2009). The RSV mortality rate is rather low in the US, with around 350 infant deaths per year attributed to the virus (Shay et al., 2001).

The estimated costs of infant RSV hospitalizations nationwide totals nearly $400 million per year (Paramore et al., 2004). Based on data from the California Linked Birth and Inpatient Database, the average cost of an RSV admission in California is about $17,000 for an otherwise healthy infant, and averages over $56,000 for infants with underlying risk factors. Infants who are born with underdeveloped lungs or underdeveloped immune systems are at an especially high risk for a severe RSV infection that could result in an inpatient admission. Because the respiratory and immune systems are not fully developed until late in the pregnancy, infants born prematurely, usually defined as before 37 weeks gestation, are considered to be at a relatively higher risk for a severe RSV infection compared to infants born after a full-term pregnancy (Glezen et al., 1986).

In September of 1998 palivizumab was introduced (brand name Synagis®, made by MedImmune, now a subsidiary of AstraZeneca) and is designed to provide high risk infants with increased passive immunity from RSV, thereby lowering the possibility of a severe RSV infection, and hence decreasing the likelihood of an RSV related hospitalization. It is the first widely available, easily administered agent designed to protect vulnerable infants from RSV infections.[1] Palivizumab is dosed to infants in the form of monthly intramuscular injections during RSV season, which in California typically runs from late October to early March (MMWR, 2008). A full regimen of this drug consists of five doses over the course of the RSV season, and each dose is priced at about $1,050 based on pharmacy data from Medi-Cal, the public insurance program for children in California. In double-blind, placebo-controlled trials in clinical settings, palivizumab is shown to reduce RSV related hospitalizations by nearly 50% among infants who are most at risk for a severe infection, namely infants younger than 12 months of age at the start of RSV season who are born at or before 28 weeks gestation, those with chronic lung disease, or those with congenital heart disease (AAP, 1998; Zempsky and Schechter, 1999).[2]

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[1] Prior to the approval of palivizumab, RSV-IVIG (brand name RespiGam®, also made by MedImmune) was approved in 1996 as a prophylactic agent to be used by infants who are at a high risk for a severe RSV infection. However, this drug proved unpopular because it has to be administered via intravenous injections, which are difficult and time consuming in infants. This drug had limited success, and was practically out of use when palivizumab, an easier to administer agent, was approved a few years later. Figure 1 shows that RSV-IGIV experienced little success in California.

[2] Chronic lung disease is a condition often present in premature infants, in which the air sacks in the lungs are underdeveloped and when surfactant, an agent that keeps airways open, is lacking. Congenital heart

If consumers of health care did not consider costs, all infants would receive palivizumab since under no circumstances will the drug increase the likelihood or severity of an RSV infection. But due to the high price of the drug and the lack of improved RSV outcomes among relatively healthy infants, the American Academy of Pediatrics (AAP) releases prescription guidelines designed to be followed by doctors in determining to which infants the drug should be administered, based on the expected relative benefits of the drug. The first set of guidelines were published in November 1998 to coincide with the release of the drug, and revisions were made in December 2003 and again in July 2009 (AAP, 1998; 2003; 2009). Similar guidelines are also issued by the California Department of Health Services which are to be followed by doctors participating in Medi-Cal (CDHS, 2003; 2004; 2005; 2006; 2009). A detailed definition of all of these guidelines is shown in Table 1. Both sets of guidelines are similar for the majority of risk factors but are not identical, so to be consistent throughout this analysis, only the AAP guidelines are used to identify infants who are eligible for palivizumab.

The combination of the high morbidity of RSV, the high price of palivizumab, and the substantial costs associated with treating infants infected with the virus results in a considerable controversy among policy makers, doctors, parents, and the maker of palivizumab about the efficient allocation of the drug. There is no cure for an RSV infection, and only supportive therapy like supplemental oxygen or the use of the medication albuterol can be used to help an ill infant regain their health (Dobson et al., 1998; Welliver, 2010). So the preemptive application of palivizumab is currently the only method to ease the burden of RSV infections. The Wall Street Journal described the

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disease is a condition that affects about 8 of 1,000 births, in which components of the heart are malformed, resulting in difficulties circulating blood throughout the body.

controversy succinctly in April 2008 by saying, "…pediatric experts are wrestling with an emotionally fraught issue: whether to let some babies at risk for a potentially serious respiratory virus take their chances with the disease or to preventatively administer an expensive drug that may or may not work" (Landro, 2008).

Although communication between doctors and parents of high risk children may be the most important determinant of the appropriate and timely application of palivizumab at the individual level, the guidelines published by the American Academy of Pediatrics that outline which risk factors qualify an infant for palivizumab treatment likely play the most important role from a public policy viewpoint. After the American Academy of Pediatrics changed these guidelines in 2009, further restricting the number of doses that are recommended for infants born from 33 to 35 weeks gestation, AstraZeneca saw its revenue from palivizumab drop 31% from the fourth quarter of 2008 to the fourth quarter of 2009, from $385 million to $263 million – this equated to a 5% drop in total yearly revenue for the company (AstraZeneca, 2010). So not only does the allocation of palivizumab have effects on infant health outcomes, it is also clear that the drug's maker has a financial motivation in promoting the benefits and usage of palivizumab to as many infants as possible (recall that there are no situations in which usage of the drug can result in negative health effects). These financial motivations are exemplified as studies that are funded by MedImmune often find that palivizumab produces large improvements in health outcomes and overall cost savings for all risk groups (Lofland et al., 2000; Feltes et al., 2003), while similar studies that are independently funded find that infants with less severe risk factors often experience minimal health benefits from using the drug accompanied by higher total RSV related costs (Joffe et al., 1999; Marchetti et al., 1999; Stevens et al., 2000).

Given the abundant prevalence of RSV, there has been extensive research conducted to determine which risk factors make infants most vulnerable to severe RSV infections (Stevens et al., 2000; Hall, 2001; Shay et al., 2001; Mai et al., 2003; Hall et al., 2009). There has been less research studying the economic burden associated with RSV infections, including the cost effectiveness of palivizumab in both preventing hospitalizations and reducing the costs and length of stay of hospitalizations (Joffe et al., 1999; Marchetti et al., 1999; Lofland et al., 2000; Schrand et al., 2001; Kamal-Bahl et al., 2002; Romero, 2003; Elhassan et al., 2006), and there have only been three studies to my knowledge that have been conducted in so called "real-world" situations related to the use of palivizumab in improving RSV outcomes among free living populations (Shireman and Braman, 2002; Wegner et al., 2004; Mitchell et al., 2006). A shortcoming of the previous research on cost effectiveness and real-world outcomes is a lack of data sources that provide both large and diverse samples that span several years and a reliable way to identify which children who are hospitalized with an RSV infection have also been previously diagnosed with risk factors that likely contributed to the severity of their infection.

The intention of this thesis is to examine the effectiveness of the drug over time in improving RSV related outcomes in a free living and diverse population – namely all infants in California born from July 1997 to June 2005. This paper focuses on the *effectiveness* of this drug, and not its *efficacy*. The distinction between the two are important: The efficacy of a drug represents how well it performs in improving outcomes in an ideal clinical setting, when the proper dosage recommendations are closely followed, and when nearly full compliance is achieved.[3] In order to be approved by the FDA, all drugs need to go through double-blind, placebo-controlled clinical trials to display their efficacy and safety. The FDA used the following formula in establishing what they call "Vaccine Efficacy" in the clinical trials of palivizumab (Neeman, 1998):

$$\begin{aligned} VE(\%) &= 100 \cdot \left(1 - \frac{P(RSVHosp \mid Palivizumab)}{P(RSVHosp \mid Placebo)} \right) \\ &= 100 \cdot (1 - \text{Relative Risk}) \end{aligned}$$

The relative risk is calculated simply as the RSV admission rate among s who are treated with palivizumab divided by the RSV admission rate among infants who receive the placebo. This formula assumes that all infants have equal environmental exposure to RSV, that infants assigned to the palivizumab group fully comply with the prescription regimen, and that infants assigned to the placebo group do not receive any doses of palivizumab.

In the initial trial, the placebo group had an RSV hospitalization rate of 12% while the group treated with palivizumab had a RSV related hospitalization rate of 5%. Hence the efficacy of palivizumab was shown to be 58%, i.e. $58\% = 100 \cdot \left(1 - \frac{0.05}{0.12} \right)$.

These clinical trials were conducted under "ideal" settings, with a population of infants who were born before 28 weeks gestation or who were born with chronic lung disease. Along with this well-selected sample, the researchers could also assure that those assigned to the treatment group received all five doses of the drug; about 95% of the infants involved in the trial were fully compliant. These studies show that

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[3] Compliance in this context means how well patients follow the doctor's orders. In the case of palivizumab, "full compliance" means that all five prescribed doses are received in a given RSV season, while "less than full compliance" means that an infant should have received five doses, but received fewer.

palivizumab is indeed an efficacious agent under optimal circumstances (AAP, 1998; Zempsky and Schechter, 1999).

Effectiveness, on the other hand, is how well the drug performs outside strictly controlled clinical settings, in so called "usual care" circumstances. The effectiveness of a drug varies with usage patterns, including compliance, along with the types of underlying conditions present in children who receive the drug (Bombardier and Maetzel, 1999). In the real-world case of palivizumab and RSV, many infants who have risk factors making them eligible for the drug do not receive it, and it is likely that some infants who may not experience large benefits from palivizumab receive the drug despite their lack of risk factors. My research will focus on the effectiveness of the drug in a free living population by attempting to answer the following question: Given the introduction and availability of palivizumab, and the published prescription guidelines, how have RSV related health outcomes of infants belonging to various risk groups changed over time in California?

1.3 Data

This research takes advantage of a unique data set, the California Linked Birth and Inpatient Database, which links birth records to subsequent re-hospitalization records at the individual level by using Social Security numbers.[4] Both the birth and inpatient records are composed of detailed and comprehensive medical data including gestational age at birth and International Classification of Diseases, Clinical Modification (ICD-9) codes specifying any medical conditions diagnosed during the hospitalization, as well as demographic information about the child, mother, and father. The linkage between these two data sets enables the complete hospitalization history of individuals to be tracked

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[4] Social security numbers are scrambled when the data are released to researchers.

from birth through the first year of life. This data set includes every birth and infant hospitalization in California from January 1997 through December 2005. Because most RSV infections occur during the winter months, I define an “RSV year” to run from July to June; for example, the RSV year for 1997 runs from July 1997 to June 1998, while the RSV year for 2004 is defined as July 2004 to June 2005. Because of this, the subset of useable observations in this data set are births from July 1997 to June 2005, of which there are approximately 4.1 million and 108,000 subsequent RSV related admissions.

A major advantage of these linked data compared to standard non-linked hospitalization discharge data is the ability to identify risk factors at birth, including gestational age by week and the presence of chronic lung disease, and to then examine these at risk births for the presence of an RSV related diagnosis in future inpatient admissions. Studies that rely on unlinked admission data inherently lack the means to identify the underlying risk factors that are present at birth making the infant especially prone to an RSV related hospitalization, as unlinked data can only provide information on the health of an infant at a single point in time. These linked data provide a complete inpatient history for each child in California from birth, and continue through their first year of life. Table 2 shows the number of births by year and gestational age group, while Table 3 shows the number and rate of RSV related hospitalizations by gestational age.

This analysis will concentrate mainly on two outcomes, RSV admissions and inpatient charges. Admissions are important from a public health point of view as the application of palivizumab is expected to reduce the burden of RSV infections on infant health, and although palivizumab is known to be effective in clinical settings, its effectiveness among free living populations is not clear.

When inpatient charges are used as the outcome, the measure will be based on inpatient charges per infant, and not inpatient charges per admission. This means that infants who are not admitted with RSV will record inpatient charges equal to $0. Because more severe RSV infections typically result in both a higher probability of being admitted and higher inpatient charges upon an admission (Kamal-Bahl et al., 2002) this measurement will be able to account for the fact that as palivizumab is applied, the severity of RSV infections will decline, which is expected to result in both fewer admissions and lower charges upon an admission. I will not attempt to study how the availability of palivizumab has altered charges conditional on an admission as there is an anticipated endogeneity that will make the mechanism that causes charges to vary over time difficult to identify. Namely, as palivizumab protects infants from RSV, it should also simultaneously decrease the hospitalization rate and reduce inpatient spending. However, those infants who would have been hospitalized without palivizumab but remained healthy because of the drug will be excluded from the inpatient group, when they should be included as inpatients but with charges equal to $0. This endogeneity problem is similar to the Heckman selection model (Heckman, 1979). By setting charges equal to $0 for infants who are not admitted, all observations will have inpatient charge data, and the estimates can be interpreted as changes in inpatient charges per infant.

Because it could be the case that any changes in RSV admission rates or charges were caused by factors that affected all infant health outcomes, not just RSV, it is necessary to test for this by comparing the results found using RSV outcomes as the dependant variable to results that instead use outcomes based on a set of control conditions as the dependant variable. These control conditions are not expected to be affected by exogenous changes in medical technology yet they could still be affected by factors that may alter infant outcomes systematically. If RSV outcomes are found to be improved while the outcomes associated with the control conditions are not improved, it can be argued that there were no systematic changes among all infant health outcomes and that palivizumab was responsible for the improvements. However, if both RSV outcomes and outcomes associated with the control conditions are shown to improve, the reason for these improvements is ambiguous, as there may have been unobserved changes occurring that affected infant outcomes across all conditions. The use of outcomes based on control conditions will be discussed in more detail below.

This data set also contains demographic and administrative variables, including parents' and child's race and ethnicity, parents' age at birth, parents' education level, ZIP code of residence, expected payer (i.e. type of insurance), infant's sex, and parity (birth order). Being able to determine if an infant is male or the first born by a mother are especially important, as newborn boys tend to have slightly less developed respiratory systems than girls (Martin et al., 2006), and because infants who are not the first born tend to have greater exposure to RSV because their older siblings frequently attend school or daycare, where the virus thrives (Hall, 2001; Leader and Kohlhase, 2003). All of these variables will be included in the regression models and are summarized in Table 4.

1.4 Efficacy versus effectiveness

The distinction between the efficacy and effectiveness of palivizumab is crucial to understanding the goals of this research. I do not aim to show that palivizumab is an efficacious agent with respect to improving RSV related outcomes. As stated earlier, there have been double-blind, placebo-controlled trials that show that palivizumab is efficacious when used as directed. There has been little research examining how the availability of palivizumab has improved RSV outcomes among the entirety of the targeted population, namely infants with risk factors making them a high risk for an RSV related hospitalization. By focusing on the population wide effectiveness of palivizumab, this research will help to determine if the drug, which has been proven effective in clinical settings, is being used appropriately under usual care conditions to produce improvements in RSV related outcomes among a large population. It is possible that because of low levels of compliance outcomes may not improve as much as the clinical trials suggest they might.

Described in the framework of analyzing treatment effects, efficacy is a “treatment on the treated” measure, while effectiveness is an “intention to treat” measure. Treatment on the treated measures examine how outcomes vary between groups of infants who are eligible for the drug and receive it (those who are treated) compared to those who are eligible for the drug but do not receive it (the untreated). In the context of a large population, such as that of all newborns in California over the period of 10 years in which upwards of 550,000 infants are eligible for the drug, several problems occur when attempting to make treatment on the treated measurements. The first difficulty is that no data source exists that adequately identifies which infants are prescribed palivizumab and which infants are not. This lack of prescription data is even more problematic given that even if data existed on who was prescribed the drug, it is even less likely for a data source to exist with records identifying which infants were physically treated with the drug. It is often the case that compliance rates in usual care settings are well below those in clinical trials (Atella et al., 2006; Gandjour, 2010), and this is even more likely to occur in the case of palivizumab in which five doses need to be administered monthly from November through March (Diehl et al., 2010) to maintain the adequate levels of passive immunity required to protect infants from severe RSV infections.

One of the few studies to attempt to estimate palivizumab compliance is by Diehl et al. (2010) and based in Pennsylvania with 245 useable observations. They show that among infants younger than two years who were identified as being pre-authorized by either a private or public insurer to receive palivizumab and who were administered at least one dose, less than 30% were fully compliant in receiving the remaining recommended doses throughout the RSV season. This does not account for infants who were medically eligible for palivizumab but who were never pre-authorized by their insurer. Diehl et al. also find that total RSV related costs, defined as the costs of RSV related hospitalizations and the price of palivizumab, are slightly less for infants who are fully complaint compared to infants who receive at least one dose but who are less than fully compliant. Given that the price of a single dose of palivizumab is over $1,000, this finding suggests that full compliance may play an important role in minimizing the total costs associated with RSV among high risk infants. To my knowledge there are no other applicable estimates of palivizumab compliance rates in the literature.

Another potential problem with a treatment on the treated measure is that although observable differences between the treated and untreated groups can be controlled for, there exists the possibility that the two groups are somehow inherently different from each other at an unobservable level and selection biases are present. Even controlling for the presence of underlying medical conditions, race and ethnicity, parental age and education, geographic location, and any other factors that may determine RSV infection status, there is still the possibility that parents who ensure their infants are treated with palivizumab are somehow different from parents who do not have their infants treated. Perhaps parents who seek palivizumab treatments for their children also smoke less, and lead "healthier lives" in general compared to the non-treated group. So regardless of the introduction of palivizumab, infants born to these more health conscious parents would likely have better RSV related outcomes than the comparison group. The potential for these selection biases between the treated and untreated groups could potentially lead to overestimations of the true effectiveness of palivizumab in reducing RSV related admissions.

Using an intention to treat measure bypasses some of these shortcomings. Although population wide data sources cannot identify which infants are prescribed and receive palivizumab, the California Linked Birth and Inpatient Database does identify which infants have risk factors making them eligible for palivizumab. Based on findings in clinical trials that estimate the efficacy of the drug under ideal circumstances, estimating RSV outcomes for a broad population of high risk infants will be constructive in determining how the real-world outcomes vary compared to outcomes that occur under full compliance and strict adherence to the prescription guidelines that were present in the clinical trials. It is almost certainly the case that there was not strict adherence to the prescription guidelines. Specifically, many infants who were eligible for palivizumab may have not received any doses, and among infants who did receive the drug compliance was not likely full. All of these deviations from the recommended prescription guidelines will lead to the population-based effectiveness of the drug varying from the clinically controlled efficacy of the drug.

1.5 Review of previous research

There have been a number of studies conducted that attempt to quantify the prevalence of RSV among the infant population in the US. These prevalence studies are based on either data abstracted from inpatient medical records or come from actual laboratory testing of cultures taken from patients that biologically identify the presence or absence of RSV. Both types of studies provide valuable information to medical practitioners and policy makers as to the prevalence of RSV but both types of studies also have potential shortcomings.

Abstracting data from medical records allows investigators easy access to broad and diverse infant populations over extended periods of time – having data from several periods is important as the duration and severity of an RSV season often varies from year to year (CDC, 2010). An imperfection of these studies is that the RSV infections are not usually verified by lab testing, but instead diagnosed by a doctor when symptoms are present and then the corresponding ICD-9 code is recorded on the patient's chart. This is in comparison to studies that explicitly biologically identify RSV infections through lab testing that provide more accurate data on the true presence of RSV. But these tests can be prohibitively expensive (Hall, 2001), and as such they do not usually span many years and the resulting samples are much smaller than those of samples composed of abstracted inpatient records.

One study that uses abstracted medical records was conducted by Boyce et al. (2000). Using data consisting of children less than three years old who were enrolled in the Tennessee Medicaid program from July 1, 1989 to June 30, 1993, Boyce and colleagues stratified infants by age and risk groups. Children were categorized into one of four age groups: 0 to < 6 months, 6 to < 12 months, 12 to < 24 months, and 24 to < 36 months. Within these age groups the following risk factors were (exclusively) identified: low risk, defined as otherwise healthy and born at full term; presence of chronic lung disease; presence of congenital heart disease; ≤ 28 weeks gestation; 29 to < 33 weeks gestation; 33 to < 36 weeks gestation; and other risk factors including various respiratory and pulmonary disorders along with immunodeficiencies.

A central finding of their study is that among infants with similar risk factors, those who are chronologically younger experience higher RSV infection rates. Among the "low risk" group, infants ages 0 to < 6 months have a hospitalization rate of 44.1 per 1,000, while the 6 to < 12 months old group has a rate of 15.0 per 1,000, the 12 to < 24 month old group have a rate of 3.7 per 1,000, and the 24 to < 36 month old group has a rate of 1.0 per 1,000. Infants with chronic lung disease are found to have a hospitalization rate (per 1,000) of 562.5 for the 0 to < 6 month old group, and 214.3 for the 6 to < 12 month old group. Infants with congenital heart disease have rates of 120.8 and 63.5, respectively for the same age groups. The results show that chronological age at the start of RSV season is likely a determinant of RSV hospitalization rates. This is because older infants, holding all else equal, have better developed lungs and immune systems at the onset of the RSV season making them less prone to severe RSV infections compared to younger infants.

Another noteworthy finding they present is that although premature birth status increases the hospitalization rate, the specific gestational age among premature births has only slight effects on the hospitalization rate. For infants under six months old, the admission rates per 1,000 births are 93.8 for the < 28 weeks gestation group, 81.8 for the 29 to < 33 weeks gestation group, and 79.8 for the 33 to < 36 weeks gestation group. The authors address this result by stating that it "may be explained partly by our use of mutually exclusive categories to define our high risk group. Thus children in our high prematurity categories had neither chronic lung disease nor [congenital heart disease]."

The preceding study is based on data collected from abstracted medical records, which as the following study will show, may result in a substantial underestimation of the true burden of RSV. Hall et al. (2009) use a sample collected for the New Vaccine Surveillance Network, part of the Centers for Disease Control. This sample consists of laboratory test results that determine the presence of RSV among children under the age of five in counties surrounding Rochester, Nashville, and Cincinnati from October 2000 through September 2005 during the RSV season of each year. Samples were collected from inpatient, outpatient, and emergency department settings. By sampling children in both inpatient and outpatient settings, and by biologically confirming RSV infections, regardless of the diagnosis recorded on the patients' records, this study has the ability to convey the true biological presence of RSV among a diverse population.

In total 5,121 children were enrolled who were diagnosed as having an acute respiratory infection which included at least one symptom of fever, cough, earache, nasal congestion, rhinorrhea, sore throat, or labored breathing. This represents 2,946 inpatients and 2,175 outpatients. The following table is reproduced from Hall et al. (2009), and shows tabulations for the subjects in their study:

	Hospitalized N=2,946		Outpatients N=2,175	
	RSV Positive N=564 (20%)	**RSV Negative** N=2,382 (80%)	**RSV Positive** N=355 (16%)	**RSV Negative** N=1,820 (84%)
Male	245 (43%)	1,045 (45%)	160 (45%)	856 (47%)
Female	319 (57%)	1,283 (55%)	195 (55%)	964 (53%)
Age in months				
0-5	328 (58%)	1,042 (46%)	88 (25%)	257 (14%)
6-11	97 (17%)	306 (13%)	85 (24%)	354 (19%)
12-23	99 (18%)	441 (19%)	75 (21%)	513 (28%)
24-59	40 (7%)	539 (23%)	107 (30%)	696 (38%)

Source: Partial reproduction of Table 1 in Hall et al., NEJM 2009

Twenty percent of the hospitalized sample were found to have an RSV infection, while 16% of outpatients had an RSV infection. As in the Boyce et al. study, Hall et al. also show that chronological age is an important determinant of RSV hospitalization rates. Among the infants hospitalized with RSV, 58% are under 6 months of age, those 6 to 11 months old and 12 to 23 months old represent 17% and 18%, respectively, of RSV inpatients, while those from 2 years to 5 years make up only 7% of RSV inpatients. This is compared to outpatients, where the distribution of RSV infections is relatively uniform across age groups. These results convey two facts about RSV infections: Among the outpatients we see that the virus is very common in children of all ages, while younger infants are prone to more severe infections, as shown by the age distribution of inpatients who are infected with the virus.

The previous studies both describe the prevalence of RSV in the infant population, and because of the high morbidity associated with the virus, its treatment and prevention are major public health concerns (Leader and Kohlhase, 2003).

In terms of intention to treat measurements, the most relevant effectiveness studies are those conducted outside of a clinical setting, in real-world situations under less controlled environments that better represent the actual usage patterns of palivizumab and subsequent RSV related outcomes under usual care conditions. One such study by Mitchell et al. (2006) took place in the province of Alberta, Canada. The Canadian public health care system is organized in such a way that different regions have some deal of autonomy in when to adopt new technologies as the standard practice. Mitchell et al. were able to take advantage of a natural experiment that came about when the health centers in Calgary decided to use palivizumab on infants born at less than 32 weeks gestation starting in the 1999-2000 RSV season, but health centers in Edmonton (just 170 miles away) did not adopt the use of palivizumab until the 2002-2003 RSV season. The basic premise of the authors' design is to use the difference-in-differences method in which infants in Calgary will be the "treatment" group, while those in Edmonton will be the "control" group, and in which 1995 to 1998 is the "pre" period and 1999 to 2002 is the "post" period. Note that this is an intention to treat study, as the authors only identify the "treated" group based on being born at an early gestation and living in Calgary after the policy was enacted. They do not know precisely which infants were given palivizumab and which were not.

