Hospitalizations associated with respiratory syncytial virus (RSV) and influenza in children, including children having a diagnosis of asthma

Edward Goldstein[1,*]

1. Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA 02115 USA

* Corresponding author; egoldste@hsph.harvard.edu

Abstract

Background: There is uncertainty about the burden of hospitalization associated with RSV and influenza in children, including those with underlying medical conditions.

Methods: We have applied previously developed methodology to estimate hospitalization rates associated with RSV and influenza for various hospital discharge diagnoses in US children from the 2003-04 through the 2009-10 seasons. Additional data on the prevalence of asthma diagnosis in children and its relation to hospital discharge diagnosis of asthma were used to estimate RSV-associated hospitalization rates in children having a diagnosis of asthma.

Results: The estimated average annual rates (per 100,000 children) of RSV-associated hospitalization with a respiratory diagnosis (ICD-9 codes 460-519) in either the principal or secondary position (excluding asthma (ICD-9 code 493) in the principal diagnosis) were 2347.1(95% CI(2223.6,2471.2)) in age <1y; 631.2(543.9,716.9) in age 1y; 322.3(272.8,372.2) in age 2y; 168.8(131.4,207.2) in age 3y; 87.7(59.3,116.2) in age 4y; 62.8(39.3,86.3) in ages 5-6y; 27.6(14.1,41.1) in ages 7-11y; and 33.8(15.2,52.6) in ages 12-17y. The corresponding rates of influenza-associated hospitalization were lower, ranging from 179.3(141.6,217.6) in age <1y to 15.9(10.5,21.3) in ages 12-17y. Children having a diagnosis of asthma had elevated risks for RSV-associated hospitalization, with the rates of RSV-associated hospitalization per 100,000 children having a diagnosis of asthma being 11415(8393,155801) in age <1y, 4343(3216,5639) in age 1y, 2842(2144,3628) in age 2y, and 1393(891.2,1923) in age 3y.

Conclusions: The estimated rates of RSV-associated hospitalization in young children were high, and declined rapidly with age. Additionally, we estimated very high rates of RSV-associated hospitalization in young children having a diagnosis of asthma, making those children potential targets for RSV prophylaxis and vaccination.

Introduction

Robust estimation of the severe outcome burden is essential for planning prevention programs. However, there is uncertainty about the rates of hospitalization associated with RSV and influenza in different age groups of children, as well as in children with underlying medical conditions. Studies of the relation between respiratory virus infections and various illness outcomes in the community (e.g. [1-5]) have documented high rates of RSV-associated hospitalization in full and pre-term infants ([1,2]) and young children [1], as well as high rates of influenza-associated hospitalization in children during certain influenza seasons (e.g. [4] vs. [5]). Moreover, those studies reveal high frequency of underlying medical conditions (particularly asthma) among children hospitalized with RSV and influenza infections ([1,6-8]). However, studies of illness outcomes in the community can suffer from limitations such as under-detection of the presence of viral infections, and suboptimal sample sizes. Estimates of hospitalization rates associated with respiratory viruses can also be derived from studies using hospital discharge data. Limitations of discharge diagnosis studies may include under-representation of the contribution of specific respiratory viral etiologies as primary or contributing causes of hospitalization (because cases may lack laboratory confirmation and etiology may be unknown), and/or incorrect assignment of viral etiology in the discharge diagnosis. Strategies for correcting missing or misclassified diagnoses by attributing certain proportions of hospitalizations with certain diagnoses to different etiologies have been used to develop burden estimates [8]. Statistical inference is a common approach for estimating the contribution of respiratory viruses to the burden of hospitalizations and other severe outcomes [10-15]. However, various assumptions underlying such statistical models may be uncertain [16,17]; moreover, when one varies the structure of inference models applied to the same data, the resulting goodness-of fit, and the estimates of the contribution of respiratory viruses may vary as well (e.g. Supporting Information for [14,15]). Overall, ameliorating the uncertainty in the estimates of the burden of severe outcomes (particularly hospitalizations) associated with respiratory virus infections, and increasing the granularity of some of the estimates in the literature (in terms of using a finer age splitting, and providing separate estimates for populations of individuals with certain underlying health conditions) could aid in the design of the corresponding mitigation strategies. In particular, while a variety of RSV vaccine candidates for different populations are currently in different stages of development [18-20], target groups for RSV vaccination beyond the infant population are uncertain.

Prevalence of asthma diagnosis in young children increases with age; for example, the estimated prevalence of asthma diagnosis in US children between 2003-2009 varied between 1.9% for children aged <1 year to 9.7% for children aged 4 years (Table 3). Moreover, frequencies of asthma diagnosis by year of age in the US change with time [21]. The etiological significance of such diagnoses can be subject to uncertainty, and diagnosis of asthma in infants and young children is challenging [22], with different mechanisms being involved in the pathogenesis of asthma-like symptoms during childhood [23]. At the same time, children with a previous diagnosis of asthma were found to be disproportionately represented among influenza-associated hospitalizations, e.g. [6-8]. Similarly, several studies [1,24-26] had suggested that asthma diagnosis in young children serves as a marker for the risk of RSV-associated hospitalization. In [1], 24/40 hospitalized children aged 2-5 years with confirmed RSV infection had a previous history of asthma. A large, population-based Danish study ([24]) has found that previous asthma hospitalization carried ~5-fold risk for a subsequent hospitalization with a confirmed RSV infection by the age of 2 years. As the rates of RSV-associated hospitalizations in young children are high, presence of additional significant risks among young children having a diagnosis of asthma can make RSV-associated hospitalization rates in those children particularly high. Evaluation of the rates of RSV-associated hospitalization in children having a diagnosis of asthma could therefor be useful for informing RSV-related mitigation efforts in those children.

In our earlier work [14,15], we introduced a new method for estimating the burden of severe outcomes associated with influenza and RSV. The structure of the inference framework in [14,15] is meant to address several limitations of some of the previously employed inference models. That structure includes the utilization of RSV and influenza (sub)type (A/H3N2, A/H1N1, and B) incidence proxies that are expected to be linearly related to the population incidence of those viruses; a flexible model for the baseline of severe outcomes not associated with influenza and RSV; a bootstrap method for inferring the confidence bounds on the estimates of the rates of influenza and RSV-associated severe outcomes that accounts for auto-correlation in the time series for the noise; and other constructs. In this paper we apply the inference method in [14,15] to US hospitalization data for the 2003-04 through the 2009-10 seasons to better estimate the rates of influenza and RSV-associated hospitalization in US children. We estimate these rates for several categories of ICD-9 coded hospital discharge diagnoses. Our main goals are to provide detailed age-specific estimates of the incidence of influenza and RSV-associated hospitalization in the general population of young children, as well as in the population of young children having a diagnosis of asthma.

Methods

Hospitalization Data

We used weekly data on US hospitalizations with different diagnoses in different age groups of children (<1y,1y,2y,3y,4y,5-6y,7-11y,12-17y). For our analyses, we included 24 states for which data on hospitalizations in infants with RSV in the principal diagnosis exhibited consistency throughout the study period (see next subsection). Those 24 states, that constituted approximately 65.8% of the US population during the study period, are "AR" "CA" "CO" "CT" "GA" "HI" "IA" "IL" "IN" "MD" "MN" "NC" "NE" "NJ" "NV" "NY" "OH" "OR" "TN" "TX" "VA" "VT" "WA" "WI".

Inference Scheme

Our methodology is based on the framework developed in our earlier publications [14,15] and is explained in detail therein.

Each season was defined as a period between calendar week 27 (mid year) of a given year, and calendar week 26 of the following year.

