**Classification:** Biological Sciences: Medical Sciences and Physical Sciences: Applied Mathematics

**Title:** Respiratory virus transmission dynamics determines timing of asthma exacerbation peaks: evidence from a population-level model

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**Abstract**

Asthma exacerbations exhibit a consistent annual pattern, closely mirroring the school calendar. Although respiratory viruses – the "common cold" viruses - are implicated as a principal cause, there is little evidence to link viral prevalence to seasonal differences in risk.

We jointly fit a common cold transmission model and a model of biological and environmental exacerbation triggers to estimate effects on hospitalization risk. Asthma hospitalization rate, influenza prevalence and air quality measures are available, but common cold circulation is not, therefore we generate estimates of viral prevalence using a transmission model. Our deterministic multi-virus transmission model includes transmission rates that vary when school is closed. We jointly fit the two models to seven years of daily asthma hospitalizations in adults and children (66000 events) in eight metropolitan areas.

For children, we find that daily viral prevalence is the strongest predictor of asthma hospitalizations, with transmission reduced by 45% (95% credible interval 41–49%) during school closures. We detect a transient period of non-specific immunity between infections lasting 19 (17–21) days. For adults, hospitalizations are more variable, with influenza driving wintertime peaks. Neither particulate matter nor ozone was an important predictor, perhaps due to the large geographic area of the populations.

The school calendar clearly and predictably drives seasonal variation in common cold prevalence, which results in the "back-to-school" asthma exacerbation pattern seen in children, and indirectly contributes to exacerbation risk in adults. This study provides a framework for anticipating the seasonal dynamics of common colds and the associated risks for asthmatics.

**Significance Statement**

Asthma exacerbations are triggered by respiratory infections of common colds. Prior studies investigating this phenomenon must swab patients to detect virus. Our study uses dynamic transmission modelling to generate common cold virus prevalence for

an entire population, thus shifting the scale from the individual to the population. We develop a transmission model for common colds with different contact patterns for adults and children, which are also modified by school vacations. We jointly fit the transmission model, while including observed variation in air quality, to daily hospitalization rates in eight large cities in Texas. This large-scale population-level study therefore allows us to determine that common cold is key to asthma exacerbations, and contributes strong new evidence to spur appropriate preventive measures.

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## Introduction

Asthma is a chronic airway condition with increasing prevalence in many countries (1,2). Exacerbations, the worsening of asthma symptoms, are a growing public health concern, resulting in millions of missed work and school days, and $50 billion in direct healthcare costs in the USA each year (3–5). Prior studies have examined environmental correlates of asthma excerbations, including air quality measures (6–8), while others have considered the role of respiratory virus infections in triggering asthma exacerbation (9–13). However, none have simultaneously considered both infectious and non-infectious factors that potentially influence the large-scale spatiotemporal dynamics of asthma exacerbations.

Asthma-related hospitalizations exhibit an extraordinarily consistent seasonal pattern from year to year (14). In children, this pattern strongly reflects the school calendar (15–17). A wave of asthma exacerbations in children ensues shortly after the return to school after summer break, shown in Fig 1 in Texas in mid-August. The return-to-school peak has been termed the "September epidemic of asthma" (14) and has been noted in the UK (18), Canada (17,19) and elsewhere (20). Asthma hospitalizations also appear to rise following the two-week winter holiday (late December through early January) and one-week spring break (late March) (Fig 1).

Respiratory virus infections, including those responsible for the common cold, are known to cause exacerbations in asthmatic children and, to a lesser extent, in adults suffering from respiratory diseases (11,21,22). In particular, rhinovirus has been widely implicated in asthma exacerbations and wheezing-related hospitalizations (13,16,23–29). Although asthma is not infectious, these aggravating viruses are. Consequently, the dynamics of asthma hospitalizations can appear as if children are serving as transmission vectors for exacerbations (19). Data on the prevalence of these common viruses is infrequently available, and is never available for large sample sizes.