These researchers found that there was a statistically significant drop in RSV related hospitalizations among at risk infants in Calgary from 7.3% in the pre period to 3.0% in the post period, compared to a statistically insignificant increase in RSV related hospitalizations in Edmonton from 5.0% in the pre period to 7.1% in the post period. Among low risk infants, who did not receive palivizumab in either city, there were no significant changes in RSV hospitalization rates.

This Canada-based study gives evidence that palivizumab is effective in a real-world, usual care setting, however it is difficult for these results to be generalized to broader populations for several reasons. First, the groups compared are relatively socially and demographically homogenous, especially compared to the infants in a state as populous and diverse as California. Second, given that this study is based in Canada, it might be especially difficult to directly apply the results to the US simply because of the differences in the structure of the insurance markets. Canada has a national insurance plan, while infants in the US are enrolled in any mixture of public or private plans, as well as those who lack insurance altogether. Despite these potential limitations of the generalizability of the Mitchell et al. study to the American infant population, it is an excellent example of how a natural experiment can be analyzed with difference-in-differences regressions to examine how the introduction and application of palivizumab may have improved infant health outcomes relative to the absence of the drug.

A major contribution of Mitchell et al. is their justification and implementation of an intention to treat measurement. Because their sample includes all eligible infants, regardless of their actual treatment status with palivizumab, their results represent an intention to treat measurement. They say:

> The inclusion of the population of infants who should have been immunized but were not, highlights the important differences between [a randomized controlled trial] and an observational study. If this had been [a randomized controlled trial], infants not recruited into the study would not have been included in the analysis and therefore their RSV admissions would have been excluded. Such use of inclusion/exclusion criteria and the potential for selection bias into the study is important for the conclusions about efficacy required from [a randomized controlled trial].

> However, in an observational, population-based study all data must be included to justify conclusions about effectiveness.

Although the next two studies are also based on free living population, they are not constructed as intention to treat studies. As I will discuss, their results may be subject to selection biases.

One of these studies that uses a free living population under usual care conditions is a retrospective cohort analysis by Shireman and Braman (2002) that uses data collected during the 1999-2000 RSV season from participants in the Kansas Medicaid program. The infants included in this sample are those born prematurely, defined as ≤ 37 weeks gestation, or with congenital heart disease, or with chronic lung disease and were classified into one of three age groups who are either born during the RSV season, 0 to < 6 months of age at the start of RSV season, or 6 to 10 months of age at the start of RSV season. Along with chronological age and risk factors, the authors were able to identify RSV admission status, demographic variables, and the number of doses of palivizumab prescribed from data obtained via the Kansas Medicaid Drug Utilization Review Program. The total sample contained 1,506 infants, 137 of whom were treated, and of the treated infants 46 were fully compliant with their prescribed palivizumab regimen.

In comparing the treated and untreated infants, the authors find that the treated sample tend to be chronologically younger and have more severe risk factors on average. In an attempt to avoid selection biases present between the treated and untreated groups, the authors use propensity scores to match the 137 treated infants to 137 similar but untreated infants. Although these matches result in similar observed characteristics between the treated and control groups, it is not immediately clear if unobserved selection biases are corrected, as it may be the case that even when controlling for identifiable health and demographic conditions that infants who are treated with palivizumab have unobserved characteristics that may have led to improved outcomes compared to the control group regardless of palivizumab treatment. Examples of unobserved characteristics that might lead to biases are parental education and smoking habits, birth order, or parental attitude towards the importance and knowledge of RSV prophylaxis, none of which are identified by the authors.

The authors find that infants treated with palivizumab are 0.47 times as likely to be hospitalized for RSV, but this estimate is not statistically significant. Conditional on an RSV related hospitalization, differences between costs and length of stay were not statistically significant between groups. Among all infants, not conditional on an RSV admission, differences in length of stay are not significant, while infants in the treated group experienced RSV hospitalization costs that were $703 lower than their control group counterparts, a result that is also not statistically significant. Given that the palivizumab costs per patient are found to be $4,687 in this study, they conclude that the costs of palivizumab are not offset by reductions in hospitalization costs.

A study by Wegner et al. (2004) uses data from the North Carolina Medicaid program collected during the 2002-2003 RSV season to analyze the cost effectiveness of palivizumab in preventing RSV. This study limits the sample to infants born between 32 and 35 weeks gestation and uses the Anderson model of access to health care services (Andersen et al., 1983) to identify covariates that may affect the probability of receiving palivizumab. The Anderson model defines three dimensions that may affect access to care which are based on risk status, enabling variables, and predisposition. In this case, risk status is based on the American Academy of Pediatric palivizumab prescription guidelines; enabling variables are those which make it more or less burdensome to receive health care, such as insurance status and income; and predisposition variables include characteristics such as sex, race, age, education, and risk aversion which Anderson et al. claim shape individual's determination of the value of health.

Limiting their sample to infants born from 32 to 35 weeks gestation, and including controls for race, sex, mother's age, mother's education, distance from health care facility, siblings in school or day care, parental smoking habits, multiple birth status, gestational age, and birth weight, they include 367 infants, 185 of whom are in the treatment group having received at least one dose of palivizumab. Between the treated and control groups, the effects of most of these characteristics are not statistically different. However, the treated group did have a statistically higher percentage of white infants with 53.5% compared to 34.1% in the non-treated group, and the treated group also has a statistically lower percentage of black infants, with 36.8% compared to 51.6% in the non-treated group. Compared to the research by Shireman and Braman discussed earlier, this study based in North Carolina has less potential for biases resulting from selection into (or out of) the treatment group because of the wide variety of control variables used, especially education, smoking habits, and the presence of older siblings, however it has been often shown (Braveman et al., 2001; Nelson, 2002; Mechanic, 2005) that even controlling for a host of variables, racial disparities are still present in the case of infant health outcomes, which may be problematic given the racial composition of the treated and untreated groups used in this study by Wegner et al.

Controlling for all of the previously mentioned covariates and using OLS regressions, the authors find that the average RSV related costs for the group of infants treated with palivizumab was $4,634 more per infant compared to the non-treated group. When the logs of the cost data are used as the outcome, the results are similar, showing that infants in the treatment group experience average total RSV costs about seven times greater than that of the non-treated group. Both of these findings are statistically significant. Interestingly, the authors find that there are no statistically significant differences in the RSV hospitalization rate between the treated and untreated groups. This lack of difference in the hospitalization rate is most likely attributable to the gestational composition of the sample, with infants being born from 32 to 35 weeks gestation having relatively well developed lungs and immune systems compared to those of shorter gestations, and hence these infants have more natural immunity to RSV even without the application of palivizumab.

Both the Shireman and Braham study and the Wegner et al. study find that palivizumab does not appear to be cost effective in terms of reducing the total costs related to RSV. Both studies also relied on data sets that represented a very specific subgroup of infants for only a single year: premature infants and infants with chronic lung disease enrolled in Kansas Medicaid during the 1999-2000 RSV season, and infants born between 32 and 35 weeks gestation who were enrolled in North Carolina Medicaid during the 2002-2003 RSV season. The results found in these studies likely cannot be generalized, given that the samples consisted entirely of Medicaid patients, who may not be representative of the entire population. Generalizability of the results over time and geographic location is also a concern, because it has been shown than the year to year severity of RSV infections can vary substantially among at risk infants and the onset, peak, and decline of the RSV season also vary from one community to another even within relatively close geographic proximity (Meissner et al., 2004).

Along with the issues associated with the lack of generalizability, the treatment on the treated measurements that both studies used may easily be susceptible to parents selecting their children into the treated groups based on some unobservable characteristics that may alter RSV outcomes regardless of palivizumab treatment. Even considering that Wegner et al. control for characteristics that may be interpreted as proxies for indicators for higher demand for good health, such as smoking habits and education, it is very difficult to assure that health outcomes for both the treated and untreated infants would be identical in the absence of palivizumab, as some parents may have an inherently higher demand for good health than others, and as a result their children may always have better outcomes even if palivizumab was not available.

2 Difference-in-differences strategy

There will be two distinct types of analysis used to examine how the availability of palivizumab has affected RSV outcomes. The first will use difference-in-differences (DD) analysis to identify how the RSV inpatient rate and inpatient charges per infant have changed as palivizumab usage increased over time. This method is commonly used in evaluating changes in outcomes given the introduction of new policies. These DD models will attempt to answer questions related to how well palivizumab has performed in reducing the health burden of RSV on a large population under usual care conditions. The second type of analysis will be described in Section 4 and will estimate the total costs associated with RSV, including palivizumab spending, RSV inpatient costs, and will also examine the outcomes expected given various levels of palivizumab spending and compliance rates.

The DD analysis is based on the intention to treat framework, which measures outcomes based on the availability of the drug along with the eligibility status of infants, and not its actual physical usage. In essence, intention to treat measurements estimate the actual changes in outcomes for the population of infants who are eligible for the drug, while treatment on the treated measurements, and more specifically clinical trials, estimate the changes in outcomes based on the assumption of full compliance. As described earlier, it has been demonstrated by several placebo-controlled, double-blind clinical trials that palivizumab can reduce RSV hospitalization rates among premature infants by upwards of 50% with full compliance. RSV infections are the leading cause of infant hospitalizations, and this drug has the potential to improve health outcomes for tens of thousands of children each year. However, there are many reasons why the published efficacy rates may not reflect the true effectiveness of the drug in improving outcomes at the population level. A major factor of why efficacy and effectiveness vary is the lack of compliance to the prescription regimen. There exists a body of literature covering pediatric specific health conditions and medications showing that poor compliance rates lead to higher hospitalization rates as drugs are not taken in the appropriate fashion compared to infants who are fully compliant (Milgrom et al., 1996; Matsui, 1997). There is also evidence showing that poor compliance rates lead to overall higher health spending, as the additional costs incurred by inpatient stays and other medical costs that are precipitated by poor compliance are much greater than the “savings” achieved by not acquiring the recommended pharmaceuticals (Huskamp et al., 2003; Goldman et al., 2007).

Gandjour (2010) describes a model in which outcomes are dependent on both the compliance of the health care provider to recognize the appropriate course of treatment and to prescribe medications as necessary, as well as on the compliance of the individual in assuring that the prescribed regimen is completed as directed. Following a similar framework in the context of palivizumab, to maximize compliance and hence to maximize the population wide effectiveness of the drug, the health care provider must be aware of the availability and proven efficacy of palivizumab, as well recognizing the potential benefits an infant can enjoy given the presence of certain risk factors. Along with the need for a doctor to prescribe the drug based on risk factors present in the infant, compliance is also improved if the infant’s parents are aware of the risks associated with a severe RSV infection and the benefits timely palivizumab treatments can provide. Hence compliance rates are determined by both the doctor prescribing the drug when necessary and the parents ensuring that all necessary doses are received by their infant.

2.1 Identifying those eligible for palivizumab

The difference-in-differences measurements in this paper are based on the knowledge that palivizumab was introduced at a discrete point in time, that uptake of the drug has increased each year since its introduction, and that eligibility for the drug is determined by the presence of specific medical risk factors. Having a data set that allows for the identification of these risk factors, and hence an infant’s eligibility for the drug, and that also identifies subsequent RSV related outcomes including hospitalization status and inpatient charges is critical for the consistency of these measurements.

2.1.1 Data

As described briefly earlier, the data set used in this analysis is the California Linked Birth and Inpatient Database. Births are the unit of observation, and the sample spans from July 1997 to June 2005. These data are composed of two sets linked at the individual level: One set is composed of birth records, which identify each birth in California, along with a host of characteristics including birth date, gestational age, other medical conditions identified by up to 25 ICD-9 codes, insurance status, demographic information, and information about the mother and father. The second set consists of records of all inpatient admissions of infants under one year old in California, which identify the diagnosed conditions, dates of admission and discharge, length of stay, charges, insurance status, and other administrative and demographic variables. The feature that makes these data unique and especially well suited for identifying infants at risk for RSV is a variable linking the birth records to inpatient records at the individual level, allowing for the identification of an infant's birth and the tracking of subsequent inpatient admissions over time. As a result of this linkage, it is possible to identify the risk factors present at birth and then examine RSV related outcomes that occur during the first year of life.

The use of birth data linked at the individual level to subsequent inpatient admissions represents a major advantage in the ability to properly identify RSV related hospitalizations among infants who are considered high risk. Several other inpatient data sets include detailed information about admissions (e.g. the National Hospital Discharge Database, the Kids' Inpatient Database, and many other state level discharge databases) and can be used to find the incidence rate of risk factors and of RSV hospitalizations.

But because these data sets only list conditions for the current inpatient admission and are not linked to conditions present at birth, notably gestational age, these non-linked data sets are not able to identify the high risk population which is absolutely necessary when examining how RSV outcomes have been affected since the introduction of palivizumab.

The linked data from California span eight RSV seasons, including all births and other infant admissions from July 1997 through June 2005. In total there are over 4.1 million births recorded, of which there are 823,232 births with ≤ 37 weeks gestation, representing 19.9% of all births. There are also 107,746 RSV related admissions, identified via the inpatient records by a diagnosis of RSV (ICD-9 code 079.6), pneumonia caused by RSV (480.1), or bronchiolitis (466.xx). Among infants born at ≤ 37 weeks gestation there are 27,159 RSV related admissions. This accounts for 25.2% of all RSV related admissions, and represents one RSV related admission for every 30 infants born at ≤ 37 weeks gestation. Table 2 shows yearly births by gestational age group, and Table 3 displays the number of RSV related admissions by gestation length.

Along with inpatient rates and charges due to RSV, I can also identify outcomes of an unrelated class of conditions for which there were no substantive medical advances that would have been expected to lead to changes in hospitalization rates or charges. Estimates for outcomes related to these conditions will help to account for changes in inpatient trends that occurred for all infants and are unrelated to the introduction of palivizumab. I define an infant to be a member of this control condition group if there is a diagnosis of gastroenteritis (ICD-9 009.x, 558.x), dehydration (276.5x), or fever (780.6) among the first five ICD-9 diagnosis variables in the data set. I limit the identification of these conditions to the first five diagnosis categories because it is often the case that these three conditions are co-morbid with other more severe and costly conditions (Martin et al., 2006), and by limiting the identification of these conditions to the first five diagnosis categories, it ensures that these control conditions are indeed the main cause of the hospitalization. Although it is technically possible for an infant to belong to both the RSV group and the control condition group, no observations in this data are members of both groups. As I will describe below, these control conditions will be used as alternative outcomes against which results from the DDs with RSV outcomes can be compared as a falsification test that identifies the potential for hospitalization trends that may be present among all infants regardless of the availability of palivizumab. Table 4 lists summary statistics for all of the variables used in the regressions, including RSV and control group outcomes. Figures 3 and 4 give a graphical representation of outcomes associated with RSV admissions and control conditions, by risk groups over time.

2.1.2 Risk factors

The likelihood of an infant acquiring a severe RSV infection is determined by several factors, including the inadequate development of the lungs or the immune system, seasonal exposure to the virus, exposure to the virus at the community level, and the application of palivizumab. The probability of a severe RSV infection faced by each infant can be expressed as

$$Pr(RSV_{it}) = f(C_{it}, E_{it}, P_{it}, \lambda_{it})$$

where the subscripts *i* represent an individual and *t* represents the birth year. C_{it} represents the presence of medical conditions that affect the development of the respiratory and immune systems, which can be identified in the data via diagnosis codes that match those risk factors the American Academy of Pediatrics describe in their palivizumab eligibility guidelines, including short gestation and chronic lung disease. E_{it} represents the within-season exposure to the virus, as RSV is more virulent in the winter months. This can be identified by using the infant's birth month. P_{it} corresponds to the likelihood of an infant receiving palivizumab. λ_{it} characterizes some measure of community exposure of the virus; part of this community exposure can be identified based on the infant's birth order, as a newborn with older siblings is more likely to be exposed to the virus as these siblings may attend school or daycare where the virus thrives. Part of this community exposure is due to random chance as some infants may simply be "unlucky" and come in contact with the virus while an otherwise similar infant may not. In this case, it will be considered a random error term.

It is important to note that P_{it} cannot be taken as an independent variable like the others can. As described earlier, receiving (and complying with) a palivizumab prescription is based on the health care provider being aware of the drug and knowing under which circumstances it should be applied, as well as the parent being aware of the benefits of the drug and ensuring all of the prescribed doses are actually received. Hence the probability of receiving palivizumab can be written as

$$\begin{cases} Pr(P_{it}) = g(C_{it}, E_{it}, Y_t, \iota_{it}) \text{ if } t \geq 1998 \\ Pr(P_{it}) = 0 \text{ if } t \leq 1997 \end{cases}$$

Note first that since palivizumab was not released until the 1998 RSV season, no infants born before then can be given the drug, hence they have 0 probability of receiving it. C_{it} and E_{it} represent the same medical risk factors and within-year exposure effects that determine the probability of an RSV infection, as infants with a higher risk profile are also more likely to be eligible for palivizumab. Y_t represents the RSV year, which is an important determinant of the probability of receiving palivizumab based on the increasing uptake effects that are present since the drug's introduction. Lastly, ι_{it} represents some measure of the parent's demand for their child's health. From the data, I will use the mother's age and education level as a proxy for this, however there are also unobserved characteristics that likely are included in this term, and hence will also be included in an error term.

By combining the factors that influence the probability of being prescribed palivizumab into the equation describing the probability of a child being hospitalized because of an RSV infection, the reduced form probability of a severe RSV infection can be written as

$$Pr(RSV_{it}) = f(C_{it}, E_{it}, Y_{it}, \lambda_{it}, \iota_{it})$$

This probability will be the underlying basis for the empirical models I will define in the following section.

Underlying medical risk factors, C_{it} in the above probabilities, are typically difficult for empirical researchers to identify from discharge data, as these risk factors, like short gestation, are not regularly recorded on non-birth discharge records. But because the data used here links birth data containing gestational age with non-birth inpatient data, which identify admissions for RSV, identifying at risk infants and analyzing their subsequent inpatient admissions for RSV infections is easily achieved. Following the American Academy of Pediatrics palivizumab prescription guidelines I can identify the presence of very specific risk factors that make each infant eligible, or not eligible, for the drug.

There are nine specific risk groups that can be explicitly identified: (1) A diagnosis of chronic lung disease (ICD-9 770.7) or congenital heart disease (746.x) during the infant's first year. (2) Born at ≤ 28 weeks gestation. (3) Born at ≥ 29 and ≤ 32 weeks gestation, with birth month between June and February (inclusive), and not having any other medical risk factors.[5] (4) Born from ≥ 29 to ≤ 32 weeks gestation, with birth month from March to May (inclusive), and not having any other medical risk factors. (5) Born from ≥ 29 to ≤ 32 weeks gestation, and having at least one other risk factor present, regardless of birth month. (6) Born at ≥ 33 and ≤ 35 weeks gestation, and having one other medical risk factor. (7) Born from ≥ 33 to ≤ 35 weeks gestation, and having two or more medical risk factors. (8) Born from ≥ 33 to ≤ 35 weeks gestation with no risk factors, and (9) born at ≥ 36 weeks gestation and having no other risk factors. Note that risk groups (4), (8), and (9) are never eligible to receive palivizumab per the AAP guidelines. In the analysis, these three groups will serve as useful comparison groups that will help determine the effectiveness of palivizumab.

To further build each infant's risk profile it is necessary to include the infant's month of birth because of within-season exposure effects. Figure 2 uses data collected in California by the National Enteric and Respiratory Surveillance System, and shows the number of lab-confirmed RSV related infant hospital admissions by month. The large peaks in the winter months and lows in the summer months provide evidence as to the dramatic seasonal changes that are associated with RSV infections. Because the virus is most active in California from December to February, infants who are of a younger chronological age at the onset of the peek virulence are at a higher risk of contracting a

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[5] These risk factors are broadly defined respiratory diseases (ICD-9 460-519), cardiovascular system diseases (390-459, 745-747), neuromuscular conditions (320-359), or immunodeficiencies (042-044, 279.x).

severe RSV infection, because holding all else equal, they have less developed respiratory and immune systems than infants of older chronological ages who have had more time to physically develop. For example, if two otherwise similar infants are born at 28 weeks gestation, one in November and one in May, the infant born in November will be only one month old when RSV virulence peaks, while the infant born in May will be seven months of age at the peak of RSV season. These six extra months of development result in the infant born in May having better developed respiratory and immune systems, hence being better suited to resist a severe RSV infection compared to the infant born in November whose lungs and respiratory system are less developed.

It will also be worthwhile to include two other risk factors, namely if an infant is the first born to the mother, and the sex of the infant. Being first born puts an infant at less risk for a severe RSV infection, as they lack older siblings who may attend daycare or school, where RSV infections can be acquired and spread back to the younger sibling. Newborn boys are also at a slightly higher risk than girls, since male infants tend to have slightly less developed immune systems at birth, making them more susceptible to an RSV infection (Welliver, 2003). Both of these characteristics are included in the data, and will be incorporated as control variables into the DD models.

2.1.3 Drug uptake effects

Drug uptake effects are defined here as the increased usage of a drug among some population over time. These uptake effects are often the result of many factors, potentially including marketing of the drug and increased awareness of the drug's benefits and availability by doctors and patients alike. The uptake effects associated with palivizumab that may lead to improved outcomes may also be the result of improved compliance over the years, whereby doctors will be more likely to prescribe the drug appropriately and parents are more likely to make sure all of the necessary doses are received by their infant.

There is strong evidence that uptake effects are indeed occurring with palivizumab. The first example of this is a steady increase in the usage of palivizumab is from Medi-Cal pharmacy benefit data. Figure 1 displays the number of yearly palivizumab doses provided by Medi-Cal, and it provides a clear indication of increased usage. Curiously in 2004 and 2005 there are declines in the number of doses provided, which is likely due to changes in the guidelines Medi-Cal uses to determine which risk factors deem an infant eligible for palivizumab. Along with the Medi-Cal pharmacy data, the yearly financial reports of MedImmune and AstraZeneca also report year after year increases in the US market for both the number of palivizumab doses sold, and the revenue generated by palivizumab (MedImmune, 2005; AstraZeneca, 2010). The inclusion of simple dummy variables indicating year of birth will be used to capture these uptake effects, and will also allow for cross-year comparisons, which will provide more insight than simple comparisons based on if the infant was born before or after the introduction of palivizumab.

2.2 Difference-in-differences models

Difference-in-differences (DD) estimates are based on the occurrence of a policy event at a discrete and well-defined point in time, and the ability to identify which individuals are expected to be affected by the policy change and which will not be affected. In the simplest case there is a single exposure variable, indicating if the individual is observed before or after the policy is instituted, and a treatment variable indicating if the policy event will affect a specific individual. An illustrative example of this method is shown by Card and Kreuger (2000) in which they compare unemployment rates as a function of the minimum wage, which was increased in New Jersey in 1992 but remained constant in Pennsylvania. In this case Pennsylvania is the "control" state while New Jersey is the "treated" state, while the years before the policy change are the "pre" period, and years after it are the "post" period.

In the context of the effect of palivizumab on RSV outcomes, the policy event is the introduction of palivizumab which occurred in September 1998, hence those born before this time are not exposed to the drug while those born after its introduction are. At the same time, the American Academy of Pediatrics issues guidelines defining which risk factors make an infant eligible for the drug, so those who are eligible can be considered the treated group and those not eligible will be the control group. Because this analysis takes the form of an intention to treat study, instead of the "treatment" and "control" terminology typically used in the context of most treatment on the treated studies, I will instead call these groups "eligible" and "non-eligible", as the identification of the groups is based on underlying risk factors making them eligible for palivizumab treatment, regardless of their actual treatment status.

In this most basic setup of a DD examining how the availability of palivizumab may have altered RSV outcomes, the following equation represents a simple way to calculate the effect of the availability of the drug:

$$DD_p = \left(R_{Eligible}^{Post} - R_{Eligible}^{Pre}\right) - \left(R_{NonEligible}^{Post} - R_{NonEligible}^{Pre}\right)$$

where DD_p is the effect of palivizumab given its availability, and the individual *R*s represent group means of RSV related outcomes, where the four groups are based on an individual's eligibility status for the drug (*Eligible* or *NonEligble*) and their exposure to the drug, in this case being born before (*Pre*) or after (*Post*) the introduction of palivizumab in 1998. So for example, in the simplest case, $R_{Eligible}^{Post}$ represents the average RSV hospitalization rate for the population of infants born after September 1998 and who are eligible for the drug.