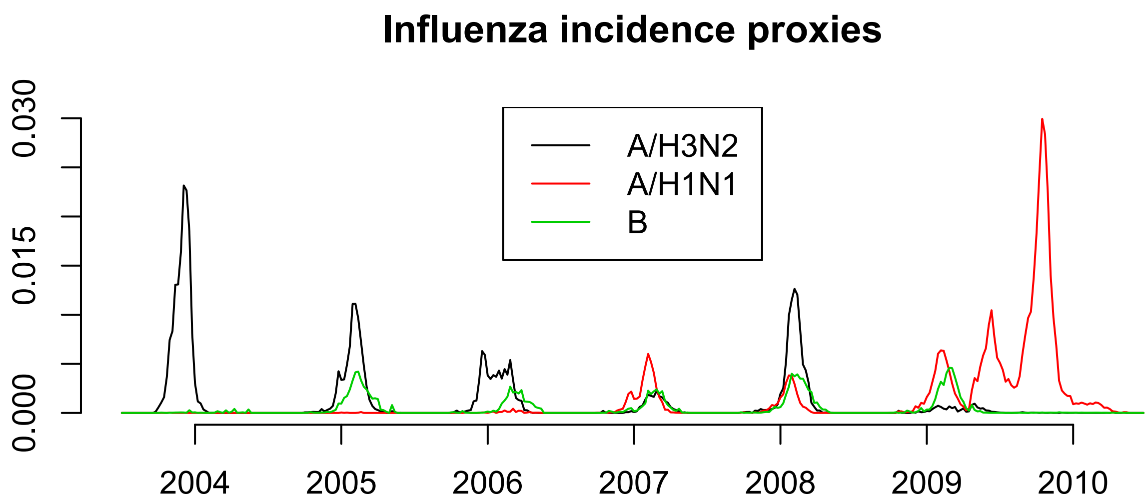
As the rates of influenza and RSV infection are difficult to estimate directly, we use *proxies* for the incidence of RSV and the major influenza (sub)types (A/H3N2, A/H1N1, and influenza B) that are expected to be proportional to the population incidence of those viruses. Those proxies are derived from the available data on RSV hospitalizations and influenza surveillance. We consider the weekly incidence proxy for RSV to be the rate of hospitalization with the principal diagnosis of RSV (ICD-9 codes 466.11, 480.1, and 079.6) among children aged <1y during that week. We use hospitalization rates in infants because there is an apparent upward trend in annual rates of hospitalization with the principal diagnosis of RSV in all age groups above two years of age, likely due to changes in testing/diagnostic practices, but no trend in the rates of hospitalization with a principal diagnosis of RSV in infants. For the influenza incidence proxies, we utilized the US CDC surveillance data [27]. We multiplied the weekly state-specific percent of medical consultations in the US CDC Outpatient Illness Surveillance Network (ILINet) that were for influenza-like illness (ILI) by the state-specific percent of respiratory specimens in the US Virologic Surveillance laboratories that tested positive for each of the major influenza (sub)types (A/H3N2, A/H1N1, and influenza B) to define state-specific weekly proxies for the incidence of each major influenza (sub)type:

Weekly influenza (sub)type incidence proxy = (1)

*= (% Consultations for ILI) * (% Specimens testing positive for the (sub)type)*

Our analyses were restricted to the collection of 24 US states described in the Data subsection, and the (sub)type-specific incidence proxy for that collection of states is defined as the sum of state-specific incidence proxies for the (sub)type weighted by the state populations, with state populations during various weeks estimated through linear interpolation (in time) for the yearly, July 1st state population estimates, borrowed from [28].

Figure 1 exhibits the incidence proxies for influenza A/H3N2, A/H1N1, and B, as well as for RSV. The incidence proxy for RSV was more periodic than the incidence proxies for the different influenza (sub)types, with the highest cumulative incidence for the RSV incidence proxy attained during the 2003-04 season.



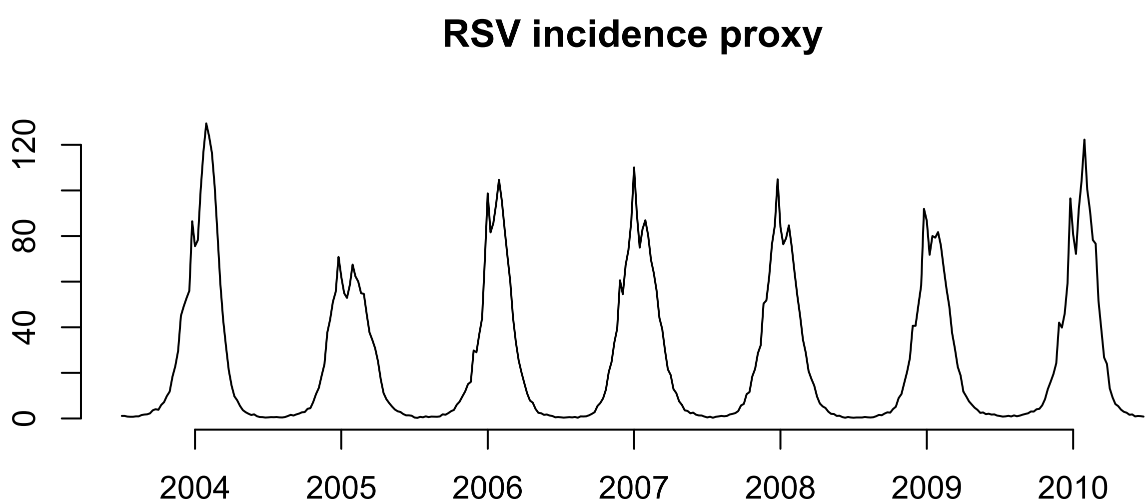


Figure 1: Incidence proxies for influenza A/H3N2, A/H1N2, and B (top panel), and for RSV (bottom panel).

The relationship between an influenza incidence proxy and the rate of associated hospitalization in a given age group may change in time due to a variety of factors [14]. One of those factors is change in the age distribution for different influenza-associated outcomes due to changes in influenza strain circulation and immunity patterns. In particular, the 2003-04 influenza season in the US was driven by a novel (Fujian) A/H3N2 strain, and higher rates of excess respiratory ED visits in school-age compared to pre-school children were estimated during the 2003-04 season compared to the 2004-05 season in NYC [13]. Additionally, the emergence of the pandemic A/H1N1 influenza strain in 2009 resulted in exceptionally high rates of pediatric influenza infections [29], and the ratios between the rates of A/H1N1-associated hospitalizations in different subgroups of children and the A/H1N1 incidence proxy are potentially different for the pandemic strain compared to the seasonal A/H1N1 strain. Figure 1 suggests that the incidence proxy for influenza A/H3N2 was exceptionally high during the 2003-04 season, while the incidence proxy for influenza A/H1N1 was exceptionally high during the 2009 pandemic. To address those considerations, we split the A/H3N2 incidence proxy into two, namely H31 equaling the A/H3N2 proxy for the 2003-04 season, with H31 being zero afterwards, and H32, being zero for the 2003-04 season, and equaling the A/H3N2 incidence proxy afterwards. Similarly, we split the A/H1N1 incidence proxy into two, reflecting A/H1N1 incidence before and after the 2009 pandemic.

The outcomes we consider are rates of hospitalization for several different diagnoses types by age group in children. In our analysis, we consider five diagnoses types: 1) diseases of the respiratory system excluding asthma (ICD-9 codes 460-519; excluding 493); 2) pneumonia and influenza (ICD-9 codes 480-488); 3) respiratory cause in the principal or secondary diagnoses excluding asthma in the principal diagnosis; 4) asthma as a secondary (non-principal) diagnosis; 5) asthma in either the principal or secondary diagnosis. The first three are used to assess RSV and influenza-associated hospitalization rates in the general population of children, while the last two are used to evaluate the rates of RSV and influenza-associated hospitalization in children having a diagnosis of asthma.

For each choice of an age group and diagnosis type, weekly hospitalization rates in that age group with that diagnosis type during the study period (*outcome*) are regressed linearly against the following covariates: incidence proxies for influenza and RSV, as well as temporal trend (modeled by a low degree polynomial in time) and a seasonal baseline (modeled by cubic splines in the calendar week with knots at every fourth week and with annual periodicity) [14,15]. If $O(t)$ is the weekly rate for the outcome on week t, and $V_i(t)$ are the incidence proxies for the various influenza (sub)types (split into time periods as described above) and RSV, the model structure is

$$O(t) = \sum_i \beta_i \cdot V_i(t) + Baseline + Trend + Noise \qquad (2)$$

To account for the autocorrelation structure in the noise, a bootstrap method devised in [14] is used to prescribe the confidence bounds for the model's estimates. Estimates in [15] suggest that several alternative inference methods (such as the maximum likelihood inference for AR(1) noise) yield very similar results.