Common cold viruses spread rampantly—typically causing two to four relatively mild infections in adults and three to eight infections in children annually (30,31). Although asthmatics tend to experience more severe and prolonged illness upon infection, studies suggest that the frequency of infection is similar for asthmatics and non-asthmatics (21). Yet, little is known about the transmission dynamics of these

viruses or the extent to which they account for the complex annual cycles of asthma exacerbations. Mathematical models of viral transmission are widely used for estimating epidemiological parameters, such as transmission rates, from disease surveillance data (32–34). Such data are rare for common colds, since most infections are sub-clinical, never entering the healthcare system. Here, we exploit asthmatics as a "sentinel" population for the common cold to infer the transmission dynamics of these viruses.

Although viral infections are an important trigger for asthma exacerbations, they are not the only not the only cause of asthma hospitalizations. In particular, poor air quality is thought to be a critical risk factor, and the link between pollution and asthma has been studied extensively (8,35–39). Elevated particulate matter and ozone levels have both been associated with increased asthma exacerbations and hospitalization events.

By fitting a mathematical model of viral transmission jointly with a model of non-infectious drivers to asthma hospitalization data from eight metropolitan populations in Texas, we are able to both estimate epidemiological characteristics of common cold viruses and rigorously assess the relative contributions of proposed infectious and non-infectious drivers of asthma exacerbations. Our analysis provides insight into the dynamics of common cold viruses and a robust framework for predicting times of heightened risk and thus key periods for clinical intervention in the growing population of asthmatic people.

## Results

### Predictors of asthma hospitalizations

We tested models with different combinations of predictive variables and determined which explained the hospitalization data best. The variables tested are shown in Table 1 and the components of the best fitting model are indicated in the right-most column. The best fitting model from our study included common cold prevalence, influenza prevalence, daily low temperature, a baseline hospitalization rate specific to each city, a term modifying the baseline rate on each day of the week, and a long-term temporal trend in hospitalization rates. Fitted values for this model are shown in Fig. 3 for children and adults, and coefficients for each parameter of the best fitting model are given in SI Appendix Table S2. Bayesian model selection procedures excluded ozone

and particulate matter variables as informative predictors of asthma hospitalization rate. A full description of each model compared is given in SI Appendix Section 10.

The coefficient of the day-of-the-week variable has a pronounced pattern in both adults and children (Fig. 4b), where the contribution to the hospitalization rates steadily declines from Monday through Saturday. This pattern has been observed in asthma hospitalizations previously, for example in Canada (40). Baseline hospitalization rates differ across metropolitan areas, as shown by higher or lower addition to the baseline hospitalization rate (Fig. 4d and e). The rate differences are not correlated in children and adults in the same metropolitan areas (Fig. 4c).

## Temporal variation in exacerbation triggers

To investigate if there was a different dominant driver of asthma exacerbations at different times of year, we determined the contribution of each variable to the hospitalization rate on certain days. In each of the panels in Fig 3c-e, the total height of the bars is the fitted hospitalization rate on that day. We found that the key predictors of asthma exacerbations vary in importance through the year. For example, in 2003 in the Dallas-Fort Worth-Arlington metropolitan area, the common cold hardly contributes to late summer asthma activity (Fig. 3c) because prevalence is low in the summer when children are out of school and thus have a lower transmission rate. Common cold prevalence substantially impacts the back-to-school wave of exacerbations (Fig. 3d). During winter break, low temperatures, common cold prevalence and influenza all have moderate effects (Fig. 3e) because the temperature is low, and common cold and influenza prevalence are moderate. The other years of the study and metropolitan areas exhibit similar temporal patterns, and further examination of the contribution of each variable to the fitted rate is given in SI Appendix Section 18.

## Common cold transmission rates

The common cold SIRS transmission model has six estimated parameters (Table 2). The posterior mean and 95% credible intervals suggest that children infect each other much more than do other combinations of age groups. Specifically, the estimated adult-to-child and adult-to-adult transmission rates are 2.5% (1.4–4.2%) and 42% (35–48%) of the child-to-child rate, respectively. We estimate that when schools close

for weekends and holidays, transmission rates between children decrease by 45% (41–49%). Furthermore, we estimate that the common cold has an average infectious period of 3.0 days (2.6–3.5 days), and following recovery, cross-protective immunity lasts an average of 19 days (18–21 days).