This simple DD estimate and resulting standard errors are also produced by the following OLS regression:

$$R_{it} = \alpha + \beta_1 \left(Eligible_i \right) + \beta_2 \left(Post_t \right) + \delta \left(Eligible_i \cdot Post_t \right) + \varepsilon_{it}$$

where R_{it} is the RSV related health outcome for child *i* at time *t*, $Eligible_i$ is a dummy variable indicating if the infant is eligible for palivizumab treatment, $Post_t$ is a dummy variable indicating if the child is born after the introduction of palivizumab, and the interaction of these two variables identifies if the child is both eligible for palivizumab and born at a time when it is available. Note that in the above equations, $DD_p = \delta$. One benefit of the regression model is that control variables that vary within the exposure and treatment groups can be easily included, in which case the model is written as

$$R_{it} = \alpha + \beta_1 \left(Eligible_i \right) + \beta_2 \left(Post_t \right) + \delta \left(Eligible_i \cdot Post_t \right) + \boldsymbol{\gamma X} + \varepsilon_{it}$$

where $\boldsymbol{\gamma}$ represents a vector of estimated coefficients of the controls and $\boldsymbol{X}$ is a matrix of control variables.

To obtain unbiased results from this type of analysis two assumptions must hold true. First, both the eligible and non-eligible groups need to be homogenous in their unobserved characteristics. This assumption would be likely violated as infants born prematurely tend to have different traits and experiences that are not observed in the data.

For example, premature infants are often kept as inpatients for longer periods compared to full term infants and hence both groups have different community exposure rates to RSV. It has also been shown that risky behaviors by the pregnant mother, like smoking and drug use, may lead to premature births (CDC, 2010). It could be said that mothers who engage in such activities while pregnant may not value the health of their baby as much as mothers who do not and these differences in the demand for their child's health may lead to disparate infant health outcomes regardless of prematurity status. Second, unbiased results are only achieved when the treatment is adopted discretely and universally by the treated group at the time it is introduced. This assumption is also violated in the case of palivizumab, as uptake effects are occurring over time, meaning that holding all else equal infants born in the later years of the sample are more likely to receive palivizumab and experience the benefits of its protection compared to infants born in earlier years.

Despite the apparent violations of these two assumptions it is possible to alter the model to take these shortcomings into account. One simple way to improve the homogeneity of unobservables is to limit the sample in a way such that the non-eligible group is more similar to the eligible group. In this case, the sample can be limited to infants who are born at ≤ 37 weeks gestation. The rationale is that because infants who are born during or after the 38th week of gestation with no other risk factors are never eligible for palivizumab, the drug will never affect their RSV related outcomes. At the same time, infants born at 36 or 37 weeks gestation have less developed lungs and immune systems compared to newborns of longer gestations. Table 2 shows that there are just over 500,000 infants born at 36 or 37 weeks gestation, while there are over 3.2

million infants born at ≥ 38 weeks gestation, while Table 3 shows that RSV hospitalization rates are declining with gestational age. If infants of all gestations are kept as the control group, the outcomes of the 36 and 37 weeks gestation infants could effectively be overpowered by outcomes to infants of longer gestations. Excluding infants born at ≥ 38 weeks gestation creates a control group that is more similar to the group who will be eligible for palivizumab.

Another way to enrich difference-in-differences models is to classify infants into one of several risk categories within the population. In the case of palivizumab eligibility, this is achieved by identifying specific risk factors based on the AAP prescription guidelines which use gestational age, birth month, and underlying medical conditions to establish who should receive the drug. Having separate risk groups allows for the comparison of outcomes between these groups, which will provide important insights as to how outcomes vary between infants with different risk factors, because it has been shown that infants with more severe risk factors tend to receive relatively greater improvements in health outcomes compared to eligible infants with less severe risks when palivizumab is applied (Welliver, 2003). Following a similar rationale, including specific year dummy variables instead of the simple "pre/post" indicator will account for improved identification of the increased uptake of the drug since its introduction. These individual year dummies allow for comparisons between birth cohorts, which will be important as the probability of receiving palivizumab most likely increases in later years of the sample. Interactions of these risk-specific dummies and year dummies will be the basis of interpreting the effects of the availability of palivizumab in the empirical models I will soon describe.

Including a set of control variables will provide estimates of how certain social and demographic characteristics affect health outcomes. Because the biological activity of the virus peaks in the winter months, infants born in different months of the year will be of different chronological ages, and hence have more or less developed respiratory and immune systems when the virus is at its most active in December through February. Including a set of birth month indicators will control for these exposure effects. Similarly, variables indicating if the infant is the first born, and if the infant is male will also be included as these characteristics alter the infant's risk profile. Lastly, variables indicating the mother's age and education level (categories of less than high school, high school diploma, some college, bachelor's degree or beyond), race and ethnicity, and type of insurance[6] (public or private) will be included, as all of these characteristics likely impact infant health outcomes (Braveman et al., 2001).

One more potential limitation that could affect the interpretation and robustness of DD estimates measuring RSV related outcomes is the presence of systematic changes in the market for infant health care over time. For example, if infant inpatient rates declined over time for all conditions because hospitals became more likely to treat infants as outpatients instead of admitting them, this would result in declines in the RSV admission rate being spuriously associated with the introduction and increased uptake of palivizumab, when in reality inpatient admission rates would have declined regardless of palivizumab. This will be especially useful in interpreting results related to inpatient charges. Because health care costs have been steadily increasing over time (Ginsburg et al., 2006), it could be the case that RSV related hospitalizations increased in cost, which

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[6] In this data set, just over 98% of infants are recorded as being covered by either public or private insurance. There are very few uninsured children as if they lack insurance, they are almost always eligible for the Medi-Cal public plan.

would appear to indicate a lack of effectiveness of palivizumab in controlling costs, but if this increase in costs are less than the increase of costs of other conditions it could be interpreted as a relative improvement in outcomes compared to admissions for other conditions.

Because of the richness of the data set being used, it is possible to identify admissions for a host of non-RSV related admissions that are also common among infants but have experienced minimal innovations to decrease their burden, such as gastroenteritis, dehydration, and fever. By running DD models for outcomes related to these "control" conditions (with the same independent variables as in the RSV DD regressions) the estimates will provide a test as to the validity of claiming that palivizumab was responsible for a decline in RSV admissions or charges, relative to exogenous trends in health care. If these control DD models show similar trends to the RSV DD models, it is likely the case that there were economy wide, systematic changes in all infant health outcomes during this sample period. If, however, the control DD models do not show evidence of changes in the control outcomes, it would imply that there were no systematic changes in the provision of health care to infants, and that the results from the RSV related DDs are likely being driven by the introduction and uptake of palivizumab.

2.3 Empirical models and estimation

The sample used in these estimations will be limited to infants born from July 1997 through June 2005 who have risk factors making them eligible for palivizumab along with infants who are born at ≤ 37 weeks gestation who are not eligible for palivizumab. Limiting the sample in this fashion will facilitate in creating a control group of infants who are not eligible for palivizumab with health characteristics that are more similar to those who are eligible for the drug than if infants born after a full term gestation were also included. There will be two outcomes measured separately for both RSV admissions and for infants admitted with the control conditions of fever, dehydration, and gastroenteritis. These outcomes are an inpatient admission (with coefficients multiplied by 1,000 to reflect the admission rate per 1,000 infants) and inpatient charges per infant. The use of inpatient admissions as an outcome is straightforward, with improved health of the infant population resulting in lower admission rates. The decision to use inpatient charges per infant rather than charges per hospitalization is more complicated and can be justified because the important estimate in regards to how palivizumab has changed the population wide burden of RSV is the total spending related to RSV hospitalizations. If palivizumab does lessen the burden of RSV infections, it is expected that the hospitalization rate will drop, resulting in more infants incurring $0 inpatient charges, while infants who are hospitalized may also have less severe infections, resulting in decreased charges. The combination of these two effects would lead to less RSV related inpatient spending.

But it is not entirely clear how to interpret changes in mean charges conditional on a hospitalization. The mean charges per admission are simply defined as

$$\frac{\sum_{i=1}^{N} C_i\left(Severity_i\right)}{N\left(Severity\right)}$$

where C_i is the amount charged in dollars to inpatient *i*, which is dependent on the severity of the RSV infection of inpatient *i*, and *N* is the number of RSV hospitalizations, which is a function of the population wide severity of RSV infections. Because the application of palivizumab is expected to reduce the severity of RSV infections, it will also reduce the total charges. At the same time, if the severity of an infection is decreased enough, charges will be reduced to the minimum of $0, i.e. the infant is not admitted, in which case *N* will also decrease. So the use of palivizumab creates an endogeneity in the measurement by affecting both the numerator and the denominator, and it is not clear how this measurement would be interpreted. As this study aims to evaluate the population wide effectiveness of palivizumab, the appropriate outcome related to inpatient charges is thus the charges per infant.

2.3.1 Models

This analysis will employ the use of two basic models. These models will incorporate interacted terms which will be used to calculate the difference-in-differences estimates, by constructing comparisons across risk groups and years, to explore how the availability of palivizumab has affected changes in outcomes among infants with various levels of risk.

Along with a set of control variables and birth month variables, models will include dummy variables indicating the infant's year of birth, and either a single variable identifying if an infant is eligible for palivizumab, or a set of dummy variables indicating membership to one of nine specific risk groups and these models also include interaction terms between the year dummies and eligibility status or the year dummies and the individual risk factor dummies, which serve as the DD estimates. Standard errors calculated for the estimated coefficients will be robust to clustering of unobservable characteristics at the ZIP code level, with 3,072 clusters. This is justified because it is likely that the individuals within a ZIP code will be exposed to similar treatment patterns via homogeneity in doctors and hospitals, along with similar community level exposure to the virus, and will hence their estimated error terms will be correlated. However, the errors will not be correlated across ZIP codes as infants in different locations will experience different treatment patterns and community exposure to the virus.

Models that will be used to calculate the difference-in-differences estimates are written as

$$Outcome_{it} = \alpha + \boldsymbol{\gamma X} + \sum_{m=May}^{March} \beta_{BM}^{m} \left(BMonth_{im} \right) + \sum_{t=1998}^{2004} \beta_{Y}^{t} Y_{t} + \beta_{Elg} Eligible_{it}$$
$$+ \sum_{t=1998}^{2004} \beta_{Elg}^{t} \left(Y_{t} \cdot Eligible_{it} \right) + \varepsilon_{it}$$

when a single eligibility variable is used, or as

$$Outcome_{it} = \alpha + \boldsymbol{\gamma X} + \sum_{m=May}^{March} \beta_{BM}^{m} \left(BMonth_{m} \right) + \sum_{t=1998}^{2004} \beta_{Y}^{t} Y_{it} + \sum_{r=1}^{8} \beta_{RF}^{r} Risk_{ir} +$$
$$+ \sum_{t=1998}^{2004} \sum_{r=1}^{8} \beta_{RF}^{rt} \left(Risk_{ir} \cdot Y_{it} \right) + \varepsilon_{it}$$

when the set of specific risk factors are used. $Outcome_{it}$ represents one of four dependant variables: RSV hospitalization status, control condition hospitalization status, real RSV inpatient charges, real control condition inpatient charges.[7] On the right hand side of these regressions, $\boldsymbol{X}$ is a matrix representing the variables for mother's age (linear), mother's education (less than high school, high school diploma [the omitted category], some college, bachelor's degree or more), race and ethnicity (white non-Hispanic [the omitted category], white Hispanic, black non-Hispanic, black Hispanic, Asian, other races), first born indicator, type of insurance (private insurance [the omitted category], public insurance), and sex of the infant (male). $BMonth_{im}$ is a dummy variable at the

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[7] Real charges are calculated using the medical care component of the consumer price index published by the Bureau of Labor Statistics, with 2004 as the base year.

individual level for birth month *m*, with births in April the omitted category. Y_{it} is a dummy variable at the individual level indicating the RSV season, with 1997 the reference season.[8] $Eligible_{it}$ is a dummy variable indicating if an infant has risk factors making him or her eligible for palivizumab. This variable is based on eligibility at the specific time of birth, so note that guidelines were revised in 2003 in such a way that an infant born at 33 weeks gestation with a single additional risk factor in 2002 will have $Eligible_{it} = 1$, but an infant with identical risk factors will have $Eligible_{it} = 0$ if born is 2003. $Risk_{ir}$ is a dummy variable indicating the presence of specific risk factor *r* for individual *i*, with the reference group composed of infants born from 36 to 37 weeks gestation with no additional risk factors. ε_{it} is the disturbance term.

Because these regressions are complicated by multiple years and risk indicators, as opposed to the simple DD regressions with pre/post, treated/control, and interaction variables, the difference-in-differences estimators need to be constructed via linear combinations of the relevant coefficients. These linear combinations are based on the premise that difference-in-differences estimators are differences in group means of the outcome, recalling

$$DD_p = \left(H_{Eligible}^{Post} - H_{Eligible}^{Pre}\right) - \left(H_{NonEligible}^{Post} - H_{NonEligible}^{Pre}\right)$$

is the form of the basic estimator when there are simple binary indicators for “pre” or “post” and for “eligible” and “non-eligible”. When considering the interpretation of the coefficients estimated in the above regressions, it is important to recognize how they are related to the group means. While constructing the DD estimates, the coefficients on the

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[8] Recall that the RSV season is defined as July to June. For example, the 1997 RSV season runs from July 1997 through June 1998.

constant, the year dummy variables, the eligibility or risk group dummy variables, and the interacted terms are used to find the group means for differences between groups, while the other variables control for exogenous variation between individuals. For example, the most primal DD estimate is between those who are eligible and not eligible for the drug and between 1997 and 1998. From the regression coefficients, the four group means are constructed as follows

	Eligible	Not eligible
1997	$\alpha + \beta_{Elg}$	α
1998	$\alpha + \beta_{Y}^{1998} + \beta_{Elg} + \beta_{Elg}^{1998}$	$\alpha + \beta_{Y}^{1998}$

And with the DD estimate calculated as $\left(H_{Elg}^{1998} - H_{Elg}^{1997}\right) - \left(H_{Non}^{1998} - H_{Non}^{1997}\right)$ where H_{R}^{Y} represents a mean outcome for risk/eligibility group *R* born in year *Y*. This is represented by the linear combination of

$$\begin{aligned} DD_{E-N}^{98-97} &= \left(H_{Elg}^{1998} - H_{Elg}^{1997}\right) - \left(H_{Non}^{1998} - H_{Non}^{1997}\right) \\ &= \left[\left(\alpha + \beta_{Y}^{1998} + \beta_{Elg} + \beta_{Elg}^{1998}\right) - \left(\alpha + \beta_{Elg}\right)\right] \\ &\quad - \left[\left(\alpha + \beta_{Y}^{1998}\right) - \left(\alpha\right)\right] \\ &= \beta_{Elg}^{1998} \end{aligned}$$

In this simple case, the all of the coefficients cancel, with the exception of β_{Elg}^{1998} which is the coefficient that represents the interaction of 1998 and eligibility indicators. This same method is used to calculate several other DD estimators, with comparisons made between birth years and eligibility status or between birth years and the various risk groups. For brevity in notation, I will refer to each specific risk group as R1, …, R9, defined as follows:

Risk Group	Condition
R1	CLD or CHD
R2	≤ 28 WGA
R3	29-32 WGA, Jun-Feb
R4	29-32 WGA, Mar-May (not eligible)
R5	29-32 WGA, other risks
R6	33-35 WGA, 1 risk
R7	33-35 WGA, ≥ 2 risks
R8	33-35 WGA, 0 risks (not eligible)
R9	36-37 WGA, otherwise not at risk (not eligible – control group)

Using a DD equation of a similar form, it is quite easy to examine the potential effects of uptake effects by incorporating coefficients of different years. To do this I will compare 1997 effects to those of 1999 as this will show if outcomes improved after the drug was available for a full year. I will also compare 1998 estimates to those in 2003 and 2004, to examine how increased uptake could have improved outcomes conditional on both comparison groups being eligible for palivizumab. These three models are written as

$$\begin{aligned} DD_{E-N}^{99-97} &= \left(H_{Elg}^{1999} - H_{Elg}^{1997}\right) - \left(H_{Non}^{1999} - H_{Non}^{1997}\right) \\ &= \left[\left(\alpha + \beta_{Y}^{1999} + \beta_{Elg} + \beta_{Elg}^{1999}\right) - \left(\alpha + \beta_{Elg}\right)\right] - \left[\left(\alpha + \beta_{Y}^{1999}\right) - \left(\alpha\right)\right] \\ &= \beta_{Elg}^{1999} \end{aligned}$$

$$\begin{aligned} DD_{E-N}^{03-98} &= \left(H_{Elg}^{2003} - H_{Elg}^{1998}\right) - \left(H_{Non}^{2003} - H_{Non}^{1998}\right) \\ &= \left[\left(\alpha + \beta_{Y}^{2003} + \beta_{Elg} + \beta_{Elg}^{2003}\right) - \left(\alpha + \beta_{Y}^{1998} + \beta_{Elg} + \beta_{Elg}^{1998}\right)\right] \\ &\quad - \left[\left(\alpha + \beta_{Y}^{2003}\right) - \left(\alpha + \beta_{Y}^{1998}\right)\right] \\ &= \beta_{Elg}^{2003} - \beta_{Elg}^{1999} \end{aligned}$$

$$\begin{aligned} DD_{E-N}^{04-98} &= \left(H_{Elg}^{2004} - H_{Elg}^{1998}\right) - \left(H_{Non}^{2004} - H_{Non}^{1998}\right) \\ &= \left[\left(\alpha + \beta_{Y}^{2004} + \beta_{Elg} + \beta_{Elg}^{2004}\right) - \left(\alpha + \beta_{Y}^{1998} + \beta_{Elg} + \beta_{Elg}^{1998}\right)\right] \\ &\quad - \left[\left(\alpha + \beta_{Y}^{2004}\right) - \left(\alpha + \beta_{Y}^{1998}\right)\right] \\ &= \beta_{Elg}^{2004} - \beta_{Elg}^{1999} \end{aligned}$$

Along with using the DD framework to analyze simple "eligible/non-eligible" differences over time, the coefficients found from the regression identifying specific risks can also be combined in a similar fashion to compare differences within specific risk groups. Instead of displaying how population wide availability of palivizumab has altered RSV related outcomes based simply on eligibility status, the comparison of outcomes among slightly different risk groups will be telling as to how slight variations in risk factors affect RSV hospitalizations in the presence of palivizumab. Perhaps the best comparison of this sort is between infants born from 29 to 32 weeks gestation from June to February who are eligible for palivizumab (risk group R3) to infants born of the same gestation but from March to May who are not eligible as they are at least six months old when RSV season begins in October (risk group R4). Like in the case of the "eligible/non-eligible" models, the year specific comparison can be altered to test for the immediate effect of the availability of palivizumab by comparing the 1997 coefficients to the 1998 and 1999 coefficients, and uptake effects can also be tested by comparing 1998 coefficients to 2003 and 2004 coefficients. These models are written as

$$\begin{aligned} DD_{R3-R4}^{98-97} &= \left(H_{R3}^{1998} - H_{R3}^{1997}\right) - \left(H_{R4}^{1998} - H_{R4}^{1997}\right) \\ &= \left[\left(\alpha + \beta_{Y}^{1998} + \beta_{R3} + \beta_{R3}^{1998}\right) - \left(\alpha + \beta_{R3}\right)\right] \\ &\quad - \left[\left(\alpha + \beta_{Y}^{1998} + \beta_{R4} + \beta_{R4}^{1998}\right) - \left(\alpha + \beta_{R4}\right)\right] \\ &= \beta_{R3}^{1998} - \beta_{R4}^{1998} \end{aligned}$$

$$\begin{aligned} DD_{R3-R4}^{99-97} &= \left(H_{R3}^{1999} - H_{R3}^{1997}\right) - \left(H_{R4}^{1999} - H_{R4}^{1997}\right) \\ &= \left[\left(\alpha + \beta_{Y}^{1999} + \beta_{R3} + \beta_{R3}^{1999}\right) - \left(\alpha + \beta_{R3}\right)\right] \\ &\quad - \left[\left(\alpha + \beta_{Y}^{1999} + \beta_{R4} + \beta_{R4}^{1999}\right) - \left(\alpha + \beta_{R4}\right)\right] \\ &= \beta_{R3}^{1999} - \beta_{R4}^{1999} \end{aligned}$$

$$\begin{aligned} DD_{R3-R4}^{03-98} &= \left(H_{R3}^{2003} - H_{R3}^{1998}\right) - \left(H_{R4}^{2003} - H_{R4}^{1998}\right) \\ &= \left[\left(\alpha + \beta_{Y}^{2003} + \beta_{R3} + \beta_{R3}^{2003}\right) - \left(\alpha + \beta_{Y}^{1998} + \beta_{R3} + \beta_{R3}^{1998}\right)\right] \\ &\quad - \left[\left(\alpha + \beta_{Y}^{2003} + \beta_{R4} + \beta_{R4}^{2003}\right) - \left(\alpha + \beta_{Y}^{1998} + \beta_{R4} + \beta_{R4}^{1998}\right)\right] \\ &= \left[\beta_{R3}^{2003} - \beta_{R3}^{1998}\right] - \left[\beta_{R4}^{2003} - \beta_{R4}^{1998}\right] \end{aligned}$$

$$\begin{aligned} DD_{R3-R4}^{04-98} &= \left(H_{R3}^{2004} - H_{R3}^{1998}\right) - \left(H_{R4}^{2004} - H_{R4}^{1998}\right) \\ &= \left[\left(\alpha + \beta_{Y}^{2004} + \beta_{R3} + \beta_{R3}^{2004}\right) - \left(\alpha + \beta_{Y}^{1998} + \beta_{R3} + \beta_{R3}^{1998}\right)\right] \\ &\quad - \left[\left(\alpha + \beta_{Y}^{2004} + \beta_{R4} + \beta_{R4}^{2004}\right) - \left(\alpha + \beta_{Y}^{1998} + \beta_{R4} + \beta_{R4}^{1998}\right)\right] \\ &= \left[\beta_{R3}^{2004} - \beta_{R3}^{1998}\right] - \left[\beta_{R4}^{2004} - \beta_{R4}^{1998}\right] \end{aligned}$$

The final comparison I will make takes advantage of a policy change that affected how infants born from 33 to 35 weeks gestation who were eligible for palivizumab if they had one additional underlying risk factor,[9] but starting in the 2003 RSV season, the requirements for this gestational group were increased such that infants had to have at least two underlying risk factors. This change in policy creates a quasi natural experiment, as infants with a single additional risk factor were eligible to receive palivizumab from 1998 to 2002, but starting in 2003 infants with a single risk factor were not eligible while those with several risks were. It is not clear if this change in policy was entirely exogenous, as the benefits palivizumab provides this gestational group have been debated for some time (Joffe et al., 1999; Stevens et al., 2000; Groothuis and

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[9] These underlying risk factors include a diagnosis broadly including a respiratory, cardiovascular, or immune system disorder.

Nishida, 2002; Romero, 2003). Because of this, I will make two comparisons across time. The first will measure the immediate policy change, comparing 2002 coefficients to 2003 coefficients for the relevant risk groups. But these comparisons may be tainted as some doctors may have foresaw the policy changes and adapted their prescription patterns in 2002 before the change, while other doctors may not have been aware of the change and could have prescribed palivizumab to newly non-eligible infants in 2003 despite the change in guidelines. Hence, the other comparison will be between those born in 2001 and those born in 2004. Given that the policy change still intersects these groups, the comparison is still relevant, while at the same time it is unlikely doctors would preemptively changed their prescription patterns in 2001, and it is also the case that more doctors will have learned about the policy change by 2004. These models can be written as

$$\begin{aligned}
DD_{R6-R7}^{03-02} &= \left(H_{R6}^{2003} - H_{R6}^{2002}\right) - \left(H_{R7}^{2003} - H_{R7}^{2002}\right) \\
&= \left[\left(\alpha + \beta_{Y}^{2003} + \beta_{R6} + \beta_{R6}^{2003}\right) - \left(\alpha + \beta_{Y}^{2002} + \beta_{R6} + \beta_{R6}^{2002}\right)\right] \\
&\quad - \left[\left(\alpha + \beta_{Y}^{2003} + \beta_{R7} + \beta_{R7}^{2003}\right) - \left(\alpha + \beta_{Y}^{2002} + \beta_{R7} + \beta_{R7}^{2002}\right)\right] \\
&= \left[\beta_{R6}^{2003} - \beta_{R6}^{2002}\right] - \left[\beta_{R7}^{2003} - \beta_{R7}^{2002}\right]
\end{aligned}$$

$$\begin{aligned}
DD_{R6-R7}^{04-01} &= \left(H_{R6}^{2004} - H_{R6}^{2001}\right) - \left(H_{R7}^{2004} - H_{R7}^{2001}\right) \\
&= \left[\left(\alpha + \beta_{Y}^{2004} + \beta_{R6} + \beta_{R6}^{2004}\right) - \left(\alpha + \beta_{Y}^{2001} + \beta_{R6} + \beta_{R6}^{2001}\right)\right] \\
&\quad - \left[\left(\alpha + \beta_{Y}^{2004} + \beta_{R7} + \beta_{R7}^{2004}\right) - \left(\alpha + \beta_{Y}^{2001} + \beta_{R7} + \beta_{R7}^{2001}\right)\right] \\
&= \left[\beta_{R6}^{2004} - \beta_{R6}^{2001}\right] - \left[\beta_{R7}^{2004} - \beta_{R7}^{2001}\right]
\end{aligned}$$

In general, if the availability of palivizumab has decreased the RSV related admission rates among those to whom it is available, the coefficients of DD_{E-N}^{Y} and DD_{R3-R4}^{Y} should be negative and significant, indicating that the availability of the drug has reduced RSV admissions. However DD^{Y}_{R6-R7} measures a policy change that restricts palivizumab distribution, unlike the other DD measures that test how making palivizumab more available changes outcomes. At the same time, this policy change was put into place based on the idea that only the frailest infants born from 33 to 35 weeks gestation will benefit from the drug. If the resulting coefficient is positive and significant, this would imply that the infants from whom the drug was withheld experienced poorer health outcomes, but if the coefficient is 0 then that would imply that the infants born from 33 to 35 weeks gestation never benefitted from palivizumab in the first place, in which case not giving them palivizumab is the efficient policy.

