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## Risk of Childhood Asthma Following Infant Bronchiolitis During RSV Season

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### Keywords

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### To the Editor:

The etiology of asthma remains unclear but is thought to include non-modifiable risk factors such as family history and genetic predisposition, as well as potentially modifiable risk factors including viral bronchiolitis in infancy<sup>(1;2)</sup>. During the winter months, the predominant virus detected in infants with viral bronchiolitis is respiratory syncytial virus (RSV)<sup>(3)</sup>. By 1 year of age approximately 70% of children have been infected with RSV, and this increases to almost 100% by 2 years of age<sup>(4)</sup>. Infant RSV bronchiolitis is associated with recurrent wheeze or asthma throughout childhood and even into early adulthood<sup>(5;6)</sup>, with a dose-response relationship identified between the severity of the bronchiolitis and the risk of developing asthma<sup>(7)</sup>, and evidence for a causal relationship<sup>(8)</sup>. The aim of our study was to determine what proportion of childhood asthma is associated with infant bronchiolitis during RSV season.

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We analyzed cohort data of children born from 1996–2003 cared for at Northern California Kaiser Permanente (KPNC), an integrated healthcare delivery system, and children born from 1995–2003 enrolled in Tennessee Medicaid (TennCare). KPNC and TennCare provide health insurance for approximately one-third of Northern California residents and approximately one-half of infants born in Tennessee, respectively. Eligible infants had a minimum gestation age of 32 weeks, no chronic lung disease, and were continuously enrolled in either TennCare or KPNC during the first year of life. The main predictor variable was infant bronchiolitis during RSV season defined by ICD-9 codes for bronchiolitis and limited to the RSV season, October through March, during the first year of life. The main outcome variable was early childhood asthma determined using an algorithm of ICD-9 codes for asthma and asthma-specific medication utilization between ages 4.5–6 years. The Vanderbilt University Institutional Review Board and the KPNC Institutional Board for the Protection of Human Subjects approved the study. The Bureau of TennCare approved use of Tennessee Medicaid data.

To ascertain the proportion of childhood asthma in the TennCare or KPNC population that is associated with bronchiolitis exposure during RSV season, we calculated both the attributable risk of infants with a bronchiolitis event during infancy, and the population attributable risk. We estimated the attributable fraction of bronchiolitis from adjusted risk ratios that were calculated from multivariable Poisson regression models with a robust error variance for the early childhood asthma outcome. Adjustment covariates included gender, race, gestational age, birthweight, siblings, maternal age, and maternal smoking. Statistical analyses were performed with R version 2.12.1 software.

A total of 264,010 infant births (KPNC 81,550, TennCare 182,460) were included in this study and followed until 6 years of age. Table I highlights key characteristics of the two cohorts. Compared to the TennCare population, the KPNC population had more Hispanic and Asian participants, less African American participants, higher rates of maternal education beyond high school, and lower rates of maternal smoking. Overall, 15% of infants had bronchiolitis during RSV season.

The proportion of children diagnosed with asthma among the KPNC and TennCare cohorts was 8% and 12%, respectively, for those without a history of infant bronchiolitis during RSV season, and 16% and 23%, respectively, for those with a history of infant bronchiolitis during RSV season. The population attributable risk for asthma contributed by infant bronchiolitis during RSV season was 10% for the KPNC cohort, and among the subset of children with infant bronchiolitis during RSV season, the attributable risk was 49% (95% CI:47%,52%); in TennCare, it was 13% and 47% (95% CI:45%,48%), respectively (See Fig 1). The unadjusted risk ratio of childhood asthma following infant bronchiolitis during RSV season for KPNC was 1.97 (95% CI:1.87,2.09) and the multivariate adjusted risk ratio of childhood asthma following infant bronchiolitis during RSV season was 1.94 (95% CI: 1.84,2.05); for TennCare it was 1.87 (95% CI:1.82,1.92) and 1.81 (95% CI:1.77,1.86), respectively. In our analysis restricting to term infants (gestational age  $\geq$  37 weeks), results remain unchanged (data not shown).