As further validation, we used the model to estimate the average number of common cold infections in each adult and child per year. Even though the model was fitted to different data (daily asthma hospitalizations), the estimated number of colds per year were remarkably consistent with those reported in the literature and widely endorsed by public health agencies (Fig 4a) (30,31). In addition, when school start dates in Texas were delayed by 10 days in 2007 due to legislative change, the September asthma peak shifted accordingly. Our model provides a mechanistic link between the school calendar and asthma exacerbations, and readily captures this epidemiological transition (Fig. S16).

## Robustness of common cold model

To further assess whether common cold prevalence is a critical predictor of asthma exacerbations, we performed likelihood ratio comparisons between the full model and two linear models that lacked the SIRS-driven common cold variable. One included only the other variables from the best-fit model to test whether the common cold variable was necessary; the other also included a school closure indicator variable, to test whether the school effect is linked to attendance at school rather than viral transmission at school. The likelihood ratio test indicated that the alternative models were significantly inferior ($p<.01$, $p<.01$), further supporting the fundamental role of common colds in shaping large-scale spatiotemporal dynamics of asthma exacerbations (see SI Appendix Sections 11-12 for further details).

## Discussion

Asthma hospitalization rates in children clearly reflect the school calendar. We hypothesized that this is mediated by viral transmission within schools rather than by alternative triggers associated with the school environment. Through explicit modeling of respiratory virus circulation, and comparison of model components, we found that the prevalence of respiratory infections explained asthma hospitalization

patterns much better than the academic calendar alone. Our study combines both infectious and non-infectious drivers of asthma exacerbation; this two-tiered modeling strategy—coupling an asthma regression model with a respiratory virus transmission model—allowed us to simultaneously infer predictors of asthma hospitalization rates and epidemiological characteristics of the viruses that trigger asthma exacerbations.

We found that common cold infection is the primary determinant of asthma-related hospitalization patterns in children across eight major Texas metropolitan areas. Further, the transmission of common colds is integrally linked to the school calendar, thus explaining the relationship between school vacation periods and asthma exacerbation. For adults, hospitalization rates have a different temporal signature, dominated by a combination of common cold and influenza prevalence. In both age groups, low temperatures are a significant risk factor, and asthma hospitalization rates vary by day of the week.

It is critical to use a transmission model to generate the common cold prevalence input to our model because actual viral prevalence data are not available for these study populations. Indeed common cold prevalence is not known for any population on this scale, or for long time periods, as in the seven consecutive years of our study. Since common cold viruses cause mild, self-limited infections in healthy populations, there is little motivation for large studies to determine prevalence of these infections through time. By using very large-scale data, we are able to infer prevalence, which demonstrates the power of transmission models to answer diverse public health questions.

Our viral transmission model captures the non-linear interplay of waning immunity, cross-protection between different viruses, and contact patterns that both vary across age groups and change when schools are closed. The “September epidemics” noted in other asthma studies can be attributed to a resurgence of viral transmission at the beginning of the school year after an accumulation of susceptible children during summer vacation when transmission is lower. Later peaks occur following population-level waning of immunity during school vacation days, such as following Thanksgiving break.

Understanding the impact of school closures on the transmission of respiratory viral infections is valuable not only for asthma control, but also for designing school

232 closure strategies in planning for seasonal and pandemic influenza. We estimated
233 transmission rates during school closures that are comparable to published estimates
234 based on influenza surveillance data (41), sociological surveys (42), and measles
235 outbreak dynamics (43). Unlike previous estimates, our analysis reflects contact
236 patterns in "normal" vacation periods, rather than during severe outbreaks for which
237 there may be additional changes in behavior that affect transmission rate.