RSV-associated hospitalizations in children having a diagnosis of asthma

We extrapolate the rates of RSV-associated hospitalization in children having a diagnosis of asthma from the rates of hospitalization with asthma in either the principal or secondary discharge diagnosis in the general population of children, data on the prevalence of asthma diagnosis by age group in children, and certain additional data. Specifically, for any given age group, let

A. AD be RSV-associated hospitalizations with asthma in either the principal or secondary discharge diagnosis
B. HA be RSV-associated hospitalizations that are in children having a (previous) diagnosis of asthma
C. $AD\&HA$ be RSV-associated hospitalizations that are in children having a diagnosis of asthma and that have asthma in either the principal or secondary discharge diagnosis

We are interested in estimating the number $|HA|$ of RSV-associated hospitalizations in a given age group that are in children having a diagnosis of asthma. We have

$$|HA| = |AD| * \frac{|AD\&HA|}{|AD|} / \frac{|AD\&HA|}{|HA|} \qquad (3)$$

The quantity $|AD|$ can be found from our estimates of the rates of RSV-associated hospitalization with asthma in either the principal or secondary discharge diagnosis (Inference Scheme subsection). The quantity $\frac{|AD\&HA|}{|AD|}$ is the proportion of RSV-associated hospitalizations with asthma in either the principal of secondary discharge diagnosis that are in children who already have a diagnosis of asthma. The quantity $\frac{|AD\&HA|}{|HA|}$ is the proportion of RSV-associated hospitalizations in children who already have a diagnosis of asthma that have asthma in either the principal of secondary discharge diagnosis. For influenza-associated hospitalizations for the 2003-04 through the 2009-10 seasons from the FluServ-Net surveillance database [30,6], the ratios $\frac{|AD\&HA|}{|AD|} / \frac{|AD\&HA|}{|HA|}$ were above 1 in children aged <1y,1y,2y,3y, and 4y, ranging from 1.37(1.18,1.57) for children aged 1y to 1.88(1.58,2.23) for children aged 3y. The corresponding ratios could be different for RSV-associated hospitalizations compared to influenza-associated hospitalizations. Symptoms associated with RSV infections in young children could be more likely to resemble asthma-like-symptoms compared to symptoms for influenza-associated infections, though the significance of this for the assignment of hospital discharge diagnoses of asthma is unclear as the proportion of influenza hospitalizations in children that have a discharge diagnosis of asthma is high (e.g.

[6]), and comparable to our estimates for the corresponding proportions for RSV-associated hospitalizations. While the estimated ratios $\frac{|AD\&HA|}{|AD|}/\frac{|AD\&HA|}{|HA|}$ for influenza hospitalizations were above 1 for all age subgroups of young children, we adopt the estimate $\frac{|AD\&HA|}{|AD|}/\frac{|AD\&HA|}{|HA|} = 1$ for RSV-associated hospitalizations in eq. 3 in the hope that this estimate is conservative, namely that the volume of RSV-associated hospitalizations in children having a diagnosis of asthma is underestimated in this manner. Thus we estimate $|HA| = |AD|$ for RSV-associated hospitalizations. Correspondingly, the rate of RSV-associated hospitalization per 100,000 children having a diagnosis of asthma is estimated to be the rate of RSV-associated hospitalization with asthma in either the principal or secondary diagnosis per 100,000 children divided by the prevalence of asthma diagnosis in the corresponding age group. Data on the prevalence of asthma diagnosis by year of age are described in [21], with the corresponding annual averages between 2003-2009 provided to us by Dr. L. Akinbami.

Results

Figures 2-5 exhibit model fits for hospitalizations with a respiratory cause in either the principal or secondary diagnosis (excluding the principal diagnosis of asthma), pneumonia and influenza in the principal diagnosis, asthma as a secondary diagnosis, and asthma in either the principal or secondary diagnosis in US children from the 2003-04 through the 2009-10 seasons. The plots suggest that the model fits were generally temporally consistent, particularly for children aged 0-3 years. For older children, the model fits were generally temporally consistent for hospitalizations with pneumonia and influenza (P&I) in the principal diagnosis. The model fits for older children were somewhat less temporally consistent for hospitalizations with a respiratory cause in either the principal or secondary diagnosis (excluding the principal diagnosis of asthma), with even a lesser degree of temporal consistency for asthma hospitalizations.

Tables 1 and 2 present the estimates of the average annual rates of hospitalization associated with influenza and RSV for various discharge diagnoses (Methods) in select age subgroups of children. Table 1 shows the results for hospitalizations for respiratory causes (excluding asthma) in the principal diagnosis, as well as for hospitalizations with a respiratory cause in either the principal or secondary diagnosis (excluding asthma in the principal diagnosis). Table 2 shows the corresponding results for hospitalizations for pneumonia and influenza (P&I) in the principal diagnosis, as well for hospitalizations with asthma as a secondary diagnosis, and asthma in either the principal or secondary diagnosis.

For all age groups and diagnosis types studied (except P&I hospitalizations in children aged 7-17y), the estimated rates of RSV-associated hospitalization are higher than the estimated rates of influenza-associated hospitalization. The estimated rates of RSV-associated hospitalization with a respiratory cause in either the principal or secondary diagnosis (excluding the principal diagnosis of asthma) were highest in children aged <1y (Table 1) and declined rapidly with age. For the more restricted category of respiratory causes in the principal diagnosis, the rates of RSV-associated hospitalization were somewhat lower (Table 1); a sizeable fraction of those hospitalizations in different age groups (except infants aged <1y) had P&I in the principal diagnosis (Table 2). Comparing the results for hospitalizations with asthma as a secondary diagnosis vs. asthma in the principal or secondary diagnosis (Table 2), we see that inclusion of hospitalizations with asthma in the principal diagnosis does not accord well with the structure of the inference model (eq. 1), with poor estimates for the rates of influenza-associated hospitalization. For RSV-associated hospitalizations (whose volume is higher than the one for influenza-associated hospitalizations), the results appear more robust (particularly for younger children), and the estimated rates for RSV-associated hospitalization with asthma in either the principal or secondary diagnosis are higher than the corresponding rates of RSV-associated hospitalization with asthma as a secondary diagnosis.

Age group / Diagnosis	Hospitalizations with a respiratory cause (excluding asthma) in the principal diagnosis		Hospitalizations with a respiratory cause in the principal or secondary diagnosis (excluding asthma in the principal diagnosis)	
	Flu	RSV	Flu	RSV
<1y	140.9 (114.1,168.4)	2128.6 (2044.1,2214)	179.3 (141.6,217.6)	2347.1 (2223.6,2471.2)
1y	66.3 (41.3,91.4)	561.2 (483,639.4)	80.7 (53.6,108.4)	631.2 (543.9,716.9)
2y	41.2 (28.1,53.9)	265 (223.2,307.3)	57.4 (41.7,73.3)	322.3 (272.8,372.2)
3y	32.1 (22.8,41.7)	140.9 (111.2,171)	44.5 (32.7,56.5)	168.8 (131.4,207.2)
4y	26.5 (19.8,33.3)	66.1 (44.3,88.1)	36.8 (28.2,45.5)	87.7 (59.3,116.2)
5-6y	27.6 (22.2,33)	41.5 (23.6,59.2)	36.8 (29.6,44)	62.8 (39.3,86.3)
7-11y	14.7 (12.3,17.1)	16.8 (9.2,24.5)	20.4 (16.3,24.4)	27.6 (14.1,41.1)
12-17y	9.9 (8.5,11.3)	14 (9.3,18.8)	15.9 (10.5,21.3)	33.8 (15.2,52.6)

Table 1: Average annual rates of influenza and RSV-associated hospitalization with a respiratory cause (excluding asthma) in the principal diagnosis (ICD-9 codes 460-519 excluding 493), and with a respiratory cause in the principal or secondary diagnoses (excluding asthma in the principal diagnosis) per 100,000 US children in different age groups, 2003-04 through the 2009-10 seasons.