All of the above difference-in-differences estimates will also be computed using the control condition outcomes representing gastroenteritis, fever, and dehydration as the dependant variable. Because there have been no major medical advancements for the prevention or care of these conditions over this period, any significant results are likely because of underlying trends in the infant health care market.

The final comparison will be between the DD estimates of RSV related outcomes and the control conditions outcomes. This is accomplished by performing a Wald test with the null hypothesis of $DD^{Y}_{R}\left(H_{RSV}\right)-DD^{Y}_{R}\left(H_{Control}\right)=0$ where the estimates are obtained from regressions using either RSV outcomes or control outcomes. If the null hypothesis is not rejected, this implies that the trends found for RSV are equal to the trends found for the control conditions, meaning that any changes in the RSV outcome are not likely due to the introduction of palivizumab, but may be likely due to changes in general trends occurring in infant health. If, however, the null hypothesis is rejected, this would imply that the trends related to RSV are different from those related to the control conditions, which can be interpreted as palivizumab being effective at improving RSV related outcomes.

3 Regression and difference-in-differences results

Summary statistics for the variables used in the regressions are shown in Table 4. It is important to keep in mind that this sample is limited to births of ≤ 37 weeks gestation. In total there are 764,775 births that are included in the sample, of which 26,727 (3.5%) were admitted as inpatients for an RSV related condition and 17,662 (2.3%) were admitted with a control condition which includes gastroenteritis, dehydration, and fever. Among this sample, the total charges of RSV inpatient stays are over $702 million, which equates to $918 per infant, or $26,303 per admission. For the control conditions total inpatient spending equals about $338 million, which is $442 per infant, or $19,137 per admission. Of this sample there are 87,025 infants (11%) who are eligible for palivizumab based on the AAP guidelines. This means that most of the observations have no risk factors for RSV, with 663,334 infants born from 33 to 37 weeks gestation and who have no other underlying medical conditions.

Insurance status is relatively evenly split, with 49% of the sample having publically funded insurance and 51% having private plans. As I briefly mentioned earlier, infants who are uninsured are omitted from the sample as these uninsured infants are very scare in California with less than 2% of the 4.1 million total births in California from 1997 to 2004 lacking insurance. This low figure is expected, as almost all otherwise uninsured infants are eligible for public health insurance programs and can be enrolled by the hospital at the time care is provided.

Education level of the mothers is also relatively evenly distributed with 32% having less than a high school diploma, 29% having a high school diploma, 19% having some college experience, and 20% having a bachelor's degree or higher. These statistics are slightly skewed towards lower levels of education compared to all births in California because the sample is composed of prematurely born infants. This shift in the distribution is expected as teenage mothers are more likely to give birth prematurely (Fraser et al., 1995), and teenage mothers are less likely to have finished high school at the time of birth given that they have not reached the typical age of graduation.

Births to Hispanic mothers account for 44% of all births in this sample. This is higher than the national average of 24% of births being to Hispanic mothers, but considering that California has over twice the percentage of Hispanic population compared to the national average, this value is also expected. It has also been shown that children in Hispanic families often have slightly better health outcomes compared to the population average (Williams et al., 1986), so it is not likely that this large percentage of Hispanic births will have any major effects on the results.

3.1 Regression results

Tables 5 to 8 contain the coefficient estimates from the difference-in-differences regressions. Tables 5 and 6 show results for models in which an inpatient admission is the outcome of interest, while Tables 7 and 8 show estimates when real inpatient charges are the dependant variable. All tables show regression estimates from a dependant variable based on RSV outcomes in the left column, and estimates from a dependant variable based on the control conditions of fever, gastroenteritis, and dehydration in the right column. Each table is also split into two panels, with Panel A showing estimates for the sociodemographic and month of birth variables, and Panel B showing coefficients for the specific DD variables, namely year of birth, eligibility status of risk group, and interactions between the two. The standard errors for all estimates are calculated to be robust to unobservable heterogeneity across individuals by clustering at the ZIP code level. All hypothesis tests are two-tailed and reported at the 10%, 5%, and 1% confidence levels.

All of the DD results presented in subsections 3.1.1 and 3.1.2 use births in 1997 who are not eligible for palivizumab (or the group of infants born from 36 to 37 weeks gestation when individual risk groups are used) as the comparison group. Richer comparisons that use linear differences between specific risk groups and different birth years will be presented in subsection 3.1.3.

3.1.1 Results using admissions as the outcome

Table 5 and Table 6 show estimates for regression models in which inpatient admissions are the outcome. Table 5 estimates the following regression model that has a single dichotomous variable indicating an infant's palivizumab eligibility status:

$$\begin{aligned} Admission_{it} = \alpha + \boldsymbol{\gamma X} + \sum_{m=May}^{March} \beta_{BM}^{m}\left(BMonth_{im}\right) + \sum_{t=1998}^{2004} \beta_{Y}^{t} Y_{it} + \beta_{Elg} Eligible_{it} \\ + \sum_{t=1998}^{2004} \beta_{Elg}^{t}\left(Y_{it} \cdot Eligible_{it}\right) + \varepsilon_{it} \end{aligned}$$

While Table 6 uses a similar model, except that separate risk factors are identified and subsequently interacted with year of birth dummies. This model is written as:

$$\begin{aligned} Admission_{it} = \alpha + \boldsymbol{\gamma X} + \sum_{m=May}^{March} \beta_{BM}^{m}\left(BMonth_{im}\right) + \sum_{t=1998}^{2004} \beta_{Y}^{t} Y_{it} + \sum_{r=1}^{8} \beta_{RF}^{r} Risk_{ir} + \\ + \sum_{t=1998}^{2004} \sum_{r=1}^{8} \beta_{RF}^{rt}\left(Y_{it} \cdot Risk_{ir}\right) + \varepsilon_{it} \end{aligned}$$

In either model $Admission_{it}$ is a dichotomous variable indicating if infant *i* is admitted as an inpatient in year *t*. The independent variables consist of the matrix $\boldsymbol{X}$ which includes the previously mentioned sociodemographic variables, and $BMonth_{im}$ is a matrix of indicators representing the infant's birth month. Coefficients found for these variables are shown in Panel A of Table 5 and Table 6. The remaining variables represent the DD estimates and include dummy variables indicating the infant's birth year, Y_{it} with t = 1998, …, 2004. Dummy variables are also used to indicate each infant's palivizumab eligibility status, with the first model using a single dichotomous variable, $Eligible_{it}$,to indicate if the infant is eligible for the drug, while the second model identifies eight specific risk factors outlined by the AAP guideline, shown by $Risk_{ir}$ with r = 1, …, 8. For both models, the actual DD coefficients are produced by interactions between the year of birth dummies and the eligibility or risk dummies, represented by $Y_{it} \cdot Eligible_{it}$ and $Y_{it} \cdot Risk_{ir}$, respectively.

The results from Panel A of Tables 5 and 6 are very similar as they both estimate sociodemographics and birth month effects of the same group, so for brevity I will only discuss these results from Table 5, from the model that uses a single palivizumab eligibility status indicator. Results show that those with public insurance experience 14.40 more RSV admissions per 1,000 births, and the admission rate is 9.15 higher per 1,000 for admissions due to gastroenteritis, fever, and dehydration. Mother's education follows the expected pattern for both RSV and the control conditions with infants to mothers who have less than a high school diploma having slightly higher admission rates compared to those with a high school diploma, and infants to mothers with some college or a college degree having relatively fewer admissions for both causes compared to mothers with a high school diploma. The coefficient on mother's age follows this pattern as well, with each additional year at the time of birth yielding reductions to the admission rates.

Male infants have 9.76 more RSV admissions per 1,000 births than female infants, while males experience only 4.21 more gastroenteritis, fever, and dehydration admissions per 1,000 births compared to females. Both estimates are statistically significant, and the estimates are statistically different from each other, showing that being male is likely a risk factor that contributes to higher probability of a severe RSV infection. The results also show that being the first born infant to a mother also substantially reduces the probability of an RSV admission, with first born infants having 12.30 fewer admissions per 1,000 infants than those of greater parity. At the same time, the effect is much smaller for admissions due to gastroenteritis, fever, and dehydration with an improvement of 1.99 fewer admissions per 1,000 infants.

The seasonality of RSV compared to other causes of inpatient admission is also evident when examining the coefficients on the birth month variables. Among the non-RSV admissions caused by gastroenteritis, fever, and dehydration there are no noticeable seasonal variations. However, RSV admission rates are clearly affected by birth month, with infants born from October through January having increased admission rates of between 21.96 and 33.15 per 1,000 infants compared to infants born in April. The change between coefficients is also monotonically increasing from April to December, and then monotonically decreasing from January to April. All results measuring the effect of birth month on RSV admissions are highly statistically significant.

Table 5 – Panel B shows DD estimates for year of birth, a single palivizumab eligibility indicator, and interactions between the two. Those eligible for palivizumab have higher admission rates for both palivizumab and for the control conditions compared to those who are not eligible for the drug. RSV admissions are increased by 34.03 per 1,000 infants and admissions for the control conditions are increased by 9.16 per 1,000 infants. Both results are statistically significant, and they are statistically different from each other. These results are expected, as being eligible for palivizumab means that an infant has at least one risk factor that could lead to a severe RSV infection; at the same time these risk factors make infants more susceptible to other conditions as well, hence the increase in admissions for the control conditions.

Coefficients on the birth years, from 1998 to 2004, show slight improvements in RSV outcomes in the later years, along with small improvements in admission rates for the control conditions. The interacted terms of Eligible*1998 to Eligible*2004 show the difference-in-differences estimates for those who are eligible for palivizumab. It is clear that there are no effects for the control conditions, meaning that there were likely no unobserved effects that altered admission patterns in general for these infants. Among the interacted estimates measuring RSV admissions, there are no significant results from 1998 to 2001. Given that the drug was available for these years but there were no improvements in the admission rate for those who were eligible to receive it, this could mean that the compliance rates were too low for noticeable health improvements to be achieved at the population level. However, from 2002 to 2004, those who were eligible for the drug did show improved admission rates, with 7.35, 8.55, and 11.38 fewer RSV admissions per 1,000 infants in 2002, 2003, and 2004 respectively compared to the control year of 1997 when the drug was not available. These DD results taken together could be viewed as evidence that palivizumab did experience poor uptake during the early years after its introduction, but once doctors and parents became more aware of the drug and its usage was increased, health benefits were experienced by those who are at a high risk for a severe RSV infection.

Table 6 – Panel B shows estimates from regressions that measure how RSV admissions and admissions for the control conditions of gastroenteritis, fever, and dehydration were affected when controlling for specific risk factors. For notational purposes these risk factors are labeled as R1 through R9, with the following definitions. Note that in the regressions R9 is the omitted category.

Risk Group	Condition
R1	CLD or CHD
R2	≤ 28 WGA
R3	29-32 WGA, Jun-Feb
R4	29-32 WGA, Mar-May (not eligible)
R5	29-32 WGA, other risks
R6	33-35 WGA, 1 risk
R7	33-35 WGA, ≥ 2 risks
R8	33-35 WGA, 0 risks (not eligible)
R9	36-37 WGA, otherwise not at risk (not eligible – control group)

The first important result among these estimates is that the presence of severe medical risk factors results in higher RSV admission rates compared to the relatively healthy R9 control group. This is shown by infants in the R1 risk group, who are diagnosed with chronic lung disease or congenital heart disease, and who experience 105.69 more RSV admissions per 1,000 births than infants in the R9 group. Risk group R5 is composed of infants born from 29 to 32 weeks gestation who also have an additional respiratory, immune, or pulmonary related condition. These infants experience 48.10 more RSV admissions per 1,000 births compared to the R9 group. Similarly, infants in risk groups R6 and R7, who are born from 33 to 35 weeks gestation and who also have risk factors, also experience elevated RSV admission rates.

Although less pronounced in magnitude for risk groups that are based on only gestation and exclude those who have additional medical risk factors, those who are at a higher risk based on gestational age, also experience increased RSV admission rates, which decrease as gestational age increases.

Among the coefficients estimating interactions between risk groups and birth years, there is suggestive evidence of slight improvements in the RSV admission rate for later years. Interactions of birth years and R1, the CLD and CHD risk group, show estimates that indicate a decline in the RSV admission rates over time, while at the same time this group does not see improved outcomes for gastroenteritis, fever, and dehydration. This could imply that palivizumab is improving the health of this group, however the coefficients describing changes in the RSV admission rate are not significant. Results follow a similar pattern for the interactions involving the R2 risk group, composed on infants born at ≤ 28 weeks gestation. Again there is suggestive evidence that this group experience improved RSV admission rates in the later years, but the results lack statistical significance, meaning that the changes in admission rates are not statistically different from 0. There is little controversy about the benefits of palivizumab in improving RSV outcomes among both of these groups among medical practitioners (Romero, 2003; Welliver, 2003), so it is likely that the lack of significance in these results may be the result of poor compliance rates, meaning that either that doctors are not prescribing the drug to these infants, or that parents are not ensuring that all doses required to maintain an effective level of immunity are being administered in a timely manner.

There is some controversy (Joffe et al., 1999; Marchetti et al., 1999; Lofland et al., 2000; Stevens et al., 2000; Feltes et al., 2003) about the efficacy of the drug among the infants in risk groups R3 and R4, who are all born from 29 to 32 weeks, with group R3 being born during the RSV season and who are eligible for the drug, and group R4 who are born during spring and summer months when RSV virulence is relatively low and who are not eligible for palivizumab. The interactions between the R3 group and birth years show statistically significant improvements in RSV outcomes for this group starting in 2002, with RSV admission rates lowered by 8.82, 10.66, and 7.71 per 1,000 in 2002, 2003, and 2004 respectively. The interactions between the R4 risk group and birth years hint towards improved RSV outcomes in the later years but lack statistical significance. These results may be interpreted in two ways. The first is that infants of this gestation who are born during the winter months should receive palivizumab as it is shown that the group's RSV admission rates are falling over time when the drug is being used. Another interpretation could be that the infants in the R4 risk group, who do not receive the drug, are not experiencing improved outcomes, which is expected since their immunity to RSV is not increased by the use of the drug. But it could be the case that if they were given the drug their outcomes could improve, however, these results cannot be used to support that claim. In any case, it does appear that infants in risk group R3 are experiencing improved RSV outcomes.

Risk group R8 is composed of infants born from 33 to 35 weeks gestation who are otherwise healthy. Comparing the coefficients of the interactions between this group and birth years show that there are no statistical differences in RSV or control conditions outcomes relative to the group of infants who are born from 36 to 37 weeks gestation. Several studies funded by MedImmune have stated that infants born from 33 to 35 weeks gestation may receive benefits from palivizumab (Lofland et al., 2000; Feltes et al., 2003), while studies funded independently show that there are no benefits received by this gestational group (Joffe et al., 1999; Marchetti et al., 1999; Stevens et al., 2000). This result supports the independently funded studies as the estimates show no significant difference in RSV admission rates between infants born from 33 to 35 weeks gestation compared to those born from 36 to 37 weeks gestation.

To conclude the discussion on the results found when RSV inpatient admission is the outcome, the results are mixed. The models that use a single variable to indicate palivizumab eligibility status show that there were modest improvements in the RSV admission rate starting in 2002. On the other hand results from the regressions that use specific risk factors to identify palivizumab eligibility do not show such clear cut improvements. Although the results tend to show improved outcomes in the later years, the estimates lack the statistical significance needed to be certain that improvements in the RSV admission rate are occurring for specific risk groups. Because it has been shown through various clinical studies that palivizumab does reduce the RSV admission rate among at risk groups when used appropriately, these results do suggest that compliance rates in California were likely very low in the years immediately after the drug's introduction in 1998 as there were no signs of improved outcomes in early years, but that compliance rates may have increased in the later years given the improvements that these regression results suggest. At the same time, this improved compliance does not seem to be concentrated in a particular risk group, given that entire group of infants who are eligible for the drug show signs of improvement via Table 5 – Panel B, while specific risk groups do not show systematic improvements in outcomes, as shown in Table 6 – Panel B.

3.1.2 Results using inpatient charges as the outcome

Models that use inpatient charges as the outcome come from similar models to those that use inpatient admissions. The regressions that use a single palivizumab eligibility status indicator as the identification method are from this equation:

$$Charges_{it} = \alpha + \boldsymbol{\gamma X} + \sum_{m=May}^{March} \beta_{BM}^{m} \left(BMonth_{im} \right) + \sum_{t=1998}^{2004} \beta_{Y}^{t} Y_{it} + \beta_{Elg} Eligible_{it} \\ + \sum_{t=1998}^{2004} \beta_{Elg}^{t} \left(Y_{it} \cdot Eligible_{it} \right) + \varepsilon_{it}$$

While the estimates produced from regressions using specific risk indicators are based on this equation:

$$Charges_{it} = \alpha + \boldsymbol{\gamma X} + \sum_{m=May}^{March} \beta_{BM}^{m} \left(BMonth_{im} \right) + \sum_{t=1998}^{2004} \beta_{Y}^{t} Y_{it} + \sum_{r=1}^{8} \beta_{RF}^{r} Risk_{ir} + \\ + \sum_{t=1998}^{2004} \sum_{r=1}^{8} \beta_{RF}^{rt} \left(Y_{it} \cdot Risk_{ir} \right) + \varepsilon_{it}$$

Note that these regressions use identical notation for variables and coefficients on the right hand side. The results from these regressions are shown in Tables 7 and 8, with estimates using RSV inpatient charges as the outcome shown in the left column, and estimates from the regression using the control conditions of gastroenteritis, fever, and dehydration shown in the right column. Recall that all charges are in real terms based on the medical component of the Bureau of Labor Statistics Consumer Price Index with a 2004 base year.

It is important to recall that infants who are not admitted are assigned inpatient charges equal to $0. As stated earlier, this ensures that the estimates can be related to all infants used in the sample not just those who are hospitalized. Hence the estimates should be interpreted as changes in charges per infant, and not per hospitalization. Because charges are per infant, it is likely that admission rates are a major influence on charges, given that as more infants avoid admissions, these infants also record $0 charges. It could also be true that even if palivizumab does not necessarily decrease the inpatient rate for certain groups, which was shown to be the case in the previous section for several risk groups of infants, that usage of the drug may result in less severe infections that may still require an admission. If palivizumab is effective in reducing RSV related inpatient charges, it is likely that the mechanism by which charges are reduced is a combination of both of these effects.

Panel A of Table 7 and Table 8 shows the estimated effects of sociodemographic characteristics and month of birth. Given that the regressions used in these two tables use the same sample and only vary in that the regressions in Table 7 use a single palivizumab eligibility indicator while the regressions in Table 8 use specific risk indicators, the results on the sociodemographic and birth month variable are similar and so only one set will be discussed, those from the regression with a single eligibility indicator shown in Table 7 – Panel A.

The estimates show that infants who are enrolled in public insurance plans experience inpatient RSV charges that are $509 greater than infants with private insurance. Those with public insurance also experience increased charges of $276 per infant compared to infants with private insurance for admissions caused by gastroenteritis, fever, and dehydration. The effects of maternal education are not significant for either RSV or the control conditions, however the coefficients do show that increased maternal education may be correlated with lower inpatient charges.

Known RSV risk factors display the expected sign and significance, with male infants having RSV related charges of over $200 more than female infants, and infants who are first born to their mother experience reductions in RSV charges of nearly $250. Results for the same coefficients found in the models with the control conditions as the outcome are of the same signs but are smaller in absolute terms by an order of magnitude. Month of birth coefficients show that infants born during the winter months have higher RSV costs than those born in the spring and summer months, with births in September and October having per infant RSV related charges over $400 more than infants born in April, and infants born in November, December, and January having increased RSV charges of nearly $750, $850, and $900 per infant, respectively, compared to births in April. Among results for the control conditions there are no strongly significant patterns in charges by birth month.

Table 7 – Panel B shows DD results for inpatient charges for models using a single dummy variable indicating palivizumab eligibility, birth year dummies, and interactions between the two. Most of these estimates show increased charges over time, although these increases are not likely due to the application of palivizumab as very few infants receive the drug as inpatients. These results may indicate that despite modest improvements in RSV admission rates shown above, that inpatient charges may be

increasing at a pace that overwhelms the decline in charges brought upon by fewer admissions per 1,000 infants. This could be a situation similar to that described by Ginsburg et al. (2006) in which despite societal improvements in health outcomes, total inpatient spending is not reduced because of more aggressive and costly inpatient procedures on those who are admitted. Regardless of the mechanism behind this lack of decreased inpatient charges, it is clear that the introduction of palivizumab has not reduced charges for the eligible population compared to those born in the 1997 base year. However, it is possible that there were year to year declines in charges, which will be discussed in the following subsection.

Table 8 – Panel B shows results for models that use specific risk factors to identify palivizumab eligibility, along with birth years, and interactions between the two sets of variables. Risk groups are defined in the same way as above, recall that the definitions are:

Risk Group	Condition
R1	CLD or CHD
R2	≤ 28 WGA
R3	29-32 WGA, Jun-Feb
R4	29-32 WGA, Mar-May (not eligible)
R5	29-32 WGA, other risks
R6	33-35 WGA, 1 risk
R7	33-35 WGA, ≥ 2 risks
R8	33-35 WGA, 0 risks (not eligible)
R9	36-37 WGA, otherwise not at risk (not eligible – control group)

The results for the interacted coefficients involving the R1 group, that includes infants with chronic lung disease and congenital heart disease, and R2, infants who are born at ≤ 28 weeks gestation do not show any significant reductions in charges. In fact infants in the R1 group experience large and significant increases in charges, which may be due to more aggressive inpatient treatments. Infants in the R2 risk group do show a modest and significant reduction of inpatient RSV related charges in 2004, equal to about a $700 decrease per infant in this group. However, given the lack of other reductions in charges among this group, it may not be the case that palivizumab is responsible for reduced charges for this risk group.

Recall that the R3 and R4 groups represent some of the controversy surrounding the AAP guidelines, as the efficacy of the drug is disputed for these groups with R3 being eligible while R4 infants are not eligible. The DD estimates for both groups show reduced charges, however the coefficients are not precisely estimated. Given that both groups have similar results here, it could be argued that RSV related charges among both groups are unresponsive to the usage of palivizumab.

Risk groups R5, R6, and R7 all include infants with additional risk factors. Again, the interacted DD results for these groups show negative changes in real inpatient charges, indicating that palivizumab usage may be decreasing charges, but at the same time the estimates are not statistically different from no changes. So again the effectiveness of palivizumab in reducing inpatient charges for these infants is inconclusive.

Lastly, the results for risk group R8, infants born from 33 to 35 weeks gestation with no other risk factors, do not show any significant difference from the control group of infants born from 36 to 37 weeks gestation. This is expected as neither group should receive palivizumab.

It should also be noted that for the models that use real charges related to admissions caused by the control conditions of gastroenteritis, fever, and dehydration, the coefficients tend to be of similar magnitude to the corresponding estimates found for the RSV outcomes, and the estimates for the charges related to these control conditions lack statistical significance.

To summarize the results from these regressions that measure changes in per infant inpatient RSV related spending, it seems clear that the introduction and application of palivizumab has not been a major contributor to reductions in RSV related charges. In fact it appears in some cases that RSV related charges have increased. From the results using inpatient charges due to the control conditions of gastroenteritis, fever, and dehydration, there does not seem to be evidence of substantial trends in their charges, meaning that there are no obvious reasons to believe that charges related to RSV could have increased because of unobserved changes in infant inpatient treatment patterns. As mentioned earlier, it may be the case that although there is evidence that RSV admissions are on the decline, that treatment for those who are admitted for RSV may have become more aggressive over time, resulting in increased charges.