238 Reducing severe asthma exacerbations remains a formidable challenge. Our analysis
239 demonstrates the critical influence of viral infections, but does not explain the
240 substantial variation in baseline asthma hospitalization rate observed between cities.
241 We did not detect a significant effect of air pollutants, perhaps because measurements
242 at the level of metropolitan areas are too coarse-grained. Our study is also limited to
243 eight major cities in Texas, and therefore may not directly pertain to regions with
244 different temperature and air quality values. We expect, however, that the common
245 cold model may be generally applicable, with transmission reduced during school
246 closures. In metropolitan areas with a high degree of heterogeneity in school calendar
247 dates, common cold waves may be less pronounced. Furthermore, our model does not
248 consider co-infection by multiple viruses, which could have a different probability of
249 triggering asthma exacerbations than single infections. Non-specific immunity may
250 influence the frequency of co-infections by some viruses (44,45), potentially leading
251 to complex interactions between strains. Our model distils the multi-virus
252 transmission dynamics of the common cold into a parsimonious yet biologically
253 plausible system, and could potentially be extended to consider additional complexity.

254 In Texas, asthmatic children tend to be at higher risk for exacerbations at the start of
255 the school year and following other school breaks. While reducing the burden of
256 common cold viruses may not be feasible, asthma interventions that decrease the risk
257 of exacerbation or hospitalization, including increased monitoring, preventive, and
258 therapeutic care can be targeted at these high-risk periods. In general, future risk
259 assessments and interventions for asthma, particularly in children, should explicitly
260 consider both the school calendar and the seasonal dynamic of infectious triggers,
261 either through spatiotemporal modelling or, when possible, viral surveillance data.
262

263 **Methods**

We used asthma hospitalization data to jointly estimate the parameters of a population-level viral transmission model and coefficients of a multi-factor linear model for asthma exacerbations, in a Bayesian framework. We compared multiple models — including different combinations of predictors — using the Deviance Information Criterion (DIC) (46).

## Hospitalization data

To calculate the daily hospitalization rate per million, we use daily hospitalization records which have principal admission code indicating asthma (ICD-9 code 493.XX) in each of the eight largest metropolitan areas of Texas from January 1, 2003 to December 30, 2009. There were 66,000 hospitalizations, stratified into school-aged children (5–18 years, 27,000 hospitalizations) and non-elderly adults (19–55 years, 39,000 hospitalizations). We excluded age groups over 55 years, due to overlapping effects and diagnoses of chronic obstructive pulmonary disease. The eight focal populations totaled 14.8 million people in 2009, which is approximately 59% of the state population. Further details of the data are provided in SI Appendix Sections 1-5.

## Common Cold Transmission Model

We developed a dynamic Susceptible-Infectious-Recovered-Susceptible (SIRS) transmission model for common cold viruses (Fig 2). The population (N) is stratified into adults and children who may be Susceptible (S), Infected (I) or Recovered (R). Recovered individuals are protected against infection. The governing equations are:

$$\frac{dS_i}{dt} = -\beta_{i,t} S_i + \omega R_i, \qquad \frac{dI_i}{dt} = \beta_{i.t} S_i - \gamma I_i, \qquad \frac{dR_i}{dt} = \gamma I_i - \omega R_i$$

where $i$ represents age group: adults (A) or children (C), $\gamma$ is the recovery rate, and $\omega$ is the rate at which cross protective immunity wanes. The age-specific transmission rates ($\beta_{i,t}$) are given by:

$$\beta_{C,t} = \beta_0 \left( \sigma_t \left( {}^{I_C}/_{N_C} \right) + \alpha_{AC} \left( {}^{I_A}/_{N_A} \right) \right)$$

$$\beta_A = \beta_0 \left( \alpha_{AC} \left( {}^{I_c}/_{N_c} \right) + \alpha_{AA} \left( {}^{I_A}/_{N_A} \right) \right)$$

where $\beta_0$ is the baseline child-to-child transmission rate, the $\alpha_{ij}$ terms are scaling factors for transmission rates between age groups, where $\alpha_{AC}$ and $\alpha_{CA}$ are assumed to be equal. $\sigma_t$ is time dependent and represents the decrease in child-to-child

transmission rates during school closures on weekends and school holidays. $\sigma_t$ is 1 when school is in session, and is estimated during weekends and vacation periods. Therefore the transmission rate of children, $\beta_{C,t}$ is time dependent. We assume that transmission rates involving adults are not affected by school closures.