Age group	Pneumonia and Influenza in the principal diagnosis		Asthma as a secondary (non-principal) diagnosis		Asthma as either principal or secondary diagnosis	
	Flu	RSV	Flu	RSV	Flu	RSV
<1y	111.9 (91.4,133.1)	360.1 (297.8,421.8)	5.5 (-0.1,11.1)	158.3 (139.4,177)	4.3 (-5.8,14.4)	209.6 (178.2,241.9)
1y	59 (46.5,71.8)	247.3 (207.4,286.8)	10.1 (3.1,17.3)	143.8 (120.2,167.6)	7.5 (-8.1,23.4)	221.4 (171.4,270.8)
2y	36.5 (28.7,44.4)	152.6 (126.2,178.3)	9.3 (4.3,14.4)	96.8 (79.4,113.8)	8.7 (-3.5,20.7)	176.4 (137.3,215.7)
3y	28.6 (20.6,36.7)	94 (69,118.9)	8.1 (3.9,12.3)	58.7 (44.4,73.1)	7.7 (-3.9,19.3)	107.7 (70.9,144.9)
4y	22.9 (17.6,28.4)	47 (29.5,64.4)	6 (2.3,9.8)	22.9 (10.1,35.5)	6.7 (-4.8,18.2)	49.3 (12.6,86.7)
5-6y	21.5 (16.8,26.3)	29.1 (13.8,44.3)	7.4 (4.2,10.7)	16.2 (5.3,27.1)	4.4 (-6.5,15)	27 (-7.2,61.6)
7-11y	11.2 (9.3,13.2)	10.4 (4.2,16.5)	5.1 (3.2,7)	10.6 (4.1,17.2)	5.6 (-1.2,12.5)	20.1 (-1.1,41.5)
12-17y	8.1 (7.1,9)	8 (5,11.1)	2 (-1,5.1)	13.9 (3.5,24.2)	4.3 (0.3,8.3)	18.6 (5,32.3)

Table 2: Average annual rates of influenza and RSV-associated hospitalization with P&I (ICD9 codes 480-488) in the principal diagnosis, asthma as a secondary (non-principal) diagnosis, and asthma in either the principal or secondary diagnosis per 100,000 US children in different age groups, 2003-04 through the 2009-10 seasons.

Table 3 presents the estimates of the prevalence of asthma by age group between 2003-2009 in young children in the US, the average annual rates of RSV-associated hospitalization in children having a diagnosis of asthma between the 2003-04 through the 2009-10 seasons in the US, and the relative risk for RSV-associated hospitalization in children having a diagnosis of asthma compared to the general population of children in the same age group (the ratio of estimates in the 3rd column of Table 3, and the rates of RSV-associated hospitalization with a respiratory cause in either the principal or secondary diagnosis in the general population of children in the same age group). Table 3 suggests very high rates of RSV-associated hospitalization in young children having a previous diagnosis of asthma, with relative risks in children aged <2 years comparable to the ~5-fold risk that previous asthma hospitalization carried for a subsequent hospitalization with a confirmed RSV infection by the age of 2 years in Danish children [24].

Age	Prevalence of asthma diagnosis	RSV-associated hospitalization rate	Relative risk for RSV-associated hospitalization for children having a diagnosis of asthma vs. all children in age group
<1y	1.9% (1.4%,2.4%)	11415 (8393,15581)	4.8 (3.5,6.6)
1y	5.1% (4.3%,5.9%)	4343 (3216,5639)	6.2 (4.4,8.3)
2y	6.25% (5.4%,7.1%)	2842 (2144.5,3628)	7.3 (5.2,9.8)
3y	7.8% (6.8%,8.8%)	1393 (891.2,1923)	6.7 (4.0,10.3)
4y	9.7% (8.5%,10.9%)	511 (126.7,909.9)	4.8 (1.1,10.5)

Table 3: Average annual prevalence of asthma diagnosis in US children between 2003-2009, average annual RSV-associated hospitalization rates in children having a diagnosis of asthma from the 2003-04 through the 2009-10 seasons in the US, and relative risks for RSV-associated hospitalization for the US children having a diagnosis of asthma from the 2003-04 through the 2009-10 seasons (ratio between the rates in column 3 and rates of RSV-associated hospitalization with a respiratory cause in either the principal or secondary diagnosis in the general population of children in the same age group).

Discussion

While a number of RSV vaccine candidates are currently in different stages of development [18-20], the design of the corresponding vaccination strategies (and other mitigation efforts) is limited by the uncertainty about the RSV-associated severe outcome burden. In this paper we apply our previously developed methodology [14,15] to estimate the rates of influenza and RSV-associated hospitalization for various discharge diagnoses by age group in US children between 2003-2010. Our estimates suggest that the rates of RSV-associated hospitalization in young children are high, and they decline rapidly by year of age, with that decline being most pronounced for the first vs. second year of life. Additionally, our results suggest that the rates of RSV-associated hospitalization in young children having a diagnosis of asthma are very high (with those rates being extremely high in infants aged <1 year), making those children potential targets for related mitigation efforts.

While the connection between RSV infection in early childhood and the subsequent risk of developing asthma has received a lot of attention in the literature [31-34], the contribution of RSV to the hospitalization burden in children having a diagnosis of asthma is less studied [35]. This fact might partly stem from the uncertainty in the etiology behind asthma diagnoses in very young children [23], with the resulting ambiguity about the criteria that would validate such a diagnosis [36]. At the same time, a number of studies have identified high rates of RSV infection in hospitalized young children with underlying health conditions, including asthma [1,24-26]. Hall et al. [1] demonstrated a high frequency of RSV infections for respiratory hospitalizations in children under the age of 5 years, with a high proportion of RSV-infected hospitalized children over the age of 2 years having a history of asthma (though the sample size for the latter result was suboptimal). A large study based on the population of Danish children has demonstrated that previous asthma hospitalization carried ~5-fold risk for hospitalization with a confirmed RSV infection before the age of 2 years [24]. Our estimates of the rates of RSV-associated hospitalization in children having a diagnosis of asthma support the results of those studies (with the relative risks for RSV-associated hospitalization for children having a diagnosis of asthma in our study being comparable to the estimates in [24]). Overall, our results provide further evidence for the notion that having an asthma diagnosis serves as a marker for the risk of subsequent RSV-associated hospitalization, which is similar to the corresponding findings about influenza-associated hospitalizations, e.g. [6-8]. In particular, the estimated rates of RSV-associated hospitalization in infants under the age of 1 year having a diagnosis of asthma are extremely high, making those children potential targets for RSV-related prophylaxis and vaccination. The estimated rates of RSV-associated hospitalization in children aged 1-2 years having a diagnosis of asthma are also very high. It might be the case that certain criteria for an asthma diagnosis are associated with additional risks for RSV-related hospitalization in children meeting those criteria, making such children over the age of 1 year potential targets for mitigation efforts related to RSV infections.

Our paper has some limitations. While we were not in possession of information on previous asthma diagnosis for the cases of hospitalization in children that we've utilized, we have devised a method to estimate the rates of RSV-associated hospitalization in children having a diagnosis of asthma using several data streams. While our inference method is meant to be conservative, this claim needs further validation through data on discharge diagnoses for RSV-associated hospitalizations. Another potential issue is the accuracy of the proposed regression framework [14,15]. Spikes in hospitalization rates during certain influenza seasons correspond visually to major influenza epidemics (as suggested by the incidence proxies that we utilize), providing additional support for the validity of our inference method for influenza-associated hospitalization rates. Inclusion of RSV into the model can be more problematic due to the relatively high periodicity of its circulation and the difficulty of separating its contribution from the annual baseline of hospitalization rates not associated with influenza and RSV. Additionally, we've used rates of hospitalization in infants with RSV in the principal diagnosis as a proxy for RSV incidence, while presence of RSV in the principal diagnosis need not be supported by a laboratory test. We've tried to remedy this by excluding states where rates of hospitalization in infants with RSV in the principal diagnosis were noticeably higher than in most states (which might suggest admixture from other etiologies in that category of hospitalizations) from the analyses (see Methods). While the resulting confidence bounds for the contribution of RSV to many of the hospitalization categories that we've considered are reasonably tight (Tables 1 and 2), and our estimates for the rates of RSV-associated hospitalization are generally consistent with the ones in the literature [9,10], further work is needed to evaluate the accuracy of our inference methodology.

