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# Factors Influencing Infant Death due to Respiratory Syncytial Virus

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## **Abstract**

*Objective:* Determine what factors are associated with increased mortality in infants <1 year old due to respiratory syncytial virus. *Methods:* Using publicly accessible infant mortality data from CDC Wonder, I used z-scores to compare infant death rates due to RSV between different groups including levels of prematurity, birth weight, and race. *Results:* When compared by race, mortality rates were highest for infants with mothers who are American Indian or Alaska Natives, followed by infants with Black mothers, and lowest for infants with White or Asian mothers. Infants born with lower weight at birth had higher mortality rates by RSV than infants with higher birth weights. Infants born prematurely, especially at <28 weeks gestation had higher RSV mortality rates. When compared by geographic region, RSV mortality rates were highest in the Southern U.S.. Sorting by mother's age, infants born to younger mothers, especially mothers <20 years old had higher mortality rates due to RSV. These findings align with previous research focusing on RSV mortality and overall trends in epidemiological factors influencing infant mortality.

**Key Words:** Respiratory syncytial virus, infant mortality, race

## Introduction/Literature Review

Respiratory syncytial virus (RSV) is a leading cause of hospitalization among infants <1 year old, commonly causing lower respiratory tract infections.<sup>1</sup> From 1997-2006, one study calculated the highest hospitalization rates from RSV for infants <3 months (48.9 per 1000) and 3-5 months age (28.4 per 1000), with lower hospitalization rates for infants >1 year age (1.8 per 1000).<sup>2</sup> Evidence shows that among infants hospitalized for respiratory syncytial virus, infants born pre-term tend to have more severe infections, longer hospital stays, more admissions to the ICU, and a higher overall cost of hospitalization than infants born at full term.<sup>1</sup> Estimates suggest that globally, over 27,000 infants under 6 months of age died from respiratory syncytial virus in 2015, with 99% of deaths from RSV occurring in developing countries.<sup>3,4</sup>

In Taiwan, “high risk” infants, including infants born premature and those with bronchopulmonary dysplasia, are given 6 months of RSV prophylaxis with palivizumab. Evidence showed that with palivizumab prophylaxis, hospitalizations due to RSV decreased by 60%.<sup>5</sup> Current recommendations by the American Academy of Pediatrics suggest considering prophylactic palivizumab for infants <1 year of age who were born at a gestational age <32 weeks and required oxygen for 28 days after birth as well as infants with other diseases.<sup>6,7</sup> While palivizumab prophylaxis for RSV is expensive and requires monthly administrations during the RSV season, it has been shown to be cost effective for prematurely born infants, infants with lung complications, and infants from remote communities.<sup>8</sup> Guidelines for RSV prevention and prophylaxis will have continued importance as many potential vaccines and monoclonal antibodies are under development.<sup>9</sup>

In recent years, while hospitalization due to RSV for children is still common, deaths from RSV are very uncommon in the United States.<sup>10</sup> The majority of RSV-related deaths occur in

developing countries.<sup>3</sup> Perhaps because of this, the majority of research in the United States surrounding RSV epidemiology focuses on hospitalizations rather than mortality. While there seems to be a considerable amount of research discussing prematurity and its association with rates of RSV hospitalizations, little recent research discusses race and there is a lack of research focused on RSV mortality.<sup>9</sup>

In this study, I investigate if race, geographic region, gestational age, and birth weight are associated with different rates of infant mortality due to RSV in the United States. This information could provide more context as to what groups in a more developed country may be at higher risk of infant death due to RSV, particularly in more recent years. This information on mortality would be particularly useful as researchers work to develop RSV vaccinations for pregnant women to reduce incidence of RSV in their infants and guidelines will need to be shaped accordingly.

### **Specific Aim**

In this project, I examine publicly accessible data to look for differences in the number of RSV-related deaths between different groups, including levels of prematurity, birth weight, geographic region, and race.

### **Methods**

#### *Context/Protocol*

For this project, I used the Infant Death database from the publicly available CDC Wonder database ([wonder.cdc.gov](http://wonder.cdc.gov)). Since the data is publicly available, there is no need for IRB approval.

### *Data Collection*

Data for this study is based on aggregate data from the CDC Wonder Infant Death database. Data was pulled from death certificates and linked to birth certificates from the years 2007-2017. I used the data focused only on deaths caused by illnesses resulting from Respiratory Syncytial Virus, and then sorted this data based on the following variables: race, region of the US, birth weight, and gestational age at birth. Data could not be sorted by multiple variables at once without some data being excluded due to potentially identifying data because of the small numbers of deaths, so each variable was sorted individually.