3.2 Linear combinations of difference-in-differences models

Tables 9 and 10 show difference-in-differences estimates calculated by linearly combining coefficient estimates obtained from the previous regression results. Each table shows ten different estimates, with models i. to iv. coming from the regressions that contained only interactions between a palivizumab eligibility status indicator and birth years, while the results in models v. to x. are based on the regression models that contain the eight specific risk factor indicator variables interacted with birth years. Each table again shows two outcomes, both the RSV related outcome and the outcome for the control conditions, and each table also shows the F statistic (and related p-value) from

Wald tests of whether the DD coefficient for the RSV outcome is statistically different from the DD estimate for the control condition. A brief description and justification of each model with be constructive in better understanding and interpreting the results:

i. $\left(Eligible \cdot 1998 - Eligible \cdot 1997\right) - \left(1998 - 1997\right)$ This model compares the estimates between those who are eligible for the drug in 1998 (and can receive the drug as it was introduced in that year) to infants who would be eligible for the drug but who cannot receive it as they were born before its introduction; this is captured by $\left(Eligible \cdot 1998 - Eligible \cdot 1997\right)$. Similarly the comparison is made between infants who are not eligible for the drug, and who should not receive any benefit from the drug, and these changes are captured by the $\left(1998 - 1997\right)$ term. Differencing these two differences shows how changes in the eligible population changes relative to changes in the non-eligible population, so that if there was some secular change in RSV outcomes unrelated to palivizumab, the non-eligible group will have similar changes to the eligible group. This estimate will measure the "immediate" effect of the drug, as the comparison is between infants born just before and after the introduction of the drug. Note that the estimate produced by this linear combination is exactly equivalent to the coefficient on $Eligible \cdot 1998$ in the regressions in Tables 5 and 7.

ii. $\left(Eligible \cdot 1999 - Eligible \cdot 1997\right) - \left(1999 - 1997\right)$ This model is similar to the above model with the exception that the comparison is made for 1999 and not 1998. This estimate still is an "immediate" effect as the drug was still relatively new in 1999. The estimate produced by this equation is identical to those shown on the coefficients $Eligible \cdot 1999$ in Tables 5 and 7.

iii. $\left(Eligible\cdot 2003-Eligible\cdot 1998\right)-\left(2003-1998\right)$ The previously defined DD models use births in 1997 as the control year, when palivizumab was not available, and test how the introduction of palivizumab affected outcomes. This model uses 1998 as the base year, so palivizumab is available for both birth cohorts. Instead of testing how the availability of the drug affects outcomes, this model tests how the potential of increased usage of the drug affects outcomes, as increased compliance and distribution of the drug means that more infants are likely to use the drug in later years than in the early years of its introduction.

iv. $\left(Eligible\cdot 2004-Eligible\cdot 1998\right)-\left(2004-1998\right)$ This estimate is similar to the above in attempting to measure uptake effects, except that 2004 is used instead of 2003.

The remaining models are from the estimates in Tables 6 and 8, with identification of palivizumab eligibility based on specific risk factors. Again, some models are based on the immediate effects of the drug comparing infants born in 1997 to those born in 1998 or 1999, while other models estimate uptake effects of the drug, by comparing infants born in 1998 to those born in 2003 or 2004. The more important distinction of the following models from the proceeding models is their use of specific risk factors opposed to simple eligibility status. Specifically there will be comparisons between two relatively similar risk groups in each model. The following models are defined and tested.

v. $\left(R3\cdot 1998-R3\cdot 1997\right)-\left(R4\cdot 1998-R4\cdot 1997\right)$ This DD will estimate the effects palivizumab may have had on similar and otherwise healthy infants born from 29 to 32 weeks gestation, as infants in the R3 group are born during the RSV season eligible for the drug but infants in the R4 group are born outside of the RSV season and are not eligible. Again, since palivizumab was introduced in 1998, those infants born in 1997 could not receive the drug, hence this DD measures the immediate effect of the drug on this gestational group.

vi. $(R3 \cdot 1999 - R3 \cdot 1997) - (R4 \cdot 1999 - R4 \cdot 1997)$ This DD is similar to the previous model, except that it compares infants born in 1997 to those born in 1999.

vii. $(R3 \cdot 2003 - R3 \cdot 1998) - (R4 \cdot 2003 - R4 \cdot 1998)$ This model also compares infants born from 29 to 32 weeks gestation who were born in season or out of season. But this model measures uptake effects rather than the immediate effects of the drug, as the comparison is between infants born in 1998 and 2003.

viii. $(R3 \cdot 2004 - R3 \cdot 1998) - (R4 \cdot 2004 - R4 \cdot 1998)$ This model is similar to the previous model as it also uses the same risk groups and measures uptake effects, but instead the years compared are 1998 and 2004.

ix. $(R6 \cdot 2003 - R6 \cdot 2002) - (R7 \cdot 2003 - R7 \cdot 2002)$ This DD model compares infants born from 33 to 35 weeks with other medical risk factors. The R6 group contains infants with a single additional risk factor, while the R7 group contains infants with two or more risk factors. The American Academy of Pediatrics altered their guidelines starting in 2003, so that infants of this gestation went from needing only a single risk factor to be eligible in 2002 (so both groups were eligible) to requiring these infants have at least two risk factors, meaning that members of risk group R6 were not eligible for the drug starting in 2003. This DD estimate measures the immediate effect of the change in policy on outcomes, as infants born in 2002 are compared to those born in 2003.

x. $\left(R6 \cdot 2004 - R6 \cdot 2001\right) - \left(R7 \cdot 2004 - R7 \cdot 2001\right)$ This final model is similar to the previous model in that the same risk groups are compared in an effort to identify changes in the policy guidelines. But this model compares infants born in 2001 to those born in 2004. As it could have been the case that some physicians were aware that the AAP were planning on changing guidelines starting in 2003, they may have started to distribute fewer palivizumab prescriptions in 2002 as well. At the same time, some doctors may not have been fully aware of the change in policy in 2003, and they could have continued prescribing the drug to infants who were now no longer indicated for it. By using 2001 and 2004, instead of 2002 and 2003, these problems are likely to be avoided, while the policy alteration is still splitting the sample.

3.2.1 Linearly combined DD Results

Tables 9 and 10 contain difference-in-differences coefficients for an RSV related outcome (first column), and the corresponding outcome for the control conditions of fever, dehydration, and gastroenteritis (second column). Each table also shows the F statistic from the Wald test that the RSV and control condition coefficients are statistically different from each other (third column). The null hypothesis of this test is that the resulting DD estimates for the RSV outcome and the control conditions outcome are the same, meaning that any changes related to RSV outcomes are likely because of changes in overall patterns of inpatient care. However, the alternative hypothesis is that the DD estimates computed for RSV outcomes and control conditions outcomes are different, meaning that RSV outcomes are affected by something other than a generic trend in inpatient care.

Table 9 shows DD results for the outcome of admission status, which is multiplied y 1,000 to represent admissions per 1,000 infants. Models i. and ii. do not show any evidence of immediate improvements of RSV outcomes upon the introduction of palivizumab. But models iii. and iv. show that among infants who are eligible for palivizumab there were reductions when comparing 2003 and 2004 to 1998. Model iii. compares 1998 to 2003 and shows a decline of 9.27 RSV admissions per 1,000 infants, while model iv. shows a reduction of 12.10 RSV admissions per 1,000 infants; both of these estimates are significant and the corresponding F statistics show that they are also distinct from the corresponding coefficients obtained from the control conditions, meaning that the uptake of palivizumab likely did play a role in reducing RSV admissions. Note that there were 11,517 infants eligible for palivizumab in 1998, and subsequently 11,334 and 12,106 eligible infants in 2003 and 2004 respectively, so the drug may have been responsible for approximately 140 avoided hospitalizations comparing 2003 and 2004 to 1998, the first year palivizumab was available.

Models v. and vi. show that there were no immediate effects on the RSV hospitalization rate between infants born from 29 to 32 weeks gestation in season (who are eligible) and out of season (who are not eligible). There is some evidence of uptake effects among these infants, with the comparison from 1998 to 2003 and from 1998 to 2004 resulting in statistically significant decreases of 14.58 and 10.69 RSV hospitalizations per 1,000 infants, respectively. However, the comparison between 1998 and 2003 yields a small F statistic, meaning that it is not entirely clear if these declines in RSV admissions were the result of the group R3 being eligible for the drug while R4 were not, or if instead there was some change in the overall inpatient patterns for these infants, resulting in systematic reductions in the admission rate for all conditions.

Models vii. and viii. show results for the uptake effects for infants born from 29 to 32 weeks who are in risk group R3 and born in season and eligible for palivizumab, compared to infants of the same gestation in risk group R4 who are born out of season and who are not eligible for the drug. Model vii. compares infants born in 1998 to infants born in 2003, while model viii. compares infants born in 1998 to those born in 2004. Both estimates show declines in the RSV inpatient rate among the groups, with infants in the eligible group having 15.58 fewer admissions per 1,000 infants for 2003 and 10.69 fewer for 2004, both of which are statistically significant. So it does appear that infants who are born from 29 to 32 weeks gestation and who are eligible for palivizumab have experienced declines in their RSV admission rates relative to similar infants who are not eligible for the drug. But comparing these declines in RSV admissions to declines in admissions for the control conditions does not produce any definitive conclusions as to whether the RSV admission rates are due to RSV or due to external factors that influenced all inpatient admissions for these infant groups. Testing whether the decline in RSV admissions between 1998 and 2003 is statistically different than the change in admissions for the same years for the control group of conditions produces an F statistic of 3.97, which means that the two estimates are significantly different at the 5% confidence level. But the F statistic of the similar test between the 1998 and 2004 coefficients yields an F statistic indicating that the change in RSV admissions is not statistically different than that of the control conditions. Although the DD results for the individual RSV outcomes show that there likely was a decline in RSV admissions due to uptake effects among this group of infants, it is not clear if these declines are entirely due to palivizumab or perhaps due to other factors that affected all admissions for all conditions among infants of this gestational age.

Lastly for the DDs with admission rates as the outcome, models ix. and x. show results that account for the policy change in 2003 in which infants born from 33 to 35 weeks gestation with a single additional risk factors became non-eligible for palivizumab (R6), while infants of this gestation with two or more additional risks remained eligible (R7). Model ix. tests for the immediate effects of this policy alteration, comparing 2002, when group R6 was eligible, to 2003 when group R6 was no longer eligible. This model shows a slight increase in admissions among the group who lost their eligibility, although it is not statistically significant. Model x., which compares 2001 with 2004 to account for the possibility of providers adjusting their prescription patterns in 2002 before the guideline change or being unaware of the guidelines and prescribing palivizumab to the R6 group during 2003 after the policy changed, shows a substantial and significant increase in the RSV admission rate which could potentially mean that those infants in R6, who lost eligibility for palivizumab suffered poorer outcomes as a result of the policy change. But during the same period there was also a large and significant increase in admissions among the two groups for the control conditions (on which palivizumab has no effect), with the result being that the changes in the RSV admission rate are not significantly different from the changes in the control condition admission rate. So although it appears that the change in policy may have made those who became ineligible for the drug worse off, it is not clear if this poorer outcome was due to the policy change or due to some other change that affected all infants in this group. And again it should be noted that there may be problems with the statistical power of this test, as there are between only 47 and 79 infants in the R7 group and between 760 and 578 infants in the R6 group for the years tested, so small changes in any of the specific group-year rates could result in large effects in the overall changes in admission rates.

Table 10 shows DD combinations using real inpatient charges as the outcome. Models i. and ii. show the immediate effects of the introduction of palivizumab on real RSV and control condition charges. Both models show increases in the real inpatient charges related to RSV, and both show that the estimates for RSV charges are statistically different than charges of the control conditions. This implies that charges related to RSV rose immediately after the introduction of palivizumab relative to charges related to other conditions among infants who are eligible for the drug. Models iii. and iv. measure uptake effects by comparing 1998 to 2003 and 2004, respectively. These results are statistically insignificant, meaning that palivizumab uptake did not result in reduced inpatient charges.

Models v. to viii. all compare risk group R3, infants born from 29 to 32 weeks gestation during RSV season who are eligible for palivizumab, to R4, infants of the same gestation born outside of RSV season who are not eligible for the drug. Models v. and vi. examine the immediate effects of the introduction of palivizumab, and both estimates show increases in RSV inpatient charges per infant but neither estimate is statistically significant. Models vii. and viii. examine the uptake effects of the drug and the estimates show declines in real charges, but these estimates are also not statistically significant. These estimates all show that changes among the eligible group of infants were no different from the changes among the ineligible infants, and can be interpreted in several ways. One interpretation could be that infants in the R3 group were given the drug while those in the R4 group were not, which follows the prescription guidelines, and that the severity of RSV infections among the R3 group were not improved enough to produce declines in inpatient charges relative to the R4 group. But recalling that this is an intention to treat measure, it could also be possible that infants in both groups received similar benefits from the drug, with doctors going against the guidelines and either prescribing palivizumab to both groups in equal proportions or not prescribing the drug to either group. In this case, if the drug is effective for both risk groups the severity of their infections could be reduced equally, and hence any changes in the real charges are cancelled out, or at the same time it could be possible that neither group benefits from the application of palivizumab and hence there were no changes in the severity of RSV infections between the two groups. In any case, it does not appear that the infants born from 29 to 32 weeks gestation from July to February have lower real inpatient RSV charges compared to those born from March to June, despite a policy making the former group eligible and the latter group not eligible.

Models ix. and x. compare the policy change that occurred in 2003. These results show that infants born from 33 to 35 weeks gestation with one additional risk factor did not fare any worse that infants of a similar gestation with two or more risk factors immediately before and after the policy change, comparing those born in 2002 with those born in 2003. But when comparing the same risk groups with outcomes from births in 2001, a year before the policy change, and those born in 2004, a year after the policy change, there does appear to be an increase in real charges. This increase is equal to $1,875 per infant but is not significant. The Wald test between this estimate and the estimate for the control conditions shows that there is no significant difference between the two estimates, meaning that it is not obvious if the increase in charges are related to the reduction in palivizumab use brought on by the policy change or if there were other factors affecting all infants in these risk groups. And to reiterate from the previous admission rate estimates, both the R6 and R7 risk groups contain a relatively small number of observations, so the estimates likely lack the statistical power to create precise measurements.

To conclude the discussion on difference-in-differences results, there does not appear to be any impact on RSV admission rates immediately after the introduction of the drug, but RSV inpatient charges do seem to have increased over the same period relative to charges related to the control conditions of gastroenteritis, fever, and dehydration. This increase in inpatient RSV charges is not likely caused by palivizumab given that very few doses of the drug are administered in an inpatient setting according to the data. When comparing results based on specific risk categories, groups of infants who are eligible for palivizumab do not appear to have experienced substantial improvements relative to similar groups of infants who are not eligible for the drug. Notably, infants born from 29 to 32 weeks gestation during the RSV season who are eligible for the drug do not have marked improvements in outcomes compared to infants of the same gestation who were born out of season who are not eligible for the drug. And although infants born from 33 to 35 weeks gestation with a single risk factor who became ineligible for palivizumab starting in 2003 saw increased RSV admission rates relative to infants of a similar gestation who have two or more additional risks who remained eligible for the drug, the changes in outcomes are not statistically different from changes in outcomes for the control conditions, meaning that the change in RSV outcomes is not necessarily due to palivizumab but may instead be caused by some unobserved changes in inpatient trends for these groups for all causes of admissions.

4 Estimating total costs of RSV

The regression results discussed in the previous section show that RSV admission rates among infants who are eligible for palivizumab have declined slightly since the introduction of palivizumab in 1998. Despite these apparent improvements in health outcomes, the total costs associated with these improvements are not immediately clear as inpatient charges associated with RSV related admissions per infant do not appear to have decreased. Along with this the spending associated with palivizumab is not easily identifiable from the data, as there are no records of whom received the drug or of how many doses were administered. Recall that the regression results are based on an intention to treat framework, where identification of the "treated" group is based on an infant's eligibility for the drug determined by underlying risk factors, and not based on the actual physical application of palivizumab to an infant. As the total economic efficiency of palivizumab is a function of the improvements in health outcomes, changes in inpatient charges, and the spending on the drug necessary to precipitate these changes, it is constructive to estimate a measure of the spending associated with palivizumab to determine the efficiency of the drug.

It should be noted that the following estimates only consider the financial costs associated with RSV hospitalizations and the application of palivizumab. An estimate of the full economic costs would need to include measures of utility decreases that are associated with inpatient hospitalizations along with consideration for the possibility of health problems at a later age that may be caused by severe RSV infections as an infant. See Stein et al. (1999) and Van Bever (2009) for examples of how infant RSV infections may lead to other respiratory conditions in the years beyond infancy. Therefore the results presented in this section should be viewed as estimates of the financial costs associated with RSV and its prophylaxis, and not necessarily the full economic costs.

In order to produce an estimate of the efficiency of palivizumab it is first necessary to determine how many doses of the drug were administered, as the total costs associated with palivizumab are simply the number of doses administered times the price of a dose. Because the total number of doses administered is not available in the data I will instead calculate the estimated compliance rate, i.e. what percentage of eligible infants received the drug. This will be done by comparing the RSV admission rates found in the IMpact RSV clinical trials (AAP, 1998) for the placebo group, who can be viewed as a group of infants with a 0% palivizumab compliance rate, and for the treated group, who can be viewed as infants with a 100% compliance rate. As I will explain below, the observed RSV admission rates in the California data always fall between the control group and the treatment group admission rates found in the IMpact study, so a simple linear interpolation will be used to predict the population wide compliance rates, and from these rates the number of total doses of palivizumab that were likely administered can be estimated.

4.1 Estimating palivizumab costs

Each year of the sample of infants from California contains over 11,000 births who are eligible for palivizumab because of gestational age or other medical risk factors. Each of these infants may be eligible for up to five doses of the drug, and when controlling for infants who are born during the RSV season and will receive fewer than five doses, the result is the potential for nearly 50,000 doses per year. Based on pricing information from Medi-Cal pharmacy data, the average real price per dose of palivizumab is calculated for each year. If each infant was fully compliant and received each dose for which they were eligible this would result in between $49 million to $58 million in spending on palivizumab per year. For each 25% reduction in the population wide compliance rate there is an expected decline of approximately $13 million in spending. Table 11 shows the yearly number of eligible infants, potential doses, price per dose, and distributions of spending on palivizumab based on compliance.

It is important to understand more fully what is meant by compliance with respect to palivizumab as it is a major determinant of total palivizumab spending. Specifically, the compliance rate will refer to the entire infant population who are eligible for the drug. Each infant who is eligible for palivizumab falls into one of three compliance categories: (1) the infant received no doses of palivizumab; (2) the infant received an incomplete regimen of the drug, e.g. the infant was eligible for five doses but received only three; and (3) the infant was fully compliant and received the full regimen as prescribed. Cases (1) and (3) are the simplest in terms of evaluating the prophylactic effects of the drug, as the infant who receives no doses has no additional immunity from the virus throughout the entire RSV season, while infants who receive all doses in a timely manner have maximum protection from a severe RSV infection throughout the RSV season. Although there may be underlying selection biases present among these two types of infants that could possibly alter outcomes regardless of palivizumab status, when comparing outcomes of these two groups to the infants in the IMpact study, the infants who do not receive any doses can be thought of as a placebo group, while those who receive all of the doses may be viewed as the treatment group. Among these two groups, compliance can be viewed as the percentage of infants who receive all required doses, and RSV admission rates are expected to have a negative relationship with this compliance rate.

However, the group of infants who receives at least one dose, but less than the recommended full regimen have a more complicated prophylaxis profile. Because palivizumab provides passive immunity, the concentration of the antibodies depletes over time in such a way that there is little if any benefit received from the drug by approximately 30 days after an injection (Groothuis and Nishida, 2002), hence the need for monthly doses during the peak RSV season. It is also the case that the virulence of RSV is not constant from November to March, as the regression results show clear differences in the RSV admission rates from month to month during the RSV season. (See Figure 2 for the monthly distribution of RSV admissions over several years or Panel A of Tables 5 and 6.) This means that if an infant is eligible for all five doses of palivizumab but receives only four, they will be unprotected for one month, and the probability of acquiring a severe RSV infection is dependent on which month this happens to be, as infants who do not receive the drug in January will have a higher infection rate than those who go unprotected in March. It will be assumed that the distribution of "missed months" is uniform across all months during the RSV season, meaning that there is no systematic preference to skip months when RSV infection rates are lower, or to conversely ensure that doses are administered during the months with the most RSV admissions. Given this assumed uniform distribution of missed doses, the resulting RSV prophylaxis profile is comparable to those of infants with no compliance or full compliance.

In general, the population wide palivizumab compliance rate is calculated as follows

$$C_{population} = \frac{\sum_{i=1}^{N} C_i}{\sum_{i=1}^{N} D_i}$$

Where C_i is equal to the actual number of palivizumab doses received by infant *i* and D_i is equal to the recommended number of doses infant *i* should have received. So the numerator is equal to the actual number of palivizumab doses received among the population, while the denominator is equal to the total number of doses that should have been received if compliance was full. Note that $D_i > C_i$ when infant *i* is not fully complaint and that $D_i = C_i$ when infant *i* is fully compliant.

With this understanding of how population wide compliance affects the presence of antibodies in an infant's immune system, and hence the subsequent ability to avoid severe RSV infections, I will now discuss the RSV admission rates found in the IMpact study. This double-blind, placebo-controlled study was conducted at 139 locations in the United States, the United Kingdom, and Canada during the 1996-1997 RSV season. The sample consists of 1,502 infants who had either chronic lung disease or who were born at or before 35 weeks gestation and who were less than six months of age at the start of the RSV season. Among the entire sample, 10.6% of the placebo group were hospitalized due to RSV while only 4.8% of the treated group were admitted with RSV. Among the premature infants, 8.1% of the placebo group were admitted with RSV and 1.8% of the treated group were admitted, and among the infants with chronic lung disease 12.8% of the placebo group were admitted and 7.9% of the treated group were admitted. Note that in the context of defining compliance, the placebo group are considered to have 0% compliance while the treated group are viewed as 100% compliant.

To compare these RSV rates to the rates among the infants in the California data, the first step is to limit the sample to infants with similar characteristics of the infants in the IMpact clinical trial. One subsample will consist of infants who are diagnosed with chronic lung disease. Note that this group varies from the R1 risk group used previously in the regressions, as that group included infants with either chronic lung disease or congenital heart disease, while this group includes only those with chronic lung disease. The second subsample will consist of infants born at or before 35 weeks gestation and who are no more than six months of age at the beginning of the RSV season. Comparing the results of this group to the similar group in the IMpact study poses a difficulty, as the AAP only recommends that infants from 33 to 35 weeks gestation are given palivizumab when complications are present, while similar infants in the IMpact study were not restricted in such a way. Because of this I will identify infants who are (1) born at ≤ 35 weeks who are eligible for palivizumab under the AAP guidelines, (2) infants who are born at ≤ 35 who are not eligible under the AAP guidelines, which consists of those born from 29 to 32 weeks gestation during the summer months and those born from 33 to 35 weeks gestation who have no additional risk factors, and (3) all infants who are born at ≤ 35 weeks gestation. Infants in group (2) are not eligible to receive palivizumab as they are not expected to gain any substantial benefits from the drug, however similar infants were given the drug in the IMpact study. Although the IMpact study does not differentiate admission rates by specific gestational age among the premature group, it is expected that outcomes between infants with gestational ages from 33 to 35 weeks will not improve because of the drug (Joffe et al., 1999; Marchetti et al., 1999; Stevens et al., 2000). In the context of the IMpact trial, this implies that the differences in admission rates between the placebo and palivizumab groups are driven by infants with gestational ages of ≤ 32 weeks, while infants born from 33 to 35 weeks gestation likely had similar outcomes regardless if they are in the placebo or palivizumab group as their relatively better developed respiratory and immune systems means that the drug provides them with little if any additional protection.

Tables 12 and 13 include infants from the California data set who have similar characteristics to those who participated in the IMpact clinical trials. Table 12 is composed of infants who are born at ≤ 35 weeks gestation and who are no more than six months of age at the onset of the peak RSV season. Note that this group of infants is composed of infants who are eligible for palivizumab under the AAP guidelines (those born at ≤ 28 weeks gestation, those born at 29 to 32 weeks gestation during the RSV season, those born from 33 to 35 weeks gestation who have additional risk factors) and infants who are not eligible for palivizumab (infants born from 33 to 35 weeks gestation with no additional risk factors). The observations included in Table 13 are limited to those who are diagnosed with chronic lung disease. These tables list the number of yearly births, RSV admissions, and RSV related charges observed in the California data.

These tables also show the estimated compliance rates which are calculated by linearly interpolating the RSV admission rates from the placebo and control groups in the IMpact study. Recall that the infants in this clinical trial had RSV admission rates of

8.1% for the placebo group and 1.8% for the palivizumab group for infants of ≤ 35 weeks gestation, while the CLD group had admission rates of 12.8% among those in the placebo group and 7.9% for the palivizumab group. Based on these clinical trial admission rates, it is calculated that each percentage point increase in compliance among the ≤ 35 weeks gestation group will result in a 0.063 percentage point decline in the RSV admission rate, found as (8.1% - 1.8%) ÷ 100 = 0.063%. A similar calculation based on the CLD group admission rates reveals that a percentage point increase in compliance is expected to result in a 0.049 percentage point decline in the RSV admission rate for this group, found as (12.8% - 7.9%) ÷ 100 = 0.049%.