We believe that despite those limitations, our work provides a granular assessment of the hospitalization burden associated with influenza and RSV infections in young children that may aid the evaluation of the impact of RSV vaccination in young children. Additionally, our results suggest very high rates of RSV-associated hospitalization in young children having a diagnosis of asthma. Those children may be considered as potential target groups for RSV-related prevention or prophylaxis.

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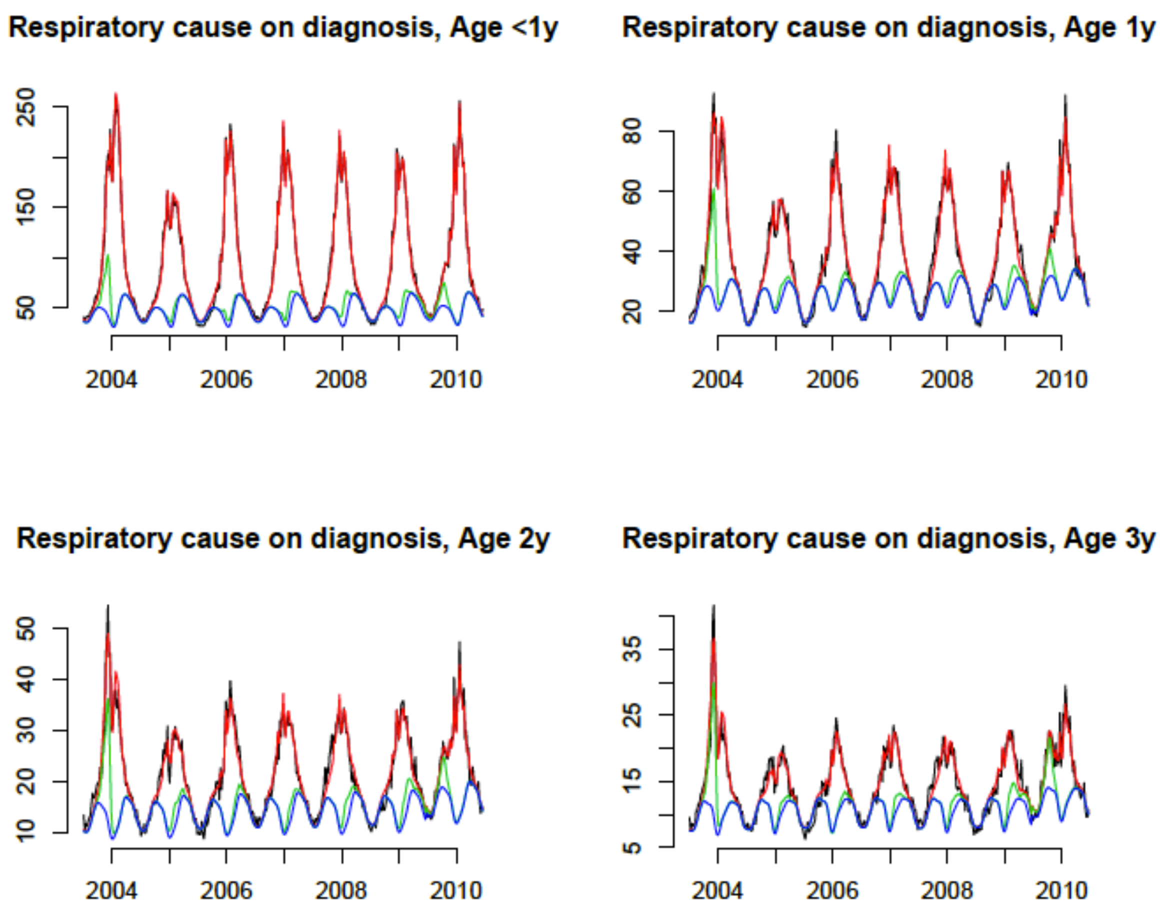
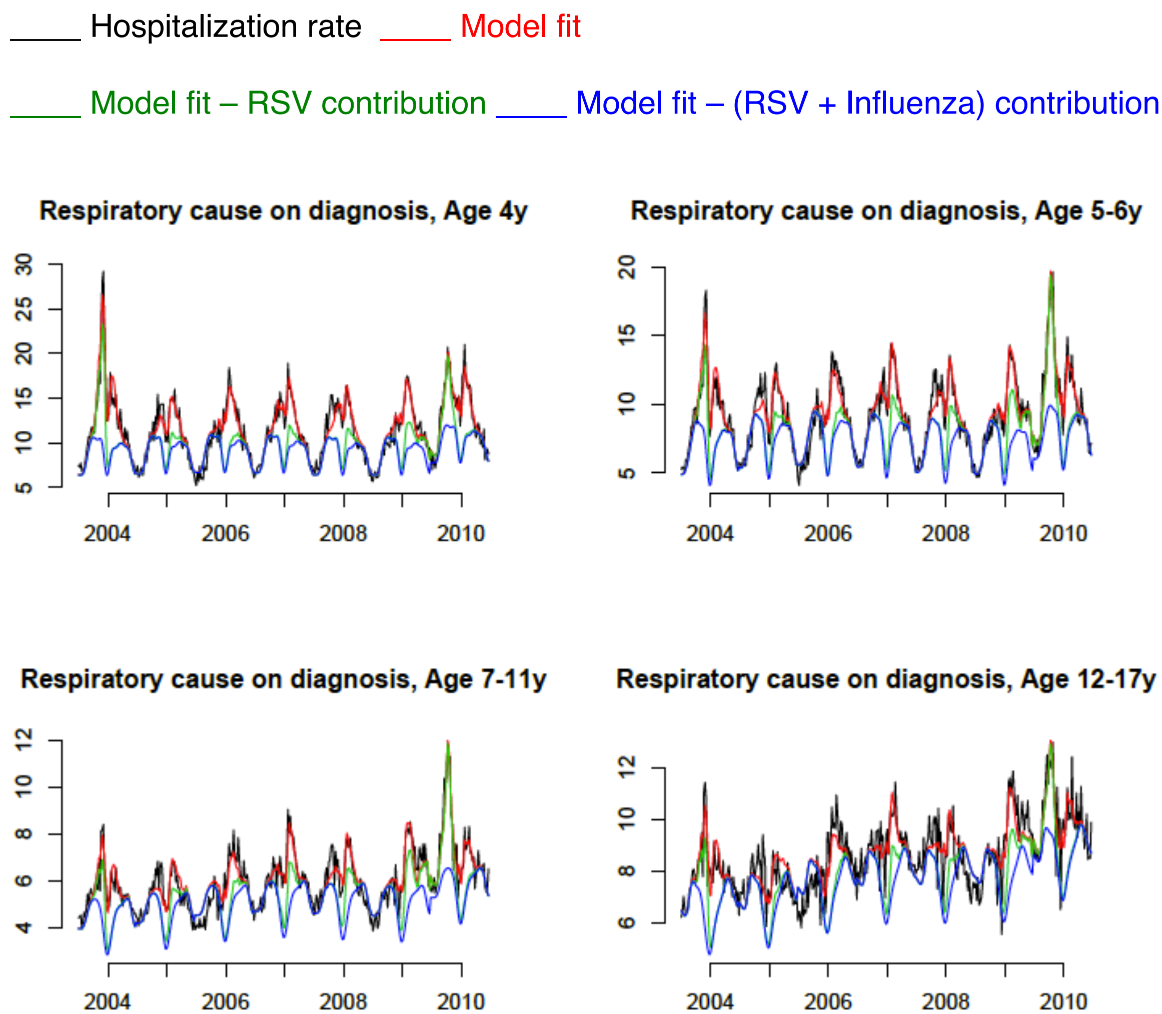
Figure 2: Hospitalization rates (per 100,000) with a respiratory cause in either the principal or secondary diagnosis (excluding the principal diagnosis of asthma) in US children (aged 0-17y), 2003-04 through the 2009-10 seasons (black), model fits (red), and contributions of RSV (red curve minus green curve) and influenza (green curve minus blue curve).