Multiple co-circulating viruses cause common colds, and recovery from one virus does not provide lasting immunity against other viruses. Thus, the Recovered class models short-term broad-spectrum immunity against all common cold viruses. Though not fully understood, broad cross-protection following infection has been noted for other respiratory viruses (47,48) and may be mediated by innate immune mechanisms (49,50). Individuals return to the Susceptible class after a period of protection, which has duration $\omega^{-1}$.

Holiday periods were collated for each metropolitan area for each year of the study from the largest (or second largest) school district in the metropolitan area (further details in SI Appendix Section 4). Temporal changes in population size and age composition were calibrated to the 2000 and 2010 Census in the two age groups. We assume that there is a maximum delay of four days between initial infection and hospitalization for asthma exacerbation (39,51–53). We solve the ordinary differential equation model using a $4^{th}$ order Runge-Kutta method with $5^{th}$ order error term.

We use this age-stratified SIRS model to generate daily common cold prevalence in adults and children, for each metropolitan area (Fig 2B). The parameters that govern transitions between compartments are estimated. The time series of prevalence values serve as inputs into our asthma hospitalization model, described next.

## Hospitalization model

We developed a linear regression model to fit the daily hospitalization rate per million adults and children in each metropolitan area using potential predictors of variation in asthma hospitalization rate (see SI Appendix). The variables included in model selection were common cold prevalence, influenza prevalence, particulate matter (2.5μm), ozone, low temperature, city-specific difference in hospitalization rate, day-of-the-week variation, and secular trend in hospitalization rate (Table 1). For common

cold, we used the SIRS model to generate daily prevalence; for influenza, we estimated daily prevalence directly from hospitalization records and did not explicitly model transmission dynamics; for all other variables, daily measurements were obtained from publicly available sources (see SI Appendix Sections 2-3). Model components were compared extensively using the DIC, where $DIC = \bar{D} + p_v$, and $p_v = 0.5var(\bar{D})$ (46,54). Lower values indicate a better fit of model to data, and a difference of five units is the customary threshold for distinguishing model variants.

We jointly fitted the transmission and hospitalization models using Markov Chain Monte Carlo (MCMC). To sample the transmission model parameters more efficiently, we explicitly marginalized over the other parameters at each step via a Laplace approximation. Further details on fitting methods and model comparison are given in the SI Appendix Sections 6-10.

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## Figure Legends

**Fig 1. Daily number of asthma hospitalizations.** Total hospitalizations in the eight largest metropolitan areas in Texas from August 2004 through August 2005, where markers indicate the 1st of the month. Daily count values (light grey) and a spline-smoothed value (dark grey) in (A) children aged 5 to 18 and (B) adults aged 19 to 55. In 2004, most Texas schools started in mid-August, took a two-week winter break in late December to early January, and a one week spring break in late March.

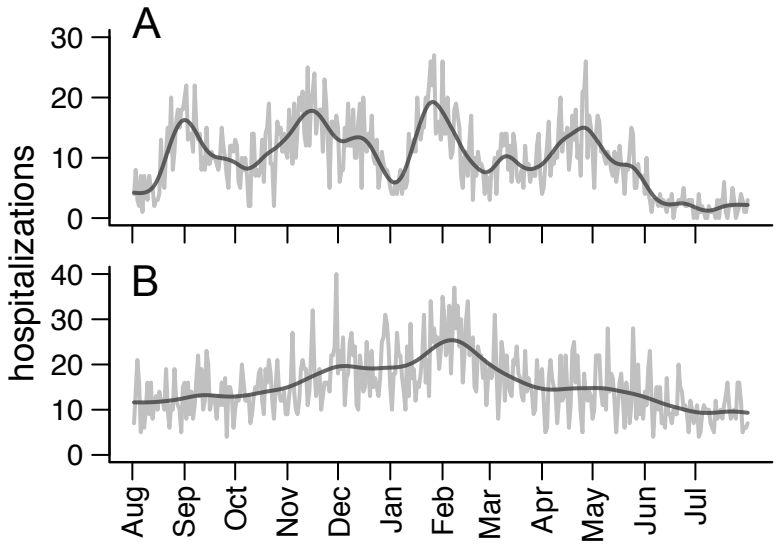
**Fig 2. The Susceptible-Infectious-Recovered-Susceptible (SIRS) dynamic transmission model of common cold circulation.** (A) The child and adult populations are each divided into three infection classes: Susceptible, Infectious and Recovered. The recovered class is immune to infection. Transitions between compartments are governed by the rate parameters indicated. (B) Example model output for children (red) and adults (blue). Weekends and vacations for the Dallas-Fort Worth-Arlington metropolitan area in 2003-4 are shown as grey areas. On those days, the transmission rate of children is decreased by $\sigma$. The prevalence of common cold infections in children more directly reflects the school calendar (i.e. weekends and holidays). Variation in adults is driven by changes in prevalence in children in the model. The estimated prevalences are incorporated into an asthma hospitalization risk model to assess the relative impact of viral transmission on asthma exacerbation rates.