### *Data Analysis*

For data analysis, I numerically analyzed the rates of mortality from RSV via Z scores for infants in different groups, including race (Black, White, American Indian, and Asian/Pacific Islander), region of the US (Northwest, Midwest, South, and West), birth weight (<499 g, 500-999 g, 1000-1499 g, 1500-1999 g, 2000-2499 g, 2500-2999 g, 3000-3499 g, 3500-3999 g, 4000-4499 g, and 4500-4999 g), gestational age at birth (20-27 weeks, 28-31 weeks, 32-33 weeks, 34-36 weeks, 37-38 weeks, 39 weeks, 40 weeks, 41 weeks, and 42+ weeks), and mother's age (15-19, 20-24, 25-29, 30-34, 35-39, and 40-44). There was a total of 166 deaths due to Respiratory Syncytial Virus in this dataset.

### **Results**

Analysis in this study showed that among infants <1 year of age, the Z score for mortality due to RSV was highest for infants whose mothers were American Indian or Alaska Natives, at 1.39, followed by infants whose mothers were Black, and lowest for infants whose mothers were

White or Asian (Table 1). Mortality rates were very similar between infants whose mothers were White or Asian.

Mother's Race	Deaths	Births	Death Rate	Z score of Death Rate
American Indian or Alaska Native	6	507606	1.18202E-05	1.39
Asian/ Pacific Islander	9	2961931	3.03856E-06	-0.74
Black	45	7135140	6.30681E-06	0.06
White	106	33695893	3.14578E-06	-0.71

When sorted by birth weight, infants born weighing 500-999 grams had the highest Z score at 2.29 (Table 2). Overall, death rates were generally higher for infants with a lower birth weight compared to higher birth weights.

Birth Weight(g)	Deaths	Births	Death Rate	Z score of Death Rate
<499	2	73897	2.70647E-05	0.29
500-999	19	240702	7.89358E-05	2.29
1000-1499	16	329559	4.85497E-05	1.12
1500-1999	14	701668	1.99525E-05	0.01
2000-2499	26	2262821	1.14901E-05	-0.32
2500-2999	20	8176343	2.44608E-06	-0.67
3000-3499	47	17267718	2.72184E-06	-0.66
3500-3999	15	11777140	1.27365E-06	-0.71
4000-4499	5	2896989	1.72593E-06	-0.69
4500-4999	1	421592	2.37196E-06	-0.67

Sorting by gestational age at birth, infants born at 20-27 weeks had the highest Z score for mortality by far at 2.30 (Table 3). Infants with a younger gestational age at birth generally had higher mortality rates than infants with an older gestational age at birth.

LMP Gestational Age	Deaths	Births	Death Rate	Z score of Death Rate
20-27	20	306600	6.52316E-05	2.30

28-31	19	534360	3.55566E-05	0.95
32-33	10	668755	1.49532E-05	0.01
34-36	22	3687722	5.96574E-06	-0.40
37-38	34	11541173	2.94597E-06	-0.53
39	29	12788208	2.26771E-06	-0.57
40	22	8569153	2.56735E-06	-0.55
41	4	3724941	1.07384E-06	-0.62
42+	4	2414061	1.65696E-06	-0.59

Comparing geographic regions of the United States, the highest mortality was in the South, with a Z score of 1.03, and the lowest was in the Northeast, with a Z score of -1.28 (Table 4).

<b>Table 4: Infant Mortality due to RSV by Geographical Region, 2007-2017</b>				
Region	Deaths	Births	Death Rate	Z score of Death Rate
Northeast	20	7092233	2.81999E-06	-1.28
Midwest	32	9318574	3.434E-06	-0.24
South	71	17009148	4.17422E-06	1.03
West	42	10880615	3.86008E-06	0.49

When comparing the age of the mothers, infants born to the youngest group of mothers (15-19 years old) had the highest mortality with a Z score of 1.46 (Table 5).