____ Hospitalization rate ____ Model fit

____ Model fit – RSV contribution ____ Model fit – (RSV + Influenza) contribution



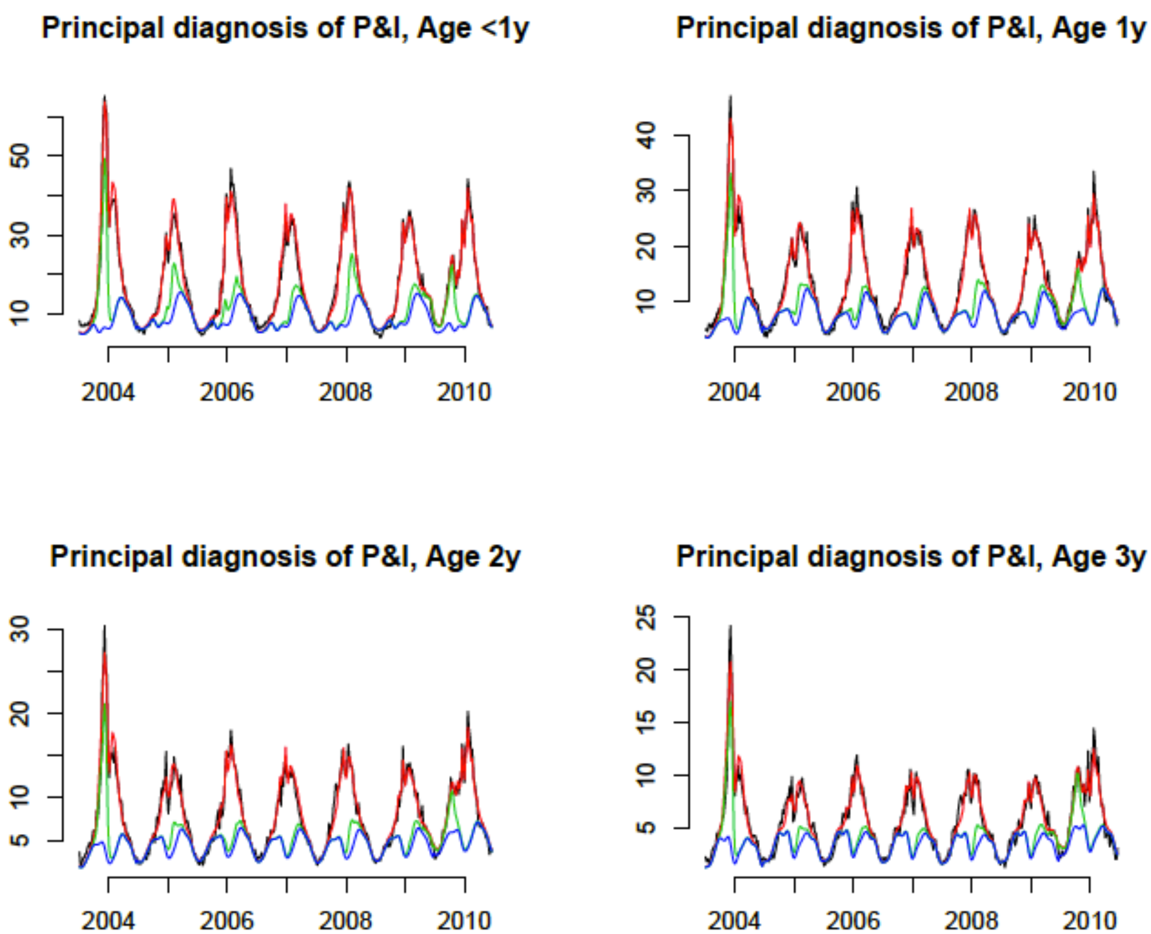


Hospitalization rate
Model fit
Model fit – RSV contribution
Model fit – (RSV + Influenza) contribution
Respiratory cause on diagnosis, Age 4y
Respiratory cause on diagnosis, Age 5-6y
Respiratory cause on diagnosis, Age 7-11y
Respiratory cause on diagnosis, Age 12-17y
2004
2006
2008
2010

Figure 3: Hospitalization rates (per 100,000) with pneumonia and influenza (P&I) in the principal diagnosis in US children aged 0-17y, 2003-04 through the 2009-10 seasons (black), model fits (red), and contributions of RSV (red curve minus green curve) and influenza (green curve minus blue curve).

____ Hospitalization rate ____ Model fit

____ Model fit – RSV contribution ____ Model fit – (RSV + Influenza) contribution



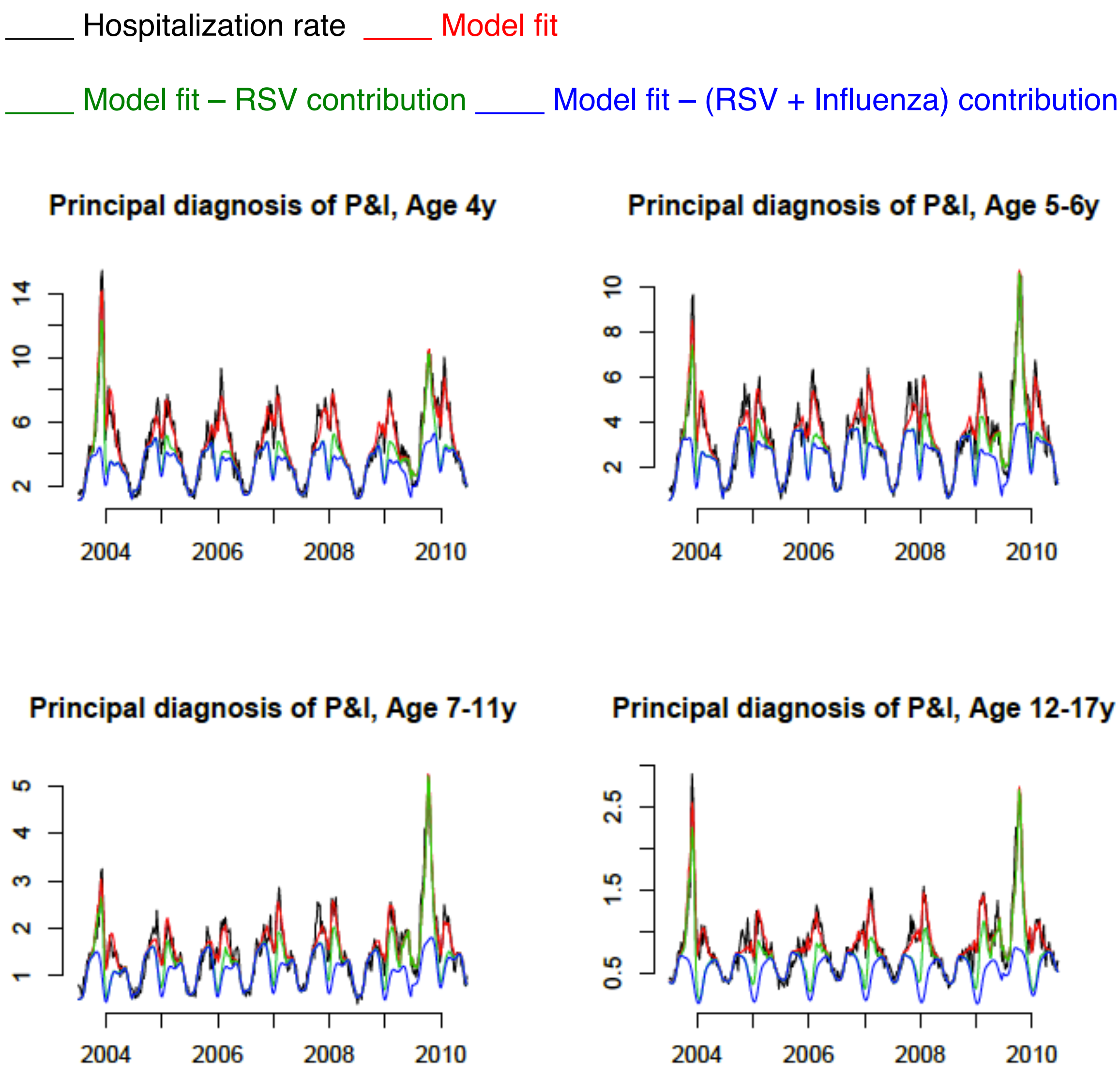
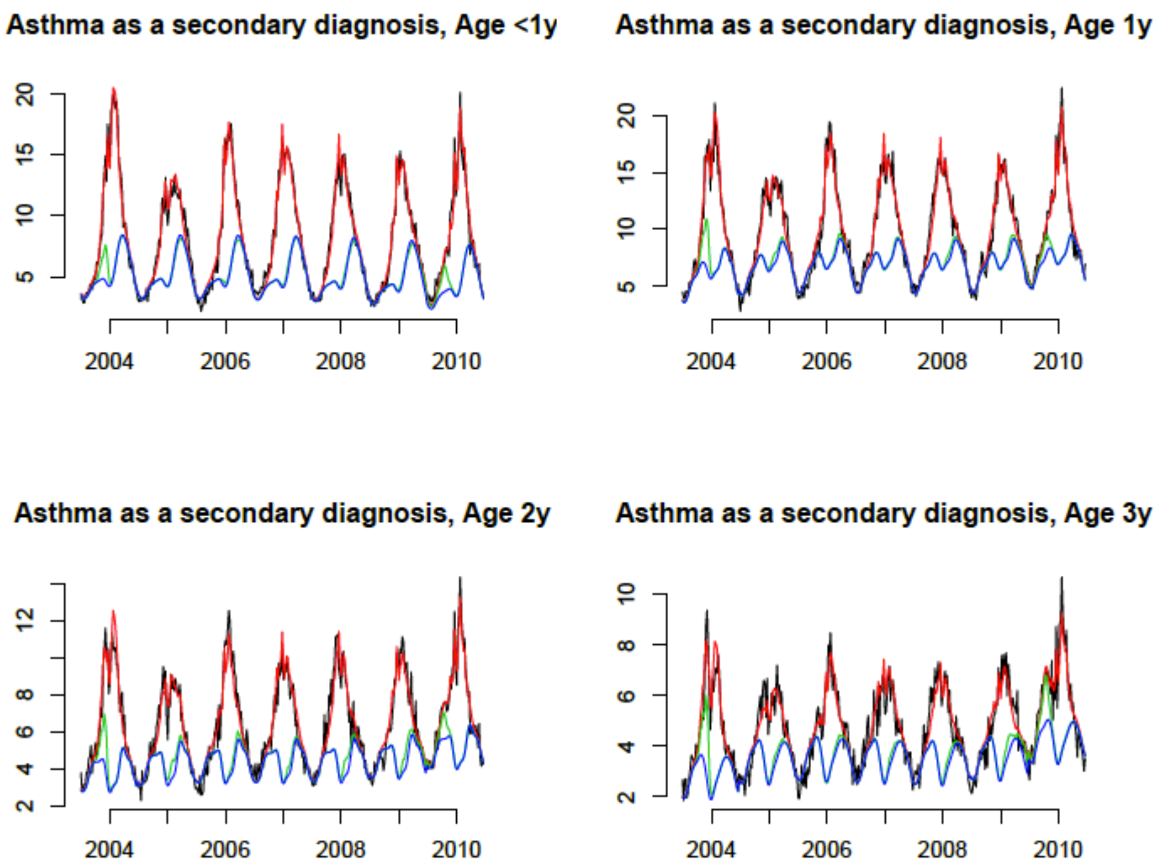