In both the KPNC and TennCare cohorts, the proportion of children who developed asthma was almost two times higher in children with a history of infant bronchiolitis during RSV season as compared to the children who did not have a history of infant bronchiolitis during RSV season. The almost identical attributable risk and population attributable risk findings are notable given the significant differences between the two populations. Adjustment of risk ratios for potential confounders did not change the results.

Despite the strengths of our large population-based study, several limitations deserve mention. This study relied on existing electronic data; however, the use of electronic data has been previously validated as both sensitive and specific<sup>(9)</sup>. Secondly, the study was unable to detect infants with asymptomatic or mild bronchiolitis during RSV season as well as those who did not seek treatment. In addition, we were unable to confirm the diagnosis of RSV as the etiology of bronchiolitis events although prior studies support that the majority of infant bronchiolitis events during RSV season are attributable to RSV<sup>(3)</sup>. In a retrospective study by Stemple et al. in which bronchiolitis was defined by ICD-9 codes for bronchiolitis, RSV was detected in the nasal wash samples of 77% of children under 2 years of age collected between October and April<sup>(10)</sup>. By limiting our study to bronchiolitis episodes during the winter months, RSV is likely to be the associated viral pathogen. Lastly, while human rhinovirus (RV) infection has also been implicated in asthma inception, infant RV bronchiolitis is far less common than infant RSV bronchiolitis, and occurs in older infants, those born to parents with asthma, or those who have already been allergically sensitized, suggesting that rather than being causal, that RV bronchiolitis is a clinical biomarker of future asthma risk<sup>(11–13)</sup>.

In summary, in two representative US populations with significantly varying baseline characteristics, there were consistent findings that nearly 50% of asthma cases in children with a history of infant bronchiolitis during RSV season were associated with bronchiolitis. On a population level, 13% of asthma was associated with infant bronchiolitis during RSV season. The mechanism to explain how infant RSV infection results in the subsequent development of asthma remains unclear, but if truly causal in nature as supported by observational<sup>(8)</sup> and mechanistic<sup>(14)</sup> studies, our findings indicate up to 13% of asthma cases could be prevented by eliminating infant bronchiolitis during RSV season. Thus, next steps are to determine if preventing or altering host response to infant RSV infections decreases both the incidence and severity of childhood asthma as a primary asthma prevention strategy.