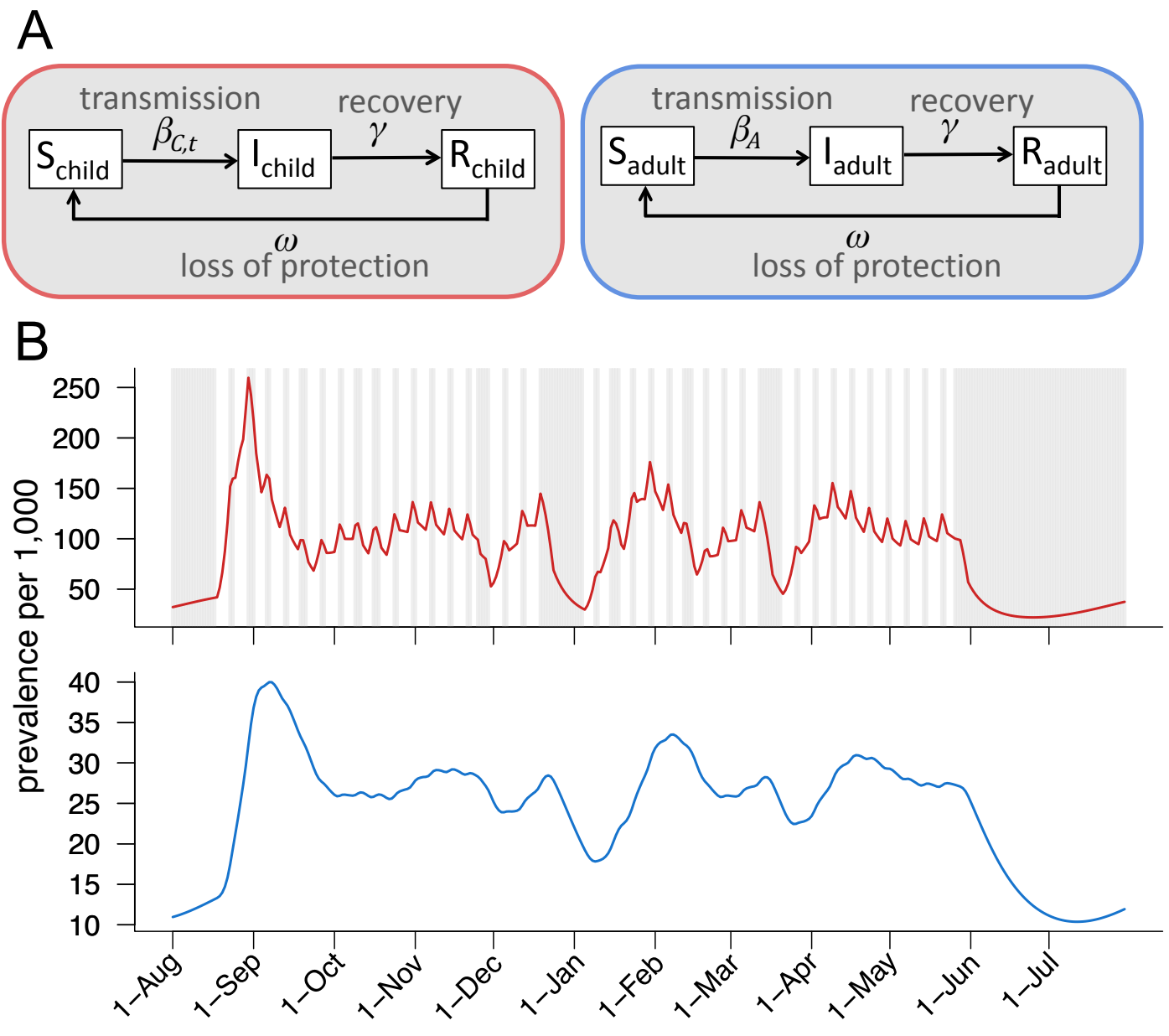
**Fig 3. Fit of the best model in children and adults.** Seven-day rolling mean of observed hospitalizations in all cities (black) and simulations from the best fitting model (red). We sampled twenty parameter sets from the joint posterior distribution, and generated five non-homogeneous Poisson simulations for each set. Hospitalizations shown for (A) children aged 5 to 18 and (B) adults aged 19 to 55. Contribution of each factor to the predicted hospitalization rate in children for (C) Monday, August 11, 2003, (D) Monday, September 1, 2003, and, (E) Monday, December 29, 2003 in the Dallas-Fort Worth-Arlington area (Metropolitan code 19100). The heights of the bars in each figure sum to the fitted total asthma hospitalization rate on those days.