Hospitalization rate
Model fit
Model fit – RSV contribution
Model fit – (RSV + Influenza) contribution
Principal diagnosis of P&I, Age 4y
2
6
10
14
2004
2006
2008
2010
Principal diagnosis of P&I, Age 5-6y
2
4
6
8
10
2004
2006
2008
2010
Principal diagnosis of P&I, Age 7-11y
1
2
3
4
5
2004
2006
2008
2010
Principal diagnosis of P&I, Age 12-17y
0.5
1.5
2.5
2004
2006
2008
2010

Figure 4: Hospitalization rates (per 100,000) with asthma as a secondary diagnosis in US children aged 0-17y, 2003-04 through the 2009-10 seasons (black), model fits (red), and contributions of RSV (red curve minus green curve) and influenza (green curve minus blue curve).

____ Hospitalization rate ____ Model fit

____ Model fit – RSV contribution ____ Model fit – (RSV + Influenza) contribution



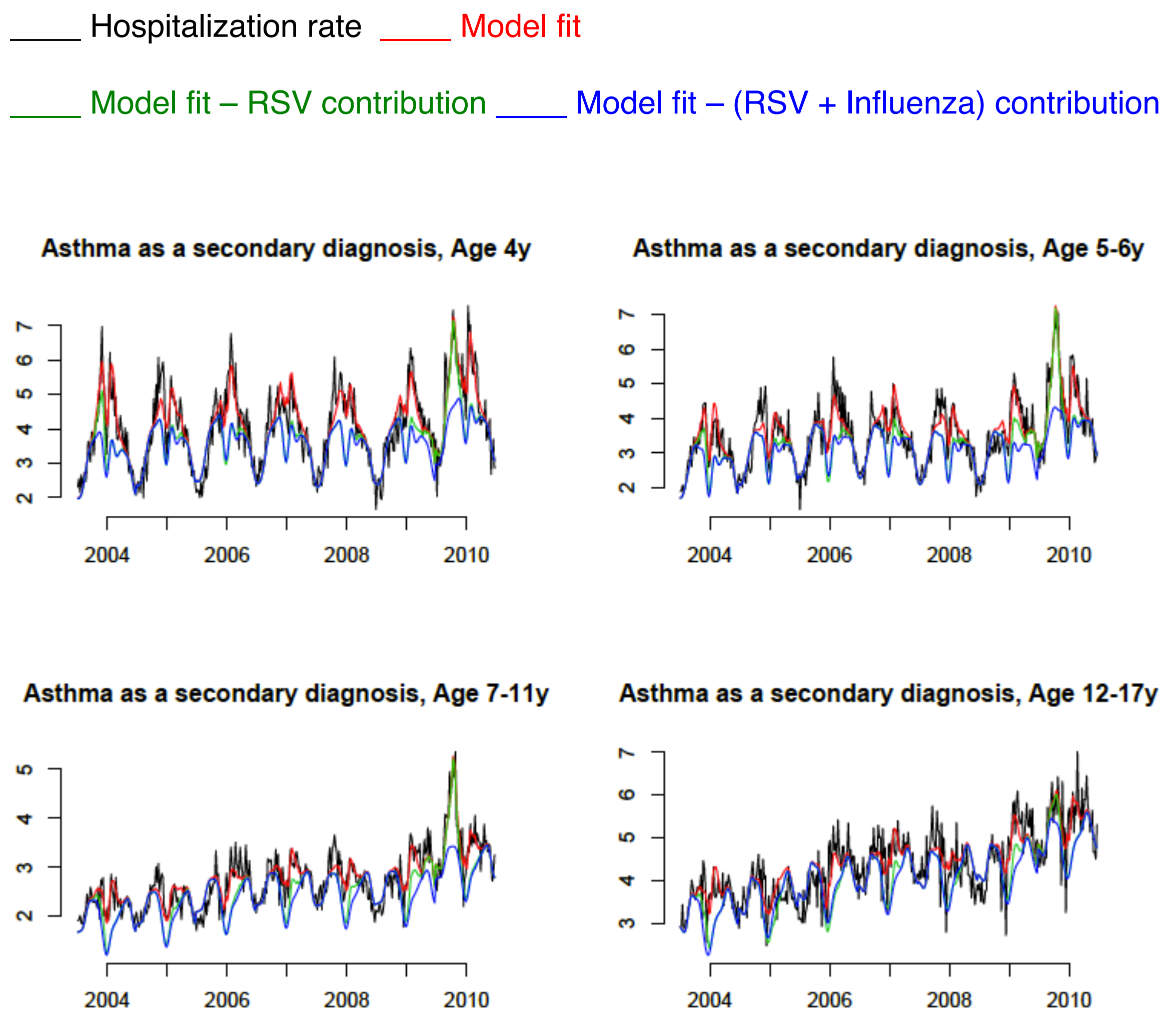
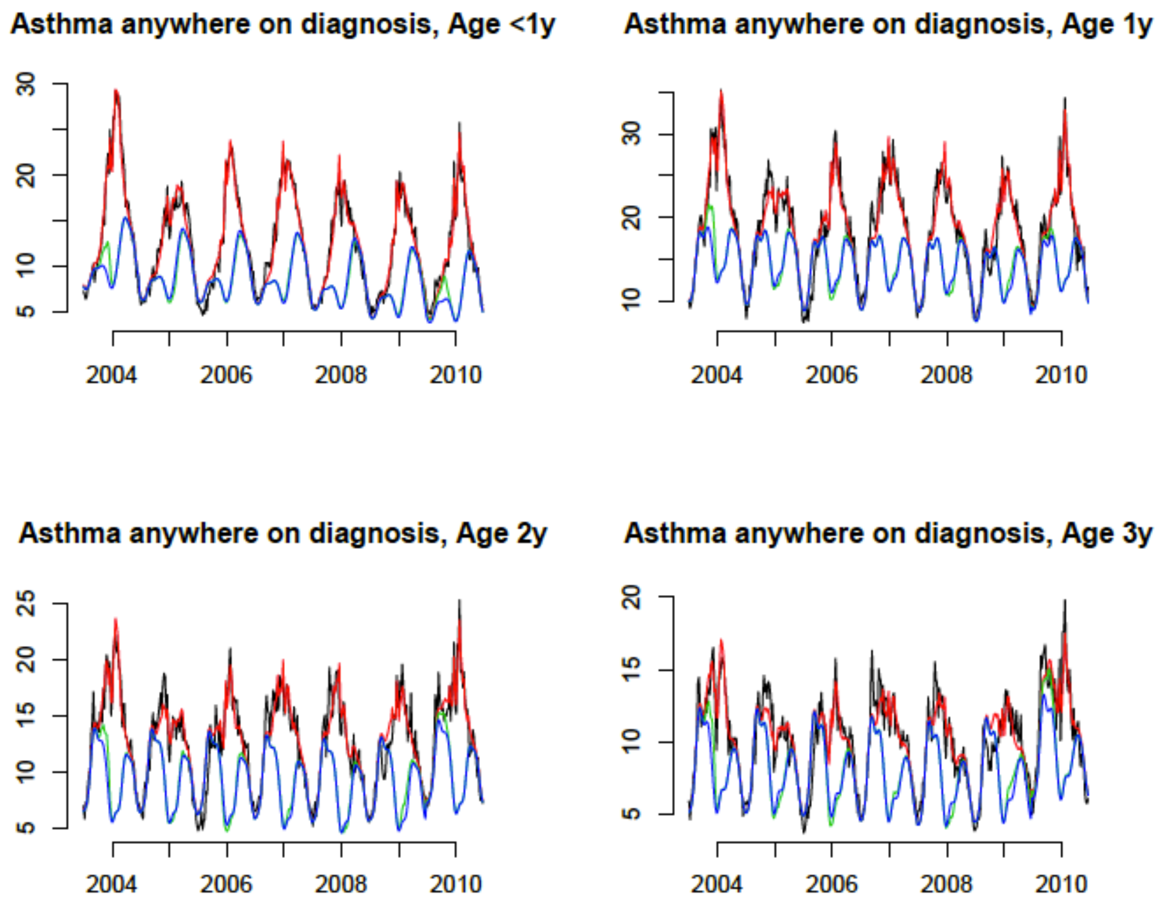
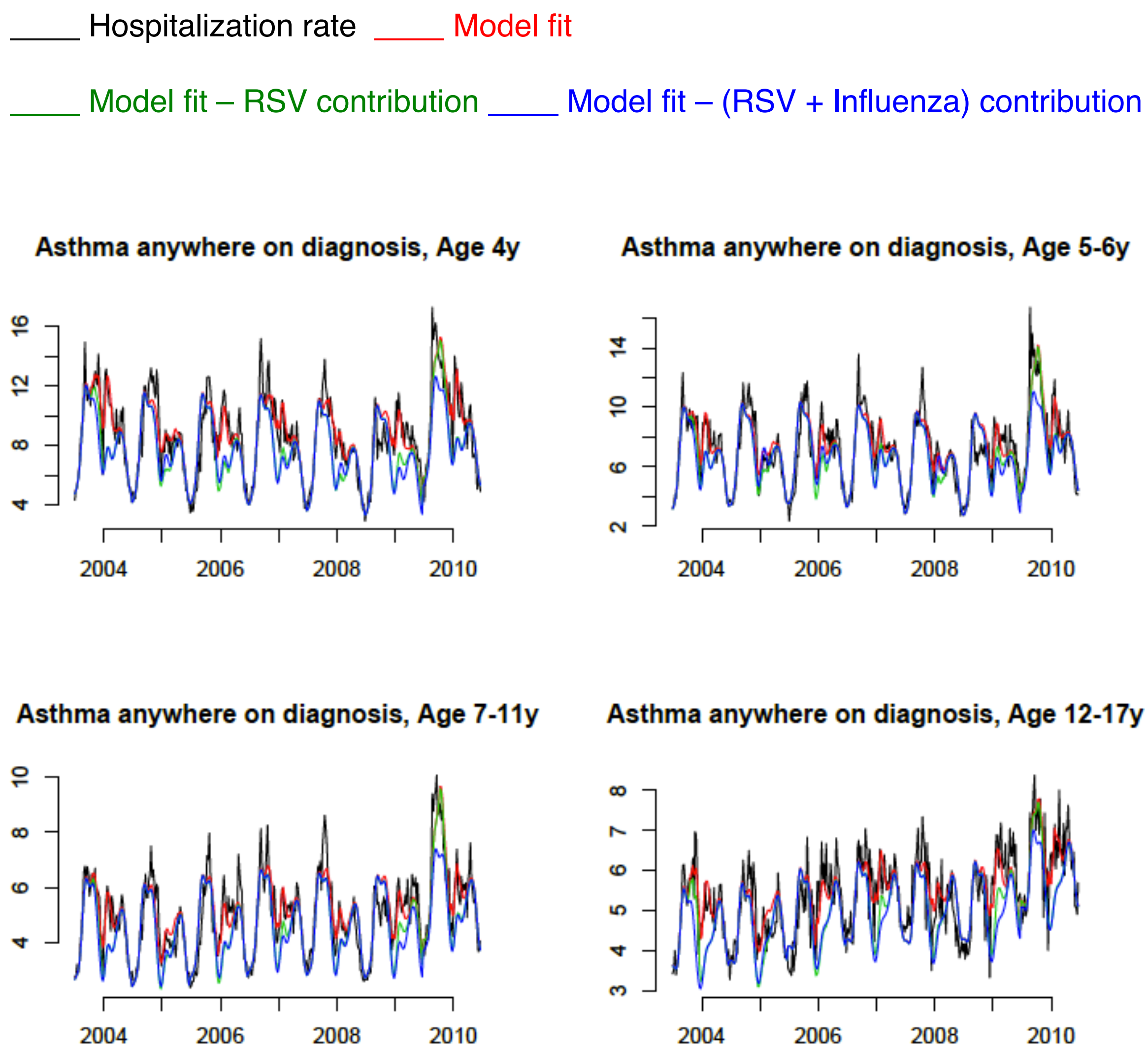

Hospitalization rate
Model fit
Model fit – RSV contribution
Model fit – (RSV + Influenza) contribution
Asthma as a secondary diagnosis, Age 4y
Asthma as a secondary diagnosis, Age 5-6y
Asthma as a secondary diagnosis, Age 7-11y
Asthma as a secondary diagnosis, Age 12-17y
2004
2006
2008
2010

Figure 5: Hospitalization rates (per 100,000) with asthma in either the principal or secondary diagnosis in US children aged 0-17y, 2003-04 through the 2009-10 seasons (black), model fits (red), and contributions of RSV (red curve minus green curve) and influenza (green curve minus blue curve).

____ Hospitalization rate ____ Model fit

____ Model fit – RSV contribution ____ Model fit – (RSV + Influenza) contribution




Hospitalization rate
Model fit
Model fit – RSV contribution
Model fit – (RSV + Influenza) contribution
Asthma anywhere on diagnosis, Age 4y
Asthma anywhere on diagnosis, Age 5-6y
Asthma anywhere on diagnosis, Age 7-11y
Asthma anywhere on diagnosis, Age 12-17y
2004
2006
2008
2010