Among the infants born at ≤ 35 weeks gestation the estimated compliance rates range from 54% to 71%, however it is likely these are over estimates of the true compliance rate, as the compliance rate is calculated to be 57% in 1997 when the true compliance rate must be 0% because the drug was not yet available. Despite the likely over estimation of compliance rates, the RSV inpatient rates are falling over time, which may be due to increasing palivizumab compliance over time which could indicate that doctors and parents are becoming more educated about the availability and potential benefits of the drug.

Among infants diagnosed with CLD, the estimated compliance rates range from 28% to 88%, but again these may be over estimated given that the estimated compliance rate in 1997 is 56% despite that the drug was not yet available. But as is the case among infants born at ≤ 35 weeks gestation, infants diagnosed with CLD are also experiencing declines in the RSV inpatient admission rate over time, which in this case is correlated with expected increases in palivizumab compliance rates.

Tables 14, 15, and 16 show estimated RSV outcomes based on theoretical palivizumab compliance rates. The row labeled “Births” is equal to the number of births per given year which are diagnosed with either chronic lung disease (Table 14) or who are born at ≤ 35 weeks gestation (Tables 15 and 16). “Observed RSV Rate” is the actual RSV admission rate among the infants and “Charges per Admission” is the observed real RSV related admission charges for a given year. Each table has five panels that estimate outcomes based on theoretical palivizumab compliance rates, with Panel A showing results when compliance is 0% (i.e. no one receives the drug) and is based on the RSV admission rates found among the placebo group in the IMpact study, while Panel E estimates outcomes based on a theoretical compliance rate of 100%, which are based on the results from the palivizumab group in the IMpact study. Panels B, C, and D represent compliance rates of 25%, 50%, and 75% respectively, and are based on RSV admission rates found from a simple linear interpolation between the 0% compliance admission rate and the 100% compliance admission rate.

In each panel, the row labeled “Admission Rate” is constant across years, and is based on the RSV admission rate associated with the given compliance rate. “Total Admissions” is simply the number of births in a given year times the admission rate, $A_{yc} = N_y \cdot R_c$, with N_y representing the number of births in year *y* and R_c representing the admission rate given palivizumab compliance of *C*%. “Total Inpatient Charges” is equal to the number of expected admissions times the average yearly RSV inpatient charges, $TIC_{yc} = A_{yc} \cdot X_y$, with X_y representing the average inpatient RSV related charges in year *y*. “Doses Provided” is calculated by $D_{yc} = \sum_{i=1}^{N_y} \left(D_i \mid Elig_i = 1 \right) \cdot C$, where D_i is the number of doses infant *i* would receive under 100% compliance, and *C* is the given compliance rate. Note that D_i is conditional on infant *i* being eligible for palivizumab. In Table 14 all infants are eligible for the drug as the sample is composed of infants with chronic lung disease. Tables 15 and 16 are composed of infants born at ≤ 35 weeks gestation. Results in Table 15 are based on the AAP prescription guidelines, where infants born from 33 to 35 weeks gestation with not additional risk factors are not eligible for the drug, and hence $D_i = 0$ for these infants, while $D_i = \{1,...,5\}$ for the others based on their birth month. Table 16 follows the IMpact study, where all infants born at ≤ 35 weeks gestation may receive the drug. This distinction of who is expected to receive the drug and who is not results in considerable differences in palivizumab spending, as will be discussed later. "Palivizumab Charges" are equal to $PC_{yc} = D_{yc} \cdot PP_y$ where PP_y is the real price for a single dose of palivizumab in year *y*. Lastly, "Total RSV Charges" are equal to "Total Inpatient Charges" plus "Palivizumab Charges", $TRC_{yc} = TIC_{yc} + PC_{yc}$. Hence the total spending associated with RSV varies by year and by the theoretical compliance rate assumed. Most of these statistics are not computed for 1997, as palivizumab was not available then.

The compliance rate that results in the lowest total RSV charges in a given year represents the most efficient use of the drug. Table 14 shows spending results among infants with chronic lung disease, and in most years total RSV charges are minimized when compliance rates are 100%, which means that the increased costs associated with increased palivizumab usage are outweighed by decreases in total inpatient charges that are caused by the lower RSV admission rate. But it should be stated that in 2000, the lowest total RSV costs are achieved when no infants receive palivizumab, which is because the RSV related average admission was just under $78,000 for that year, compared to the mean inpatient charges in other years, which range from just over $100,000 per admission to nearly $150,000.

Table 15 shows the total costs associated with infants who are born at ≤ 35 weeks gestation, and assumes that the AAP prescription guidelines are followed, meaning that infants born from 33 to 35 weeks gestation with no other risk factors never receive palivizumab. This table also shows that for most years cost minimization is achieved when compliance rates are 100%, as the increased costs of palivizumab are offset by decreases in inpatient RSV charges. But again, 100% compliance does not always result in RSV cost minimization, as the results show that in 1998 costs are minimized when the theoretical compliance rate of 0% is applied.

Table 16 shows the estimated RSV related costs when all infants who are born at ≤ 35 weeks gestation are eligible for palivizumab. This does not follow the AAP guidelines, but it does follow the IMpact study, in which all infants born at ≤ 35 weeks gestation were eligible for the drug. The results in this table show that for all years, total RSV related costs are minimized when no infants receive the drug. This result is driven primarily by the fact that there are many more infants born from 33 to 35 weeks gestation compared to those born at 32 weeks or less. Table 2 shows that from 1997 to 2004 there were over 200,000 infants born with gestational ages between 33 and 35 weeks, while there are under 100,000 infants born with gestational ages of ≤ 32 weeks. This means that in Table 16 there are approximately 25,000 infants receiving palivizumab per year compared to Table 15, and the resulting additional costs of providing palivizumab to these infants is not offset by reductions in inpatient charges.

4.2 Discussion of estimated total costs

There are two major points to take away from the results presented in Tables 14, 15, and 16. The first is that the AAP prescription guidelines seem to play an important role in containing costs. The second is that changes in the palivizumab compliance rates likely have large effects on the total spending associated with the treatment and prevention of RSV.

A simple comparison between Tables 15 and 16 shows how adherence to the AAP prescription guidelines may lead to immense savings in RSV related costs. Considering the implications of this policy are important from both an economic and a public health point of view. Assuming that otherwise healthy infants who are born from 33 to 35 weeks gestation receive little or no benefit from the drug on average, which is supported by several studies (AAP, 1998; Joffe et al., 1999; Elhassan et al., 2006), than a policy that makes this group ineligible for the drug seems to be efficient. These results also show the difficulty policy makers have in promoting guidelines that can be accepted by physicians, parents, and the larger health care community that includes insurance companies, drug makers, and the government. Table 16 provides an example of how setting the prescription guidelines based on outcomes from a heterogeneous sample of infants can lead to inefficient outcomes, as the results suggest that the drug should not be given to any premature infants. However, by simply excluding infants born from 33 to 35 weeks gestation from the drug, while providing the drug to infants born at ≤ 32 weeks produces better outcomes in both a financial sense, and by improving the health of many infants. The AAP further refined this policy among infants born from 29 to 32 weeks gestation by stating that those who are at least six months old at the start of the RSV season should not receive the drug as they do not benefit from it given they have more developed lungs and immune systems than similar infants who less than six months of age at the onset of the season.

These results also reiterate the importance high compliance rates have in improving both health and economic outcomes. In the case of infants with chronic lung disease there is little doubt among physicians or public health researchers that RSV outcomes are improved when these infants receive palivizumab (Leader and Kohlhase, 2003; Romero, 2003). The use of palivizumab among these infants results in both improved RSV health outcomes and reduced total spending on RSV treatment that offsets the cost of palivizumab. So from a policy maker's point of view, the question is not if these infants benefit from the use of the drug, but rather how to ensure that as many infants who are diagnosed with chronic lung disease receive the drug as possible.

5 Conclusions

The main question this research seeks to answer appears simple: How has the introduction of palivizumab improved RSV related outcomes among infants? But the answer to this question is rather complicated. Given the high prevalence of RSV among infants, with nearly all of them acquiring an infection before their second birthday (Glezen et al., 1986) and admission rates ranging from about 2.5% for healthy infant to over 6% for premature infants (see Table 3), the reason for concern among physicians, policy makers, and parents seems clear.

Palivizumab provides some degree of passive immunity to infants who have underdeveloped lungs and immune systems, while infants who have well developed lungs and immune systems receive no additional benefit from the drug as they already have naturally produced antibodies that provide protection from severe RSV infections. Although the use of palivizumab cannot cause RSV related health outcomes to worsen, it is the case that prophylaxis with the drug only improves outcomes if the child has these risk factors (AAP, 1998). Because of this, along with the high price of the drug, the AAP provides guidelines describing which infants should receive the drug and which infants should not. These guidelines are based on double-blind, place-controlled clinical trials (AAP, 1998; Neeman, 1998) and show that palivizumab is an efficacious agent in reducing the burden of RSV when used as directed.

Despite the drug's proven clinical efficacy, there remain doubts about its effectiveness in the free living population. Because the drug must be administered via five monthly injections, it is difficult to ensure that all doses are received in a timely manner. From an empirical viewpoint measuring the effectiveness of the drug among a large population has been difficult, as the identification of infants who are eligible for the drug is based on characteristics recorded on birth records, e.g. gestational age, while non-birth inpatient records provide data on RSV admissions. Failing a way to identify the at risk population and track them over time, knowing which RSV admissions are to infants with additional risk factors and which admissions are to otherwise healthy infants is a nearly impossible task.

However, this research benefits from the use of the California Linked Birth and Inpatient Database, which identifies risk factors at birth, and provides a linkage variable that is unique to individuals allowing for the tracking of each infant's health status over time. The result is that this research represents the first population-based study of how

RSV outcomes have been affected given the introduction of palivizumab, based on identification of risk factors allowing for the use of intention to treat measurements. The results shown in Section 3 confirm several findings from clinical trials and treatment on the treated studies, namely that the presence of risk factors like short gestation and chronic lung disease result is poorer RSV outcomes related to the outcome of otherwise healthy infants, and that birth month is correlated with the probability of an RSV admission, with higher rates in November, December, January, and February and lower admission rates in the summer months.

The results found here also show that upon the approval of palivizumab in 1998 there were no immediate improvements in RSV related outcomes among those who were eligible for the drug, and not until 2002 did the RSV related admission rate begin to fall. These results also show that there were few, if any, discernable decreases in RSV related inpatient charges among those who were eligible for the drug. Because palivizumab has a proven efficacy in improving outcomes in clinical settings when doses can be administered in a timely manner, it seems likely from the results found here that in the free living population not enough of the infants who are eligible for the drug are receiving it, or in other words the compliance rate is too low to result in improved outcomes at the population level.

The results found in Section 4 show how compliance rates and the definitions of eligibility groups affect the total spending associated with RSV. Based on the admission rates found in the IMpact study for the placebo and palivizumab groups, the results assume that as compliance rates increase, RSV admission rates fall, meaning that RSV inpatient spending falls, but at the same time spending on palivizumab increases. When the group of palivizumab eligible infants is narrowly defined, specifically when eligibility is based on the AAP guidelines, a 100% compliance rate usually results in both the lowest total RSV related spending and the lowest RSV admission rate, a result that is clearly utility maximizing. However, when the AAP guidelines are not used to define which infants are eligible for the drug, the result is that total spending is minimized when no infants receive the drug. Although this result minimizes spending, it also results in the higher RSV admission rate, so it is not clear how overall utility is affected. The theme behind the results in Section 4 is that RSV outcomes are improved when the prescription policies are based on narrowly defined risk factors.

To conclude, it may be constructive to approach this line of research from a broader economic perspective, considering not how the introduction of a single drug may have affected outcomes related to a single virus among infants, but instead how the analysis of innovations in health care can be better utilized to improve outcomes. Given that health care spending accounts for approximately 16% of the US GDP (Aizcorbe et al., 2008) it is crucial that this spending results in efficient outcomes. This research has outlined some of the difficulties in attempting to establish how to determine if an outcome is efficient, which is especially complicated when there are tradeoffs between spending and health. The use of intention to treat measurements at the population level may be a useful tool for policy makers to use in determining how well new technologies are being applied, and the results they produce can be used to create policies that promote the most efficient use of these new technologies that will result in both improved health outcomes and decreased total health care spending.

Table 1 - Indications for the use of palivizumab: American Academy of Pediatrics (AAP) and California Department of Health Services (CDHS) guidelines

	AAP Nov 1998	CDHS Feb 2003	AAP Dec 2003	CDHS Sep 2004	CDHS Oct 2005	CDHS Oct 2006	AAP Jul 2009
≤ 2 years old and has had CLD, CHD treatment within 6 months of RSV season	●	●	●	●	●	●	●
≤ 28 WGA and up to 12 months of age at start of RSV season	●	●	●	●	●	●	●
29-32 WGA and up to 6 months of age at start of RSV season	●	●	●	●	●	●	●
33-35 WGA with any risk factor [1, 2]	●	●					
33-35 WGA with at least 2 risk factors [1]			●	●	●	●	
33-35 WGA and attends daycare or has sibling < 5 years of age							● [A]
≤ 2 years of age and has had severe CLD may benefit from treatment during 2nd RSV season, with doctor's discretion			●				
≤ 12 months of age with CHD and if treated for certain conditions [3]			●				
≤ 24 months of age with CHD should not get prophylaxis if diagnosed with certain conditions [4]			●				
≤ 24 months of age at start of RSV season with CHD and approval from Cardiac Center				●	●	●	
≤ 48 months of age with medical risk factors [5]						●	
Children with approved medical exceptions [6]						●	
≤ 24 months of age at start of RSV season and comorbidity that may worsen with RSV, with approval from Special Care Center				●	●		
Children with severe immunodeficiencies	●		●		●	●	

Note:

[A] Infants who qualify under the 33-35 WGA groups should only receive prophylaxis until they turn 90 days old, or a maximum of 3 doses. The ≤ 32 WGA infants still should receive all 5 doses. Before 2009, infants were to receive all 5 doses regardless.

[1] Risk factors include child care attendance, school-aged siblings, exposure to air pollutants, congenital abnormalities of airways, severe neuromuscular disease.

[2] California does not define specific conditions in Feb 2003, but instead allows for the "doctor's discretion".

[3] Congestive heart failure, moderate to severe pulmonary hypertension, or cyanotic heart disease.

[4] If hemodynamically insignificant heart disease is present, if lesions corrected by surgery exist unless treated for CHD, or if mild cardiomyopathy who do not receive treatment.

[5] Medical risk factors are respiratory disease, cardiovascular system disease, or neuromuscular conditions with "weak cough".

[6] "An example of a medical exception is clinical evidence, supported by medical literature, that the patient has a CA Children's Services medically eligible condition that would likely cause significant cardiopulmonary deterioration and hospitalization if the patient developed an RSV infection."

Table 2 - Yearly births by gestational age group in California

RSV Year	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**Total**
Total Births	505,681	501,910	508,378	513,727	510,465	521,605	524,749	532,514	4,119,029
Weeks Gestation									
≤28	4,170	4,190	4,031	4,048	4,146	4,087	4,089	4,454	33,215
	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%
29-32	7,615	7,723	7,648	7,629	7,555	7,944	8,079	8,293	62,486
	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	1.60%	1.50%
33-35	24,941	25,402	25,324	26,281	25,049	27,215	28,191	28,036	210,439
	4.90%	5.10%	5.00%	5.10%	4.90%	5.20%	5.40%	5.30%	5.10%
36-37	61,054	61,745	62,669	63,597	62,993	66,789	68,788	69,457	517,092
	12.10%	12.30%	12.30%	12.40%	12.30%	12.80%	13.10%	13.00%	12.60%
≥38	407,901	402,850	408,706	412,172	410,722	415,570	415,602	422,274	3,295,797
	80.70%	80.30%	80.40%	80.20%	80.50%	79.70%	79.20%	79.30%	80.00%

Table 3 - RSV hospitalizations by gestational age

Weeks Gestation	Total Births	RSV per 1,000 births	Total RSV Hospitalizations
19	1,139	9.7	11
20	1,120	15.2	17
21	1,466	24.6	36
22	2,019	23.8	48
23	2,588	39.0	101
24	3,401	51.5	175
25	4,206	59.4	250
26	4,814	65.0	313
27	5,622	63.7	358
28	6,840	54.2	371
29	8,778	56.0	492
30	12,227	49.4	604
31	16,934	44.6	755
32	24,547	38.9	955
33	39,578	39.3	1,554
34	66,169	35.6	2,354
35	104,692	33.2	3,477
36	174,728	30.7	5,369
37	342,364	29.0	9,919
38	671,359	26.5	17,809
39	965,263	24.1	23,271
40	833,192	23.2	19,339
41	521,270	23.7	12,356
42	150,270	24.9	3,747
43	75,833	26.4	2,005
44	41,173	26.2	1,078
45	23,399	26.1	611
46	14,038	26.4	371
Total	**4,119,029**	**26.2**	**107,746**

Note: Births in California, from July 1997 to June 2004.

RSV hospitalizations identified by an ICD-9 code of 079.6, 480.1, 466.x on the inpatient record.

Table 4 - Summary statistics of observations used in regressions

Category	**Variable**	**Mean**	**Std. Dev.**	**Total**
Outcomes	RSV admissions per k	34.95	183.65	26,727
	Control condition admissions per k	23.09	150.20	17,662
	RSV real inpatient charges per infant ($)	918	16,771	~702m
	Control conditions real inpatient charges per infant ($)	442	11,250	~338m
Insurance	Public	0.49	0.50	373,322
	Private	0.51	0.50	391,453
Mom's Education	< High school	0.32	0.46	241,487
	High school	0.29	0.45	222,717
	Some college	0.19	0.39	147,068
	Bachelor's or more	0.20	0.40	153,503
Race & Ethnicity	White	0.34	0.48	261,350
	White-Hispanic	0.44	0.50	337,426
	Black	0.08	0.27	60,738
	Black-Hispanic	0.01	0.05	2,318
	Asian	0.08	0.26	57,817
	Other	0.06	0.24	45,126
Vitals	Male infant	0.53	0.50	404,720
	First born to mom	0.36	0.48	273,090
	Mom's age	28.05	6.65	NA
Risks	Eligible for palivizumab	0.11	0.32	87,025
	R1 - CLD or CHD	0.02	0.14	16,269
	R2 - ≤ 28 WGA	0.03	0.18	25,199
	R3 - 29-32 WGA, Jun-Feb	0.05	0.22	37,796
	R4 - 29-32 WGA, Mar-May	0.02	0.13	13,086
	R5 - 29-32 WGA, other risks	0.01	0.07	4,212
	R6 - 33-35 WGA, 1 risk	0.01	0.08	4,430
	R7 - 33-35 WGA, ≥ 2 risks	0.01	0.02	439
	R8 - 33-35 WGA, no risks	0.24	0.43	186,870
	R9 - 36-37 WGA, no risks	0.62	0.48	476,474
Total observations used in regressions				764,775

Note: Control conditions are gastroenteritis, fever, and dehydration.
Charges are in real terms, with a 2004 base year.

Table 5 - DD regressions with Eligibility*Year interactions, outcome is inpatient admissions, multiplied by 1,000 to reflect rates per 1,000 infants

Panel A - Sociodemographic and month of birth estimates

Coef.	RSV	Controls	Coef.	RSV	Controls
Public insurance	14.40***	9.15***	January	26.54***	-1.42
	[19.28]	[18.34]		[24.02]	[-1.73]
< High school	1.82***	0.97*	February	10.13***	-1.51
	[2.73]	[1.85]		[10.43]	[-1.63]
Some college	-2.48***	-0.13	March	3.01***	0.71
	[-3.92]	[-0.25]		[3.93]	[0.82]
≥ Bachelor's degree	-3.32***	-1.52***	May	2.40***	2.00
	[-5.07]	[-2.96]		[3.12]	[2.28]
White-Hispanic	4.18***	4.07***	June	2.44***	1.20
	[4.65]	[6.38]		[2.90]	[1.38]
Black	1.14	0.96	July	6.73***	0.85
	[1.07]	[1.34]		[7.86]	[0.97]
Black-Hispanic	-6.46**	-0.41	August	10.77***	-0.13
	[-1.95]	[-0.14]		[11.71]	[-0.15]
Asian	-4.44***	-1.30	September	15.16***	-1.66*
	[-5.58]	[-1.84]		[15.29]	[-1.92]
Other	-1.47*	-1.14	October	21.96***	-1.86**
	[-1.66]	[-1.53]		[21.21]	[-2.27]
Male	9.76***	4.21***	November	30.50***	-0.74
	[22.72]	[12.13]		[27.92]	[-0.84]
First born to mother	-12.30***	-1.99***	December	33.15***	-1.50*
	[-25.04]	[-5.15]		[28.40]	[-1.80]
Mother's Age	-0.49***	-0.18***			
	[-11.08]	[-5.87]			

Note: Results continued in Panel B on next page

Observations	764,778	764,778
R-squared	0.01	0.01

Note: Robust t-statistics in brackets. SEs clustered by ZIP code.
2-tailed condifence testing shown as: *** p<0.01, ** p<0.05, * p<0.10.

Table 5 (ctd.) - DD regressions with Eligibility*Year interactions, outcome is inpatient admissions, multiplied by 1,000 to reflect rates per 1,000 infants

Panel B - Birth year, eligibility status, and interaction estimates

Coef.	RSV	Controls	Coef.	RSV	Controls
Constant	23.35***	22.43***	Eligible	34.03***	9.16***
	[13.29]	[16.84]		[13.66]	[4.88]
1998	2.15**	-1.09	Eligible*1998	0.71	-0.52
	[2.38]	[-1.48]		[0.19]	[-0.21]
1999	0.92	-0.33	Eligible*1999	1.90	-0.41
	[1.04]	[-0.41]		[0.49]	[-0.16]
2000	0.47	-1.69**	Eligible*2000	-2.00	-0.74
	[0.52]	[-2.17]		[-0.57]	[-0.31]
2001	-0.86	-2.81***	Eligible*2001	-1.86	1.31
	[-0.93]	[-3.76]		[-0.53]	[0.51]
2002	-0.61	-2.58***	Eligible*2002	-7.35**	2.65
	[-0.65]	[-3.42]		[-2.07]	[0.97]
2003	-2.66***	-6.23***	Eligible*2003	-8.55**	-1.04
	[-3.01]	[-8.50]		[-2.46]	[-0.40]
2004	-2.89***	-6.57***	Eligible*2004	-11.38***	-1.73
	[-3.12]	[-9.03]		[-3.49]	[-0.73]

Note: Results continued from Panel A on previous page

Observations	764,778	764,778
R-squared	0.01	0.01

Note: Robust t-statistics in brackets. SEs clustered by ZIP code.
2-tailed condifence testing shown as: *** p<0.01, ** p<0.05, * p<0.10.

Table 6 - DD regressions with Risk Factor*Year interactions, outcome is inpatient admissions, multiplied by 1,000 to reflect rates per 1,000 infants

Panel A - Sociodemographic and month of birth estimates

Coef.	RSV	Controls	Coef.	RSV	Controls
Public insurance	14.13***	9.06***	January	28.60***	-0.69
	[18.89]	[18.20]		[25.65]	[-0.84]
< High school	1.89***	1.01*	February	12.14***	-0.79
	[2.83]	[1.93]		[12.54]	[-0.85]
Some college	-2.45***	-0.12	March	3.09***	0.75
	[-3.89]	[-0.25]		[4.00]	[0.86]
≥ Bachelor's degree	-3.39***	-1.56***	May	2.57***	2.06**
	[-5.19]	[-3.05]		[3.35]	[2.35]
White-Hispanic	4.34***	4.14***	June	4.48***	1.93**
	[4.86]	[6.49]		[5.30]	[2.21]
Black	1.20	1.05*	July	8.65***	1.53*
	[1.13]	[1.46]		[10.11]	[1.75]
Black-Hispanic	-5.81*	-0.12	August	12.55***	0.48
	[-1.76]	[-0.04]		[13.59]	[0.55]
Asian	-4.24***	-1.22*	September	17.16***	-0.96
	[-5.34]	[-1.72]		[17.16]	[-1.09]
Other	-1.40	-1.10	October	23.69***	-1.22
	[-1.59]	[-1.48]		[22.83]	[-1.48]
Male	9.66***	4.17***	November	32.46***	-0.05
	[22.56]	[12.00]		[29.56]	[-0.05]
First born to mother	-12.42***	-2.02***	December	35.18***	-0.77
	[-25.33]	[-5.24]		[30.17]	[-0.91]
Mother's Age	-0.51***	-0.19***			
	[-11.66]	[-6.19]			
Observations	764,778	764,778			
R-squared	0.02	0.01			

Note: Results continued in Panel B on next page

Note: Robust t-statistics in brackets. SEs clustered by ZIP code.
2-tailed condifence testing shown as: *** p<0.01, ** p<0.05, * p<0.10.