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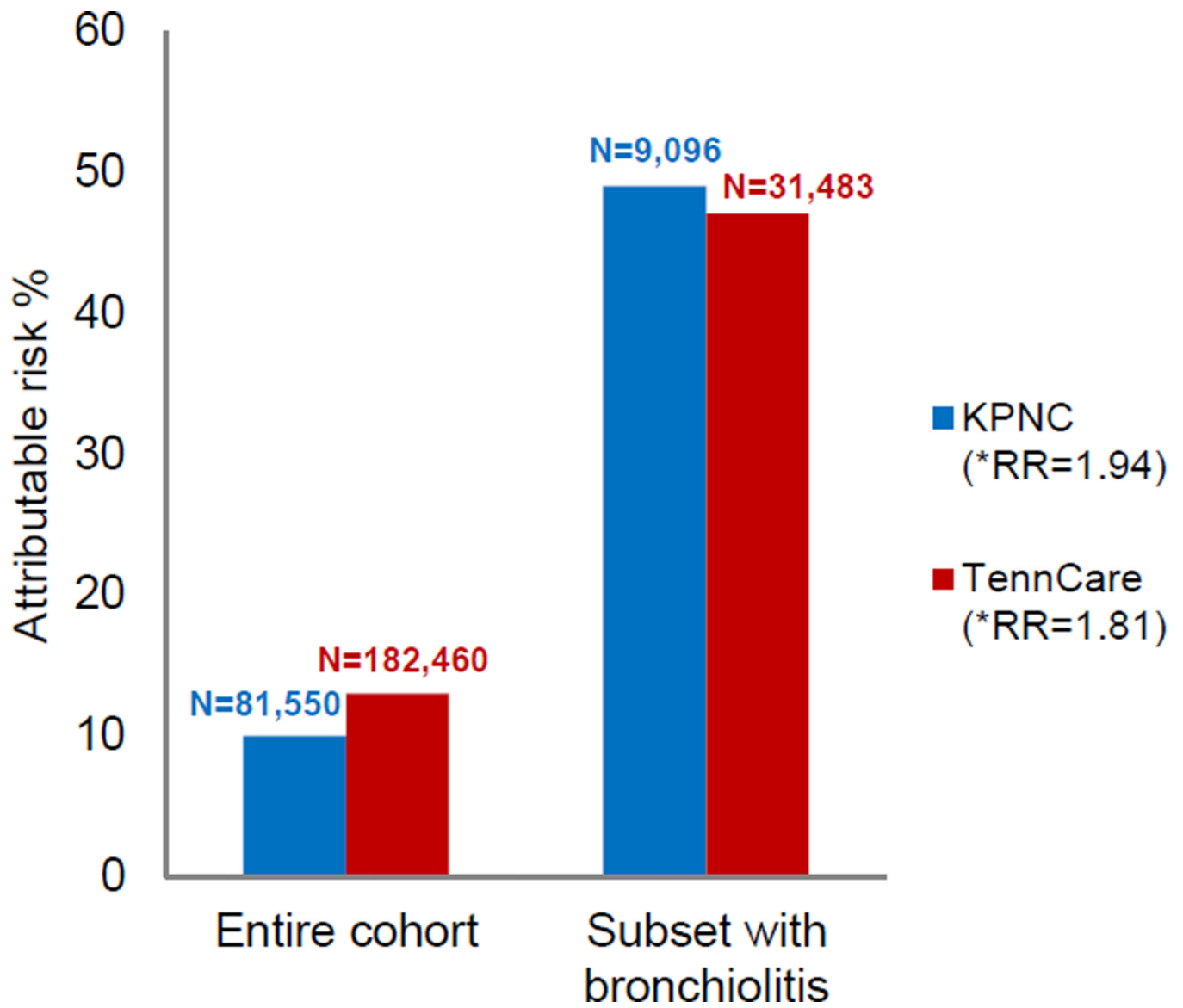
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## Abbreviations

<b>CI</b>	Confidence interval
<b>KPNC</b>	Northern California Kaiser Permanente
<b>RSV</b>	Respiratory syncytial virus
<b>RV</b>	Rhinovirus
<b>TennCare</b>	Tennessee Medicaid

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**FIG 1.** Attributable risk of asthma due to infant bronchiolitis during RSV season. \*Multivariable Poisson regression analyses were used to calculate risk ratios within the KPNC and TennCare populations.

**TABLE I**

Demographic, exposure and outcome characteristics of the KPNC and TennCare populations.

Variable	KPNC** (N=81,550)	TennCare** (N=182,460)
<u>Maternal characteristics:</u>		
Maternal age	26 31 35	19 22 26
Maternal asthma*	5%	4%
Maternal smoking	6%	27%
Maternal education > HS	62%	12%
<u>Infant characteristics:</u>		
Infant Gender (Male)	51%	51%
Infant Race	<i>White</i>	43%
	<i>Black</i>	9%
	<i>Hispanic / Latino</i>	21%
	<i>Asian</i>	20%
	<i>Other</i>	7%
Infant gestational age (weeks)	38 39 40	38 39 40
Infant birth weight (grams)	3080 3430 3771	2863 3203 3544
Proportion of infants with bronchiolitis during RSV season	11%	17%
Proportion of infants who developed asthma at 4.5–6 years	9%	14%

Continuous variable presented as a b c values, representing the lower quartile a, the median b, and the upper quartile c.

\* Among those meeting maternal enrollment criteria, KPNC: N=34,132 and TennCare: N=104,368

\*\* Infant birth year, KPNC: 1996–2003 and TennCare: 1995–2003