<b>Table 5: Infant Mortality due to RSV by Mother's Age, 2007-2017</b>				
Mother's Age	Deaths	Births	Death Rate	Z score of Death Rate
15-19	19	3448384	5.50983E-06	1.46
20-24	49	10132805	4.83578E-06	0.89
25-29	41	12647351	3.24179E-06	-0.47
30-34	32	11251805	2.84399E-06	-0.81
35-39	21	5486835	3.82734E-06	0.03
40-44	3	1201832	2.49619E-06	-1.10

## Discussion

This data shows the highest infant mortality for infants born to American Indian or Alaska Native mothers, followed infants whose mothers were Black, and lowest mortality for infants whose mothers were White or Asian. This order of mortality rates differs slightly from other research comparing infant mortality by race. Estimates of total infant mortality rate from 2014-2016 indicated total infant mortality rate for all causes when compared by race was highest for non-Hispanic black infants, followed by American Indian or Alaska Native infants, then non-Hispanic white infants, with the lowest mortality rate for Asian infants.<sup>12</sup> While this study focuses on mortality rather than hospitalization, the finding of higher mortality for black infants compared to white infants differs from an epidemiological study showing similar rates of hospitalization for black and white infants <1 year of age due to RSV in three U.S. counties from 2002-2009.<sup>13</sup> A limitation of this data set is that the race categories were not fully inclusive, defined by mother's race with no mention of father's race, and lacking categories for bi- or multi-racial mothers, Hawaiian or Pacific Islanders, and no ethnic categories for Hispanic vs. non-Hispanic mothers.

Birth weight data in this study shows higher mortality for infants with lower birth weights, with highest mortality for infants with a birth weight of 500-999g. This trend agrees with other research that there are proportionally more infant deaths from RSV among infants of lower weight compared to infants of normal weight.<sup>4,14</sup> However, other research also suggests that while mortality for infants with low birth weight in high-income countries for all causes was increased, this is mostly attributed to those infants having other comorbidities.<sup>4,12</sup> Increased mortality for infants born <32 weeks gestational age as seen in this data set is also in agreement with previous research demonstrating higher mortality for infants born at younger gestational age.<sup>14</sup>



Geographical region also showed differences in infant mortality from RSV. While this data set divided the U.S. into just four regions, the finding of higher mortality in the South and low mortality in the Northeast aligns with other documented trends for all-cause infant mortality which show highest rates in the Southeast and lowest rates in New England and the Pacific.<sup>12</sup> Mother's age also demonstrated differences in mortality, with infants born to younger mothers, especially mothers <20 years old, having higher infant mortality rates due to RSV. This aligns with older studies discussing RSV mortality in children <2 years of age.<sup>14</sup>

While mortality in U.S. cases of RSV is rare, mortality most often occurs in those infants with multiple comorbidities.<sup>4,10</sup> One limitation of the data set used for this study was that because it was based on population rather than individual data, there was no way to extricate comorbidities or compare epidemiological factors while controlling for comorbidities. Another major limitation of this data was the inability to sort by multiple variables at once in order to protect identity in a public dataset with small case numbers. Differences in infant mortality when compared by race have been shown to be inherently linked to differences in proportions of infants born very prematurely or with low birth weight.<sup>15</sup> Sorting by multiple risk categories at once would have been useful to see if infants with multiple risk factors accordingly had a compounded mortality risk, or which factor best explained increased mortality.

Fortunately, the mortality rate for infants due to respiratory syncytial virus in the United States is very low. However, the small numbers of cases limits the ability to perform many types of data analysis. Globally, 99 percent of mortality due to RSV has been estimated to occur in developing nations.<sup>3</sup> More studies focusing on identifying risk factors at birth for infant mortality due to RSV would likely have a larger global impact by studying countries with higher mortality rates than the United States.

Even with the small numbers of infant deaths in the United States due to RSV, trends identified in this study echo other studies which illustrate disparities in infant mortality between different regions and groups in the U.S.. Infants who have high-risk factors and develop RSV infections have more severe cases and longer hospitalizations.<sup>1</sup> Current American Academy of Pediatrics guidelines suggest that palivizumab prophylaxis be considered to prevent RSV in infants <1 year old born at <32 weeks gestational age who required oxygen for 28 days after birth.<sup>6</sup> Illuminating differences in risk for hospitalization or death due to RSV infection provide evidence to shape guidelines for providing prophylaxis to high-risk infants and will continue to be important as researchers attempt to develop options for preventing RSV infection and death.

## **Conclusion**

In this study, data from the CDC Wonder Infant Death Database across ten years, 2007-2017 was analyzed for infants whose cause of death included respiratory syncytial virus (RSV). The data shows higher mortality rates for infants born to American Indian/Native mothers and Black mothers, infants born at <27 weeks gestation, infants with low birth weight, infants born to younger mothers, and infants born in the South. These findings overall tend to align with the results of older studies discussing RSV mortality in infants and young children and trends in all-cause infant mortality.

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