Table 6 (ctd) - DD regressions with Risk Factor*Year interactions, outcome is inpatient admissions, multiplied by 1,000 to reflect rates per 1,000 infants

Panel B - Birth year, eligibility status, and interaction estimates

Coef.	RSV	Controls	Coef.	RSV	Controls	Coef.	RSV	Controls	Coef.	RSV	Controls	Coef.	RSV	Controls
Constant	20.82***	22.15***	R1	105.69***	31.15***	R3	14.87***	2.27	R5	48.10***	-6.95	R7	12.58	15.46
	[11.48]	[15.98]		[14.13]	[6.14]		[4.43]	[0.90]		[3.80]	[-1.17]		[0.46]	[0.57]
1998	2.18*	-1.75**	R1*1998	6.50	-0.48	R3*1998	8.10	4.60*	R5*1998	-18.36	18.66*	R7*1998	63.24	52.10
	[2.13]	[-2.06]		[0.60]	[-0.07]		[1.63]	[1.30]		[-1.16]	[1.78]		[1.27]	[1.12]
1999	1.75*	-0.79	R1*1999	17.07	8.91	R3*1999	-1.98	-2.29	R5*1999	-19.10	27.66**	R7*1999	62.40	31.16
	[1.71]	[-0.87]		[1.49]	[1.14]		[-0.41]	[-0.66]		[-1.13]	[2.45]		[1.29]	[0.72]
2000	1.19	-1.91**	R1*2000	2.93	4.50	R3*2000	-3.39	-1.15	R5*2000	-12.94	26.59***	R7*2000	24.91	-20.50
	[1.08]	[-2.07]		[0.28]	[0.64]		[-0.72]	[-0.35]		[-0.81]	[2.60]		[0.59]	[-0.64]
2001	-0.25	-3.30***	R1*2001	8.40	10.84*	R3*2001	-0.80	0.49	R5*2001	-7.58	8.70	R7*2001	104.35*	82.87
	[-0.23]	[-3.68]		[0.73]	[1.52]		[-0.16]	[0.14]		[-0.44]	[0.98]		[1.75]	[1.46]
2002	-0.90	-2.59***	R1*2002	3.51	16.30**	R3*2002	-8.82**	0.13	R5*2002	-17.83	19.15**	R7*2002	33.48	10.42
	[-0.85]	[-2.91]		[0.32]	[2.08]		[-2.00]	[0.04]		[-1.11]	[1.98]		[0.74]	[0.25]
2003	-1.57*	-6.54***	R1*2003	-6.77	2.24	R3*2003	-10.66**	-0.41	R5*2003	-16.32	17.91**	R7*2003	19.06	23.78
	[-1.54]	[-7.40]		[-0.65]	[0.31]		[-2.36]	[-0.12]		[-1.07]	[2.00]		[0.46]	[0.57]
2004	-2.33**	-6.96***	R1*2004	-14.05	3.21	R3*2004	-7.71*	-1.66	R5*2004	-28.50*	32.79***	R7*2004	-24.63	-32.57
	[-2.11]	[-8.04]		[-1.39]	[0.45]		[-1.69]	[-0.52]		[-1.83]	[3.37]		[-0.81]	[-1.20]
			R2	17.14***	4.89	R4	14.64***	0.91	R6	35.18***	20.12**	R8	5.63***	0.09
				[4.29]	[1.46]		[3.18]	[0.22]		[3.24]	[2.12]		[3.75]	[0.07]
			R2*1998	-7.79	-6.79	R4*1998	-2.81	5.32	R6*1998	-16.44	-15.41	R8*1998	-0.00	1.97
				[-1.41]	[-1.64]		[-0.44]	[0.88]		[-1.06]	[-1.26]		[-0.00]	[1.19]
			R2*1999	-2.10	-4.54	R4*1999	-7.34	4.85	R6*1999	7.24	-12.20	R8*1999	-2.44	1.35
				[-0.37]	[-1.10]		[-1.17]	[0.79]		[0.45]	[-1.05]		[-1.15]	[0.78]
			R2*2000	-0.59	-6.49*	R4*2000	-8.72	0.60	R6*2000	-3.06	2.73	R8*2000	-1.91	0.79
				[-0.11]	[-1.46]		[-1.35]	[0.10]		[-0.21]	[0.22]		[-0.90]	[0.44]
			R2*2001	-4.05	-0.36	R4*2001	-2.31	3.01	R6*2001	-25.49*	-11.91	R8*2001	-1.83	1.65
				[-0.78]	[-0.08]		[-0.37]	[0.50]		[-1.95]	[-1.00]		[-0.88]	[0.92]
			R2*2002	-5.79	-2.25	R4*2002	-1.59	0.22	R6*2002	-4.35	-4.28	R8*2002	1.30	0.06
				[-1.06]	[-0.49]		[-0.25]	[0.04]		[-0.30]	[-0.34]		[0.60]	[0.03]
			R2*2003	-6.92	-3.99	R4*2003	-6.99	-2.45	R6*2003	-13.89	-3.09	R8*2003	-3.88**	0.88
				[-1.34]	[-0.94]		[-1.19]	[-0.46]		[-0.97]	[-0.25]		[-2.10]	[0.53]
			R2*2004	-8.78*	-5.56	R4*2004	-7.93	7.12	R6*2004	-17.01	-8.30	R8*2004	-1.79	0.66
				[-1.66]	[-1.40]		[-1.32]	[1.24]		[-1.26]	[-0.74]		[-0.89]	[0.40]
Observations	764,778	764,778												
R-squared	0.02	0.01												

Note: Results continued from Panel A on previous page

Note: Robust t-statistics in brackets. SEs clustered by ZIP code.
2-tailed condifence testing shown as: *** p<0.01, ** p<0.05, * p<0.10.

Table 7 - DD regressions with Eligibility*Year interactions, outcome is real inpatient charges

Panel A - Sociodemographic and month of birth estimates

Coef.	RSV	Controls	Coef.	RSV	Controls
Public insurance	509.22***	276.75***	January	900.47***	-6.36
	[11.09]	[8.65]		[8.75]	[-0.12]
< High school	54.71	26.27	February	249.62***	-104.96**
	[0.99]	[0.59]		[3.26]	[-2.28]
Some college	-8.47	15.96	March	128.61**	72.04
	[-0.13]	[0.48]		[2.10]	[1.06]
≥ Bachelor's degree	-66.94	10.83	May	9.25	64.16
	[-1.28]	[0.31]		[0.16]	[1.20]
White-Hispanic	123.26**	21.30	June	-126.82**	4.84
	[2.35]	[0.62]		[-2.19]	[0.10]
Black	217.45*	-77.68	July	77.44	10.36
	[1.88]	[-1.52]		[0.88]	[0.13]
Black-Hispanic	281.97	-220.85***	August	105.44	-47.19
	[0.40]	[-3.42]		[1.44]	[-1.02]
Asian	-65.70	-29.49	September	422.16***	-13.06
	[-1.15]	[-0.76]		[4.80]	[-0.25]
Other	-123.18**	-10.30	October	429.74***	43.05
	[-2.01]	[-0.21]		[5.47]	[0.84]
Male	213.09***	67.23**	November	745.33***	28.59
	[5.62]	[2.44]		[8.08]	[0.43]
First born to mother	-243.36***	-73.86**	December	854.67***	6.59
	[-5.54]	[-2.50]		[9.85]	[0.13]
Mother's Age	-9.20***	3.11			
	[-2.87]	[1.18]			

Note: Results continued in Panel B on next page

	RSV	Controls
Observations	762,991	762,708
R-squared	0.01	0.01

Note: Robust t-statistics in brackets. SEs clustered by ZIP code.
2-tailed condifence testing shown as: *** p<0.01, ** p<0.05, * p<0.10.

Table 7 (ctd.) - DD regressions with Eligibility*Year interactions, outcome is real inpatient charges

Panel B - Birth year, eligibility status, and interaction estimates

Coef.	RSV	Controls	Coef.	RSV	Controls
Constant	113.40	99.18	Eligible	2,410.21***	872.36***
	[0.93]	[1.08]		[7.53]	[4.39]
1998	48.63	-39.56	Eligible*1998	476.49	-233.60
	[1.62]	[-1.24]		[0.92]	[-0.79]
1999	34.39	-8.96	Eligible*1999	1,652.50**	164.05
	[1.17]	[-0.26]		[2.42]	[0.57]
2000	95.49**	10.15	Eligible*2000	-91.97	-136.39
	[2.14]	[0.23]		[-0.20]	[-0.39]
2001	104.41***	-9.42	Eligible*2001	897.06*	126.45
	[2.69]	[-0.26]		[1.68]	[0.37]
2002	88.48**	69.25	Eligible*2002	447.59	53.31
	[2.56]	[1.39]		[0.95]	[0.19]
2003	60.09*	-70.05*	Eligible*2003	1,192.30**	-313.60
	[1.79]	[-2.26]		[2.10]	[-1.41]
2004	146.24***	37.99	Eligible*2004	125.53	-87.56
	[2.90]	[0.87]		[0.26]	[-0.30]

Note: Results continued from Panel A on previous page

	RSV	Controls
Observations	762,991	762,708
R-squared	0.01	0.01

Note: Robust t-statistics in brackets. SEs clustered by ZIP code
2-tailed condifence testing shown as: *** p<0.01, ** p<0.05, * p<0.10

Table 8 - DD regressions with Risk Factor*Year interactions, outcome is real inpatient charges

Panel A - Sociodemographic and month of birth estimates

Coef.	RSV	Controls	Coef.	RSV	Controls
Public insurance	484.98***	271.74***	January	1,099.31***	50.41
	[10.69]	[8.62]		[10.36]	[0.91]
< High school	68.92	29.67	February	451.11***	-48.18
	[1.25]	[0.67]		[5.99]	[-1.05]
Some college	-10.41	15.70	March	133.33**	74.74
	[-0.16]	[0.47]		[2.17]	[1.10]
≥ Bachelor's degree	-83.39	8.41	May	33.57	68.60
	[-1.60]	[0.24]		[0.60]	[1.28]
White-Hispanic	139.78***	25.97	June	82.63	63.63
	[2.70]	[0.75]		[1.40]	[1.31]
Black	247.19**	-70.67*	July	268.78***	64.56
	[2.15]	[-1.40]		[2.99]	[0.79]
Black-Hispanic	372.19	-198.90***	August	270.06***	1.36
	[0.53]	[-3.08]		[3.62]	[0.03]
Asian	-47.60	-23.72	September	610.69***	43.76
	[-0.84]	[-0.61]		[6.86]	[0.82]
Other	-112.11*	-6.94	October	599.35***	93.84*
	[-1.83]	[-0.14]		[7.50]	[1.77]
Male	200.06***	64.04**	November	934.01***	82.72
	[5.30]	[2.33]		[10.01]	[1.25]
First born to mother	-250.12***	-76.71***	December	1,055.59***	63.37
	[-5.75]	[-2.58]		[12.16]	[1.26]
Mother's Age	-11.44***	2.48			
	[-3.55]	[0.95]			

Note: Results continued in Panel B on next page

Observations	762,991	762,708
R-squared	0.01	0.01

Note: Robust t-statistics in brackets. SEs clustered by ZIP code.

2-tailed condifence testing shown as: *** p<0.01, ** p<0.05, * p<0.10.

Table 8 (ctd.) - DD regressions with Risk Factor*Year interactions, outcome is real inpatient charges

Panel B - Birth year, eligibility status, and interaction estimates

Coef.	RSV	Controls	Coef.	RSV	Controls	Coef.	RSV	Controls	Coef.	RSV	Controls	Coef.	RSV	Controls
Constant	-9.98	84.15	R1	8,172.43***	2,258.37***	R3	584.57***	500.10*	R5	3,330.55**	414.33	R7	952.71	580.55
	[-0.08]	[0.89]		[5.64]	[3.35]		[3.38]	[1.75]		[2.16]	[0.67]		[1.05]	[0.80]
1998	59.63*	-73.24*	R1*1998	4,602.48*	389.66	R3*1998	126.47	-357.07	R5*1998	-2,358.79	1,026.77	R7*1998	1,059.62	106.99
	[1.95]	[-1.85]		[1.86]	[0.30]		[0.46]	[-1.22]		[-1.45]	[0.75]		[0.72]	[0.12]
1999	51.10	-24.63	R1*1999	8,285.79**	695.08	R3*1999	247.00	-391.09	R5*1999	-2,343.59	-195.40	R7*1999	8,172.06	6,168.55
	[1.61]	[-0.56]		[2.44]	[0.69]		[0.90]	[-1.30]		[-1.43]	[-0.30]		[1.00]	[1.06]
2000	153.36***	-7.62	R1*2000	1,862.08	637.53	R3*2000	-264.65	-260.60	R5*2000	-1,761.37	87.27	R7*2000	1,695.11	-717.43
	[2.69]	[-0.13]		[0.81]	[0.40]		[-1.10]	[-0.74]		[-1.04]	[0.13]		[0.58]	[-0.96]
2001	106.55***	-39.68	R1*2001	6,327.54**	1,333.15	R3*2001	5.93	-393.79	R5*2001	-2,154.10	-414.06	R7*2001	308.52	-147.58
	[2.59]	[-0.88]		[2.45]	[1.09]		[0.02]	[-1.31]		[-1.27]	[-0.66]		[0.23]	[-0.18]
2002	77.73**	48.34	R1*2002	4,640.21*	657.85	R3*2002	-261.94	-304.01	R5*2002	-1,902.48	580.92	R7*2002	-452.36	-215.44
	[2.27]	[0.78]		[1.92]	[0.66]		[-1.23]	[-0.94]		[-1.09]	[0.70]		[-0.42]	[-0.23]
2003	79.10**	-94.68**	R1*2003	7,260.37***	176.96	R3*2003	-278.73	-458.98	R5*2003	-2,147.28	289.26	R7*2003	-582.66	-334.34
	[2.20]	[-2.42]		[2.86]	[0.22]		[-1.01]	[-1.58]		[-1.33]	[0.38]		[-0.56]	[-0.42]
2004	133.09**	5.92	R1*2004	3,959.54*	1,046.60	R3*2004	-119.91	-527.69*	R5*2004	-3,066.73*	323.78	R7*2004	-1,162.56	-938.62
	[2.45]	[0.10]		[1.69]	[0.99]		[-0.44]	[-1.76]		[-1.95]	[0.43]		[-1.20]	[-1.29]
			R2	1,102.16***	347.02**	R4	797.48**	92.11	R6	3,028.45*	1,891.27	R8	124.83**	-33.11
				[3.46]	[2.14]		[2.14]	[0.65]		[1.75]	[1.18]		[2.41]	[-0.71]
			R2*1998	-649.52*	-262.69	R4*1998	-480.22	139.33	R6*1998	-2,965.81*	-1,736.85	R8*1998	-8.22	110.03*
				[-1.61]	[-1.46]		[-1.22]	[0.69]		[-1.70]	[-1.08]		[-0.12]	[1.72]
			R2*1999	75.39	691.22	R4*1999	-390.37	282.04	R6*1999	1,027.21	153.06	R8*1999	-30.80	36.50
				[0.16]	[1.40]		[-0.97]	[1.16]		[0.41]	[0.08]		[-0.43]	[0.58]
			R2*2000	-496.26	-280.37	R4*2000	-603.21	41.41	R6*2000	-1,476.09	-558.11	R8*2000	-159.18*	62.70
				[-1.22]	[-1.20]		[-1.53]	[0.20]		[-0.79]	[-0.33]		[-1.90]	[0.80]
			R2*2001	293.58	655.34	R4*2001	-427.11	-115.35	R6*2001	-2,681.88	-1,348.27	R8*2001	39.29	122.01*
				[0.51]	[0.95]		[-1.08]	[-0.70]		[-1.53]	[-0.82]		[0.40]	[1.66]
			R2*2002	178.23	160.23	R4*2002	-441.87	-28.40	R6*2002	-2,257.95	751.74	R8*2002	84.69	80.61
				[0.35]	[0.45]		[-1.12]	[-0.14]		[-1.28]	[0.33]		[0.97]	[0.74]
			R2*2003	333.89	-213.87	R4*2003	-466.48	32.72	R6*2003	-2,588.96	-1,810.18	R8*2003	-36.33	86.37
				[0.58]	[-1.09]		[-1.17]	[0.18]		[-1.47]	[-1.13]		[-0.47]	[1.40]
			R2*2004	-703.09*	196.73	R4*2004	-715.29*	55.62	R6*2004	-2,277.27	-1,363.62	R8*2004	93.75	101.21
				[-1.74]	[0.43]		[-1.87]	[0.27]		[-1.26]	[-0.83]		[0.73]	[0.81]
Observations	762,991	762,708												
R-squared	0.01	0.01												

Note: Results continued from Panel A on previous page

Note: Robust t-statistics in brackets. SEs clustered by ZIP code.

2-tailed condifence testing shown as: *** p<0.01, ** p<0.05, * p<0.10.

Table 9 - Difference-in-differences results from linear combinations
Outcome is inpatient admissions, multiplied by 1,000 to reflect rates per 1,000 infants

	Model	RSV	Controls	F-Stat of Joint Significance
i.	(Elig*1998-Elig*1997)-(1998-1997)	0.71	-0.52	0.13
		[0.19]	[-0.21]	(0.72)
ii.	(Elig*1999-Elig*1997)-(1999-1997)	1.90	-0.41	0.49
		[0.49]	[-0.16]	(0.48)
iii.	(Elig*2003-Elig*1998)-(2003-1998)	-9.27**	-0.52	7.66***
		[-2.53]	[-0.21]	(<0.01)
iv.	(Elig*2004-Elig*1998)-(2004-1998)	-12.10***	-1.21	12.28***
		[-3.47]	[-0.51]	(<0.01)
v.	(R3*1998-R3*1997)-(R4*1998-R4*1997)	10.90*	-0.72	1.54
		[1.34]	[-0.1]	(0.21)
vi.	(R3*1999-R3*1997)-(R4*1999-R4*1997)	5.36	-7.14	1.78
		[0.66]	[-1.03]	(0.18)
vii.	(R3*2003-R3*1998)-(R4*2003-R4*1998)	-14.58**	2.76	3.97**
		[-2.01]	[0.43]	(0.05)
viii	(R3*2004-R3*1998)-(R4*2004-R4*1998)	-10.69	-8.06	0.09
		[-1.42]	[-1.21]	(0.76)
ix.	(R6*2003-R6*2002)-(R7*2003-R7*2002)	4.88	-12.17	0.14
		[0.10]	[-0.26]	(0.71)
x.	(R6*2004-R6*2001)-(R7*2004-R7*2001)	137.46**	119.05**	0.18
		[2.48]	[2.35]	(0.67)

Note: F-stat is computed for the test that DD(RSV)-DD(Cont)=0.
Robust t-statisitcs shown in brackets. SEs clustered by ZIP code.
P-values from F-statistics shown in parentesis.
2-tailed confidence testing shown as: *** p<0.01, ** p<0.05, * p<0.10.

Table 10 - Difference-in-differences results from linear combinations
Outcome is real inpatient charges

	Model	RSV	Controls	F-Stat of Joint Significance
i.	(Elig*1998-Elig*1997)-(1998-1997)	476.49	-233.6	6.92***
		[0.92]	[-0.79]	(<0.01)
ii.	(Elig*1999-Elig*1997)-(1999-1997)	1,652.5**	164.05	30.6***
		[2.42]	[0.57]	(<0.01)
iii.	(Elig*2003-Elig*1998)-(2003-1998)	715.81	-79.99	8.81***
		[1.10]	[-0.32]	(<0.01)
iv.	(Elig*2004-Elig*1998)-(2004-1998)	-350.96	146.04	3.64*
		[-0.68]	[0.47]	(0.06)
v.	(R3*1998-R3*1997)-(R4*1998-R4*1997)	606.69	-496.39	2.18
		[1.26]	[-1.43]	(0.14)
vi.	(R3*1999-R3*1997)-(R4*1999-R4*1997)	637.37	-673.13*	2.70*
		[1.30]	[-1.75]	(0.09)
vii.	(R3*2003-R3*1998)-(R4*2003-R4*1998)	-418.95	4.70	0.34
		[-1.18]	[0.02]	(0.56)
viii	(R3*2004-R3*1998)-(R4*2004-R4*1998)	-11.31	-86.92	0.01
		[-0.03]	[-0.39]	(0.92)
ix.	(R6*2003-R6*2002)-(R7*2003-R7*2002)	-200.72	-2,443.01	0.32
		[-0.22]	[-1.42]	(0.57)
x.	(R6*2004-R6*2001)-(R7*2004-R7*2001)	1,875.69	775.68	0.11
		[1.58]	[1.25]	(0.74)

Note: F-stat is computed for the test that DD(RSV)-DD(Cont)=0.
Robust t-statisitcs shown in brackets. SEs clustered by ZIP code.
P-values from F-statistics shown in parentesis.
2-tailed confidence testing shown as: *** p<0.01, ** p<0.05, * p<0.10.

Table 11 - Potential number of palivizumab doses and spending

					Potential palivizuamb spending, based on compliance rates ($)				
Year	**Total Births ≤ 37 WGA**	**Eligible Births**	**Potential Doses**	**Real Price of Palivizumab ($)**	**0%**	**25%**	**50%**	**75%**	**100%**
1997	94,415	11,269	0	NA	-	-	-	-	-
1998	96,085	11,516	49,016	1,163	0	14,251,402	28,502,804	42,754,206	57,005,608
1999	96,877	11,333	47,931	1,217	0	14,583,007	29,166,014	43,749,020	58,332,027
2000	98,619	11,432	48,657	1,003	0	12,200,743	24,401,486	36,602,228	48,802,971
2001	97,315	11,446	48,610	1,013	0	12,310,483	24,620,965	36,931,448	49,241,930
2002	103,923	11,805	50,377	1,011	0	12,732,787	25,465,574	38,198,360	50,931,147
2003	106,902	11,334	48,005	1,030	0	12,361,288	24,722,575	37,083,863	49,445,150
2004	107,946	12,106	51,231	1,018	0	13,038,290	26,076,579	39,114,869	52,153,158

Note: Prices and spending are in real terms, with a 2004 base year.

Table 12 - Admissions and estimated compliance rates among births ≤ 35 WGA and no more than six months of age at RSV season onset

Year	Births	RSV Admissions	Observed RSV Admission Rate	Total Inpatient Charges ($)	Charges per Infant ($)	Charges per Admission ($)	Estimated Compliance Rate (%)
1997	25,108	1,127	4.49	24,481,420	975	21,723	NA (57)
1998	25,887	1,214	4.69	23,522,881	909	19,376	54
1999	25,597	1,097	4.29	28,130,168	1,099	25,643	60
2000	26,373	1,145	4.34	24,446,941	927	21,351	60
2001	25,602	1,026	4.01	27,640,582	1,080	26,940	65
2002	27,386	1,151	4.20	28,286,162	1,033	24,575	62
2003	28,415	1,034	3.64	26,505,060	933	25,634	71
2004	28,951	1,075	3.71	28,992,374	1,001	26,970	70

Note: Charges are in real terms, with a 2004 base year.

Table 13 - Admissions and estimated compliance rates among infants with CLD

Year	Births	RSV Admissions	Observed RSV Admission Rate	Total Inpatient Charges ($)	Charges per Infant ($)	Charges per Admission ($)	Estimated Compliance Rate (%)
1997	1,858	187	10.06	14,590,366	7,908	78,023	NA (56)
1998	1,852	207	11.18	20,903,869	11,410	100,985	33
1999	1,755	200	11.40	26,022,221	14,998	130,111	28
2000	1,733	189	10.91	14,686,076	8,603	77,704	38
2001	1,642	185	11.27	20,900,446	12,838	112,975	31
2002	1,715	170	9.91	22,546,750	13,247	132,628	59
2003	1,768	175	9.90	25,216,489	14,344	144,094	59
2004	1,837	156	8.49	21,719,737	11,921	139,229	88

Table 14 - Infants with chronic lung disease, theoretical outcomes based on clinical efficacy rates

	1997	1998	1999	2000	2001	2002	2003	2004
Births	1,858	1,852	1,755	1,733	1,642	1,715	1,768	1,837
Observed RSV Rate	10.06	11.18	11.40	10.91	11.27	9.91	9.90	8.49
Charges per Admission ($)	78,023	100,985	130,111	77,704	112,975	132,628	144,094	139,229
A. Theoretical Compliance 0%								
Admission Rate (%)	12.80	12.80	12.80	12.80	12.80	12.80	12.80	12.80
Total Admissions	238	237	225	222	210	220	226	235
Total Inpatient Charges ($)	18,555,825	23,939,070	29,228,159	17,236,636	23,744,714	29,114,486	32,609,099	32,737,770
Doses Provided	NA	0	0	0	0	0	0	0
Palivizumab Charges ($)	NA	0	0	0	0	0	0	0
Total RSV Charges ($)	NA	23,939,070	29,228,159	17,236,636	23,744,714	29,114,486	32,609,099	32,737,770
B. Theoretical Compliance 25%								
Admission Rate (%)	11.58	11.58	11.58	11.58	11.58	11.58	11.58	11.58
Total Admissions	NA	214	203	201	190	199	205	213
Total Inpatient Charges ($)	NA	21,657,378	26,442,350	15,593,769	21,481,546	26,339,511	29,501,044	29,617,451
Doses Provided	NA	1,952	1,830	1,810	1,727	1,811	1,827	1,915
Palivizumab Charges ($)	NA	2,270,176	2,226,502	1,815,681	1,749,704	1,830,668	1,881,810	1,949,725
Total RSV Charges ($)	NA	23,927,554	28,668,851	17,409,449	23,231,250	28,170,179	31,382,854	31,567,176
C. Theoretical Compliance 50%								
Admission Rate (%)	10.35	10.35	10.35	10.35	10.35	10.35	10.35	10.35
Total Admissions	NA	192	182	179	170	178	183	190
Total Inpatient Charges ($)	NA	19,356,983	23,633,706	13,937,436	19,199,828	23,541,791	26,367,514	26,471,556
Doses Provided	NA	3,904	3,659	3,621	3,455	3,622	3,654	3,831
Palivizumab Charges ($)	NA	4,540,352	4,453,003	3,631,362	3,499,409	3,661,337	3,763,620	3,899,449
Total RSV Charges ($)	NA	23,897,335	28,086,709	17,568,797	22,699,236	27,203,128	30,131,134	30,371,005

Table is continued on the next page…

Note: Charges are in real dollars, with a 2004 base year

Table 14 (ctd.) - Infants with chronic lung disease, theoretical outcomes based on clinical efficacy rates

	1997	1998	1999	2000	2001	2002	2003	2004
Births	1,858	1,852	1,755	1,733	1,642	1,715	1,768	1,837
Observed RSV Rate (%)	10.06	11.18	11.40	10.91	11.27	9.91	9.90	8.49
Charges per Admission ($)	78,023	100,985	130,111	77,704	112,975	132,628	144,094	139,229
D. Theoretical Compliance 75%								
Admission Rate (%)	9.13	9.13	9.13	9.13	9.13	9.13	9.13	9.13
Total Admissions	NA	169	160	158	150	157	161	168
Total Inpatient Charges ($)	NA	17,075,290	20,847,898	12,294,569	16,936,659	20,766,817	23,259,459	23,351,237
Doses Provided	NA	5,856	5,489	5,431	5,182	5,432	5,481	5,746
Palivizumab Charges ($)	NA	6,810,528	6,679,505	5,447,042	5,249,113	5,492,005	5,645,430	5,849,174
Total RSV Charges ($)	NA	23,885,818	27,527,402	17,741,611	22,185,772	26,258,821	28,904,889	29,200,411
E. Theoretical Compliance 100%								
Admission Rate (%)	7.90	7.90	7.90	7.90	7.90	7.90	7.90	7.90
Total Admissions	NA	146	139	137	130	135	140	145
Total Inpatient Charges ($)	NA	14,774,895	18,039,254	10,638,236	14,654,941	17,969,097	20,125,928	20,205,342
Doses Provided	NA	7,808	7,318	7,241	6,909	7,243	7,308	7,661
Palivizumab Charges ($)	NA	9,080,704	8,906,006	7,262,723	6,998,817	7,322,673	7,527,240	7,798,898
Total RSV Charges ($)	NA	23,855,599	26,945,260	17,900,959	21,653,758	25,291,770	27,653,168	28,004,240

Note: Charges are in real dollars, with a 2004 base year.

Table 15 - Infants ≤ 35 WGA, theoretical outcomes based on clinical efficacy rates, assumes only AAP elligible infants receive palivizumab

	1997	1998	1999	2000	2001	2002	2003	2004
Births	25,108	25,887	25,597	26,373	25,602	27,386	28,415	28,951
Observed RSV Rate (%)	4.49	4.69	4.29	4.34	4.01	4.20	3.64	3.71
Charges per Admission ($)	21,723	19,376	25,643	21,351	26,940	24,575	25,634	26,970
A. Theoretical Compliance 0%								
Admission Rate (%)	8.10	8.10	8.10	8.10	8.10	8.10	8.10	8.10
Total Admissions	2,034	2,097	2,073	2,136	2,074	2,218	2,302	2,345
Total Inpatient Charges ($)	44,178,382	40,629,228	53,166,710	45,610,370	55,867,435	54,514,536	58,998,495	63,244,666
Doses Provided	NA	0	0	0	0	0	0	0
Palivizumab Charges ($)	NA	0	0	0	0	0	0	0
Total RSV Charges ($)	NA	40,629,228	53,166,710	45,610,370	55,867,435	54,514,536	58,998,495	63,244,666
B. Theoretical Compliance 25%								
Admission Rate (%)	6.53	6.53	6.53	6.53	6.53	6.53	6.53	6.53
Total Admissions	NA	1,690	1,671	1,722	1,672	1,788	1,855	1,891
Total Inpatient Charges ($)	NA	32,754,180	42,861,557	36,769,841	45,038,809	43,948,139	47,562,984	50,986,132
Doses Provided	NA	7,760	7,646	7,887	7,810	8,003	7,559	8,226
Palivizumab Charges ($)	NA	9,025,171	9,304,878	7,910,661	7,911,783	8,091,286	7,786,028	8,374,068
Total RSV Charges ($)	NA	41,779,351	52,166,435	44,680,502	52,950,592	52,039,424	55,349,012	59,360,200
C. Theoretical Compliance 50%								
Admission Rate (%)	4.95	4.95	4.95	4.95	4.95	4.95	4.95	4.95
Total Admissions	NA	1,281	1,267	1,305	1,267	1,356	1,407	1,433
Total Inpatient Charges ($)	NA	24,828,972	32,490,767	27,873,004	34,141,210	33,314,439	36,054,636	38,649,518
Doses Provided	NA	15,521	15,292	15,774	15,621	16,007	15,119	16,452
Palivizumab Charges ($)	NA	18,050,342	18,609,756	15,821,322	15,823,567	16,182,572	15,572,055	16,748,136
Total RSV Charges ($)	Na	42,879,314	51,100,523	43,694,326	49,964,777	49,497,010	51,626,691	55,397,654

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Note: Charges are in real dollars, with a 2004 base year.

ble 15 (ctd.) - Infants ≤ 35 WGA, theoretical outcomes based on clinical efficacy rates, assumes only AAP elligible infants receive palivizum

	1997	1998	1999	2000	2001	2002	2003	2004
Births	25,108	25,887	25,597	26,373	25,602	27,386	28,415	28,951
Observed RSV Rate (%)	4.49	4.69	4.29	4.34	4.01	4.20	3.64	3.71
Charges per Admission ($)	21,723	19,376	25,643	21,351	26,940	24,575	25,634	26,970
D. Theoretical Compliance 75%								
Admission Rate (%)	3.34	3.34	3.34	3.34	3.34	3.34	3.34	3.34
Total Admissions	NA	865	855	881	855	915	949	967
Total Inpatient Charges ($)	NA	16,753,286	21,923,063	18,807,239	23,036,696	22,478,834	24,327,774	26,078,665
Doses Provided	NA	23,281	22,937	23,661	23,431	24,010	22,678	24,678
Palivizumab Charges ($)	NA	27,075,512	27,914,633	23,731,983	23,735,350	24,273,857	23,358,083	25,122,204
Total RSV Charges ($)	NA	43,828,799	49,837,696	42,539,222	46,772,045	46,752,691	47,685,857	51,200,869
E. Theoretical Compliance 100%								
Admission Rate (%)	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80
Total Admissions	NA	466	461	475	461	493	511	521
Total Inpatient Charges ($)	NA	9,028,717	11,814,824	10,135,638	12,414,986	12,114,341	13,110,777	14,054,370
Doses Provided	NA	31,041	30,583	31,548	31,241	32,013	30,237	32,904
Palivizumab Charges ($)	NA	36,100,683	37,219,511	31,642,644	31,647,133	32,365,143	31,144,110	33,496,272
Total RSV Charges ($)	NA	45,129,400	49,034,335	41,778,282	44,062,119	44,479,484	44,254,887	47,550,642

Note: Charges are in real dollars, with a 2004 base year.

Table 16 - Infants ≤ 35 WGA , theoretical outcomes based on clinical efficacy rates, assumes all infants given palivizumab

	1997	1998	1999	2000	2001	2002	2003	2004
Births	25,108	25,887	25,597	26,373	25,602	27,386	28,415	28,951
Observed RSV Rate (%)	4.49	4.69	4.29	4.34	4.01	4.20	3.64	3.71
Charges per Admission ($)	21,723	19,376	25,643	21,351	26,940	24,575	25,634	26,970
A. Theoretical Compliance 0%								
Admission Rate (%)	8.10	8.10	8.10	8.10	8.10	8.10	8.10	8.10
Total Admissions	NA	2,097	2,073	2,136	2,074	2,218	2,302	2,345
Total Inpatient Charges ($)	NA	40,629,228	53,166,710	45,610,370	55,867,435	54,514,536	58,998,495	63,244,666
Doses Provided	NA	0	0	0	0	0	0	0
Palivizumab Charges ($)	NA	0	0	0	0	0	0	0
Total RSV Charges ($)	NA	40,629,228	53,166,710	45,610,370	55,867,435	54,514,536	58,998,495	63,244,666
B. Theoretical Compliance 25%								
Admission Rate (%)	6.53	6.53	6.53	6.53	6.53	6.53	6.53	6.53
Total Admissions	NA	1,690	1,671	1,722	1,672	1,788	1,855	1,891
Total Inpatient Charges ($)	NA	32,754,180	42,861,557	36,769,841	45,038,809	43,948,139	47,562,984	50,986,132
Doses Provided	NA	25,300	24,841	25,612	24,934	26,614	27,629	28,191
Palivizumab Charges ($)	NA	29,423,900	30,231,193	25,688,585	25,257,889	26,906,754	28,457,613	28,697,929
Total RSV Charges ($)	NA	62,178,080	73,092,750	62,458,426	70,296,698	70,854,893	76,020,597	79,684,061
C. Theoretical Compliance 50%								
Admission Rate (%)	4.95	4.95	4.95	4.95	4.95	4.95	4.95	4.95
Total Admissions	NA	1,281	1,267	1,305	1,267	1,356	1,407	1,433
Total Inpatient Charges ($)	NA	24,828,972	32,490,767	27,873,004	34,141,210	33,314,439	36,054,636	38,649,518
Doses Provided	NA	50,600	49,682	51,224	49,868	53,228	55,258	56,381
Palivizumab Charges ($)	NA	58,847,800	60,462,386	51,377,171	50,515,778	53,813,508	56,915,225	57,395,858
Total RSV Charges ($)	Na	83,676,772	92,953,153	79,250,174	84,656,988	87,127,947	92,969,861	96,045,376

Table is continued on the next page…

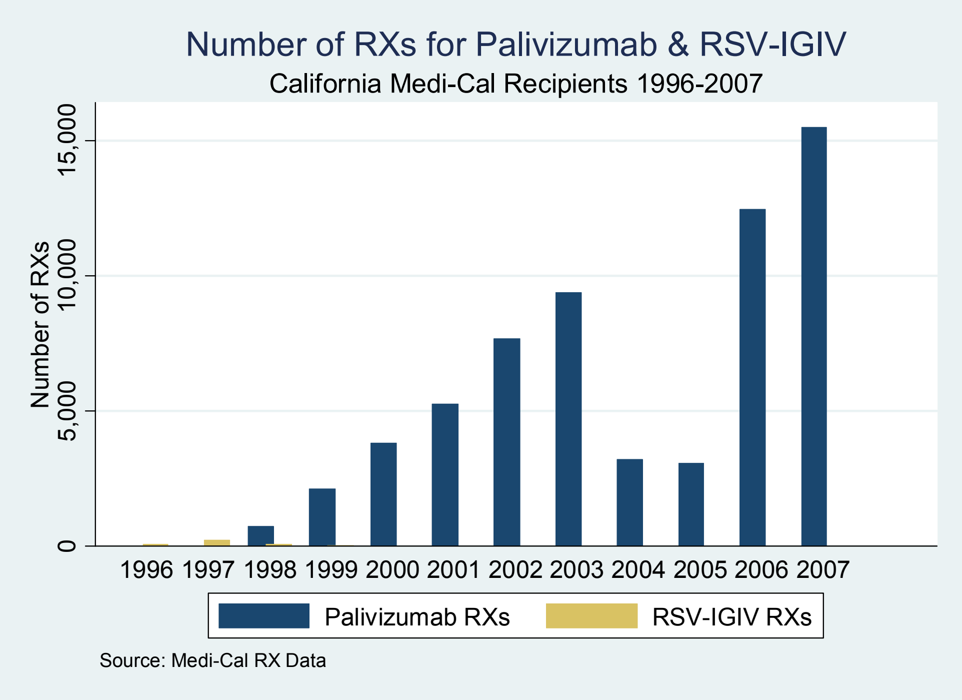
Note: Charges are in real dollars, with a 2004 base year.

Table 16 (ctd.) - Infants ≤ 35 WGA , theoretical outcomes based on clinical efficacy rates, assumes all infants given palivizumab

	1997	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**
Births	25,108	25,887	25,597	26,373	25,602	27,386	28,415	28,951
Observed RSV Rate (%)	4.49	4.69	4.29	4.34	4.01	4.20	3.64	3.71
Charges per Admission ($)	21,723	19,376	25,643	21,351	26,940	24,575	25,634	26,970
D. Theoretical Compliance 75%								
Admission Rate (%)	3.34	3.34	3.34	3.34	3.34	3.34	3.34	3.34
Total Admissions	NA	865	855	881	855	915	949	967
Total Inpatient Charges ($)	NA	16,753,286	21,923,063	18,807,239	23,036,696	22,478,834	24,327,774	26,078,665
Doses Provided	NA	75,900	74,522	76,835	74,801	79,842	82,886	84,572
Palivizumab Charges ($)	NA	88,271,700	90,693,578	77,065,756	75,773,666	80,720,262	85,372,838	86,093,787
Total RSV Charges ($)	NA	105,024,986	112,616,641	95,872,995	98,810,362	103,199,096	109,700,612	112,172,452
E. Theoretical Compliance 100%								
Admission Rate (%)	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80
Total Admissions	NA	466	461	475	461	493	511	521
Total Inpatient Charges ($)	NA	9,028,717	11,814,824	10,135,638	12,414,986	12,114,341	13,110,777	14,054,370
Doses Provided	NA	101,200	99,363	102,447	99,735	106,456	110,515	112,762
Palivizumab Charges ($)	NA	117,695,600	120,924,771	102,754,341	101,031,555	107,627,016	113,830,450	114,791,716
Total RSV Charges ($)	NA	126,724,317	132,739,595	112,889,979	113,446,541	119,741,357	126,941,227	128,846,086

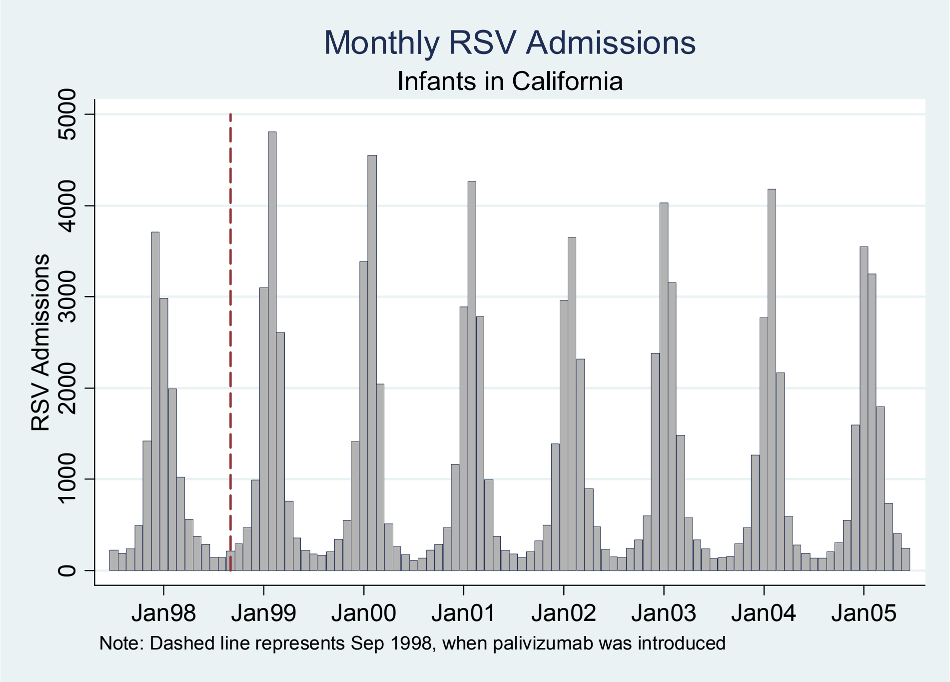
Note: Charges are in real dollars, with a 2004 base year.

Figure 1 - Yearly counts of palivizumab and RSV-IGIV prescriptions supplied by Medi-Cal



Source: Medi-Cal RX Data

Figure 2 - RSV admissions in California by month of children less than one year old



Note: Dashed line represents Sep 1998, when palivizumab was introduced

Figure 3 – Inpatient admission rates for RSV and control conditions, by gestational age and medical risk factors

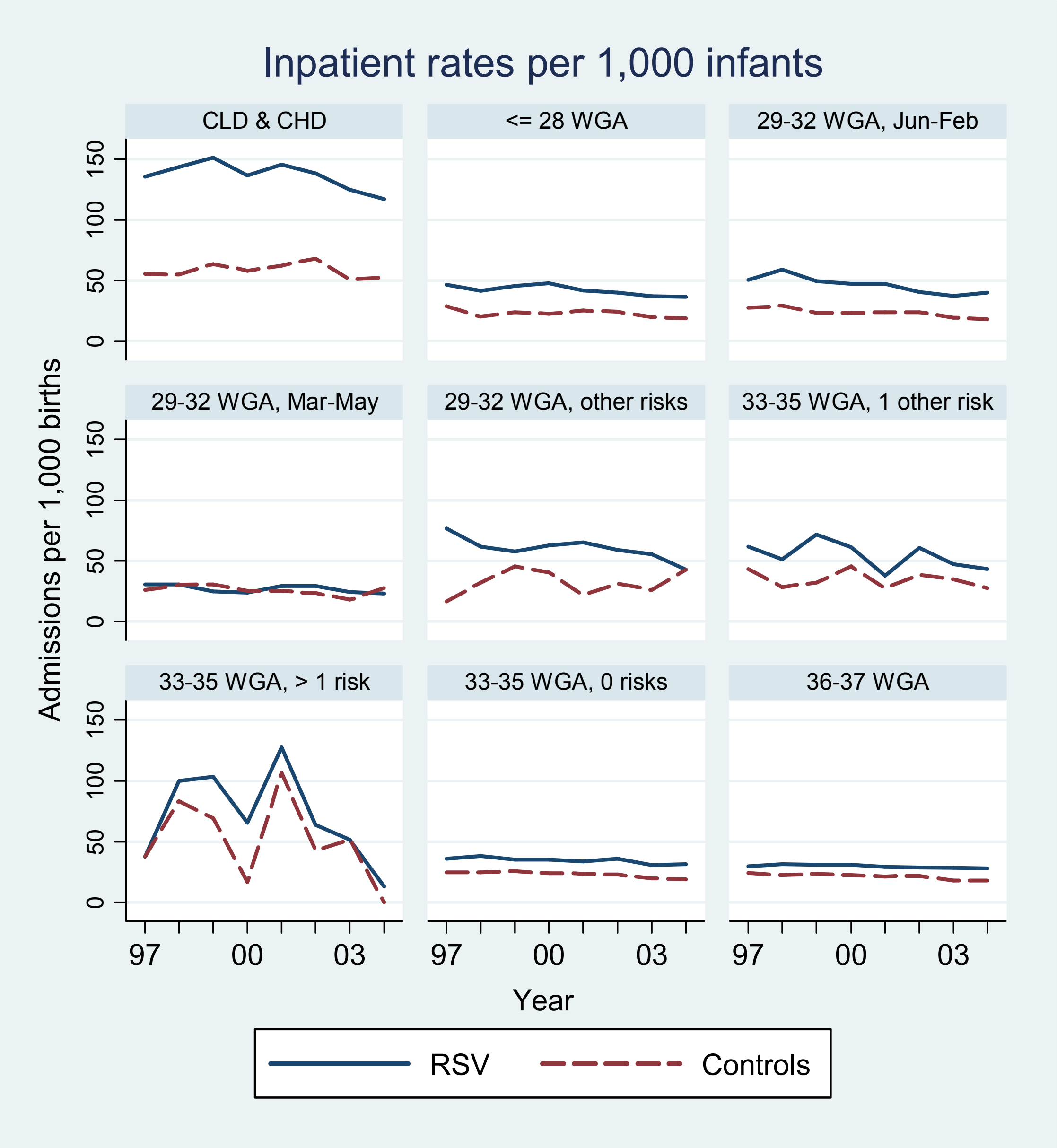
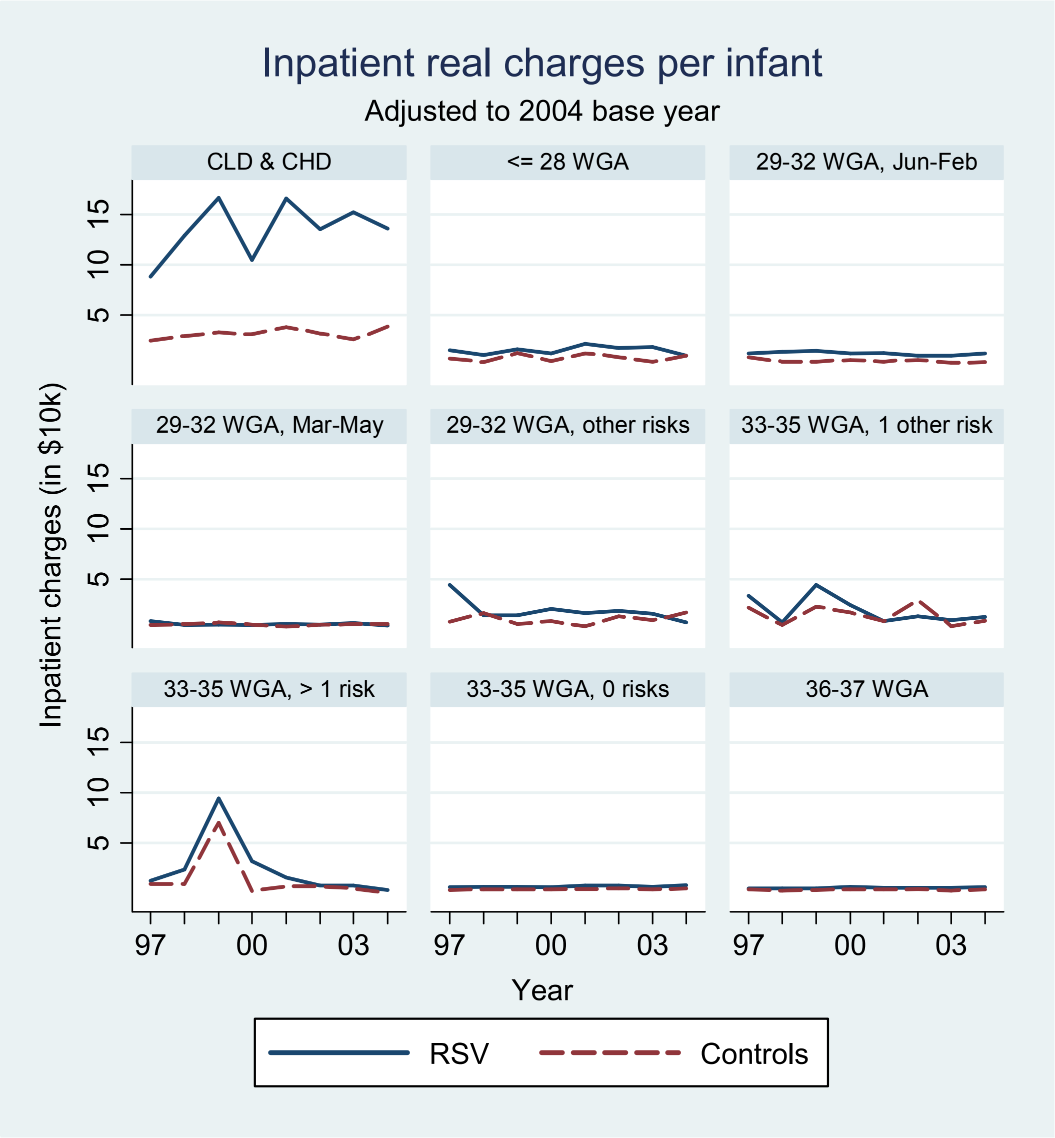


Figure 4 – Real inpatient charges of RSV and control conditions, by gestational age and risk factors



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