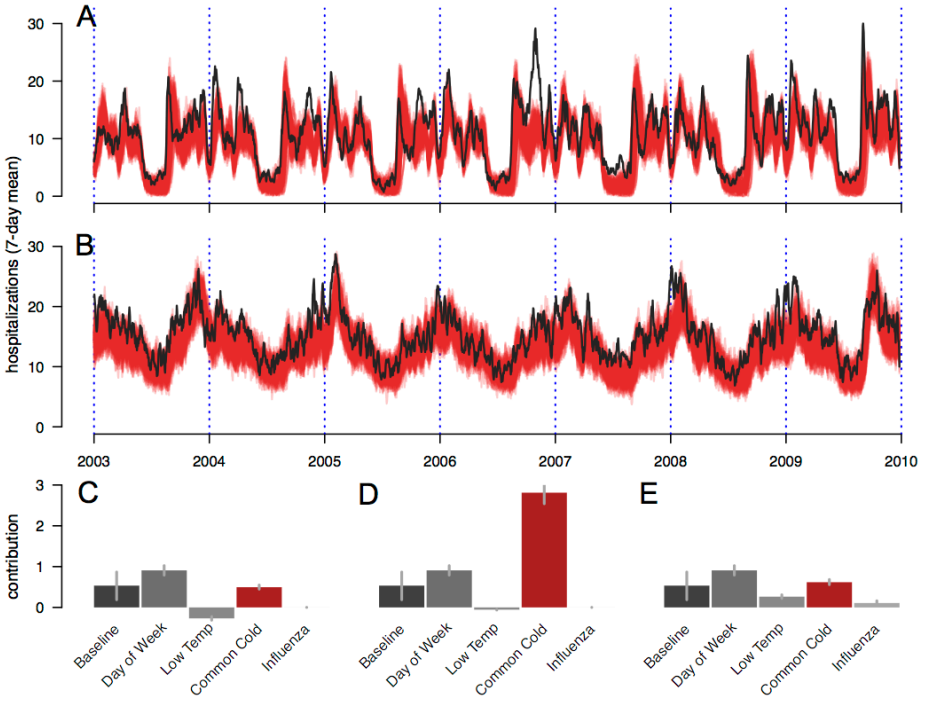
**Fig 4. Results from the best fitting model.** (A) Average number of colds in children (red points) and adults (blue points) for each of the eight metropolitan areas, predicted by the model for each year of the study. The shaded windows indicate public health estimate of 3–8 colds per year for children and 2–4 per year for adults (30). (B) Estimated day of week coefficients in the hospitalization model. Variation in these values captures, in part, variation in healthcare seeking behavior on different days of the week. (C) Correlation of baseline hospitalization rate in adults and children for each of the eight metropolitan areas in the study. (D and E) Baseline hospitalization rate in each metropolitan area for children (D) and adults (E). Values represent the city-specific addition to baseline asthma hospitalization rate. Positive values of this coefficient indicate higher baseline rate.

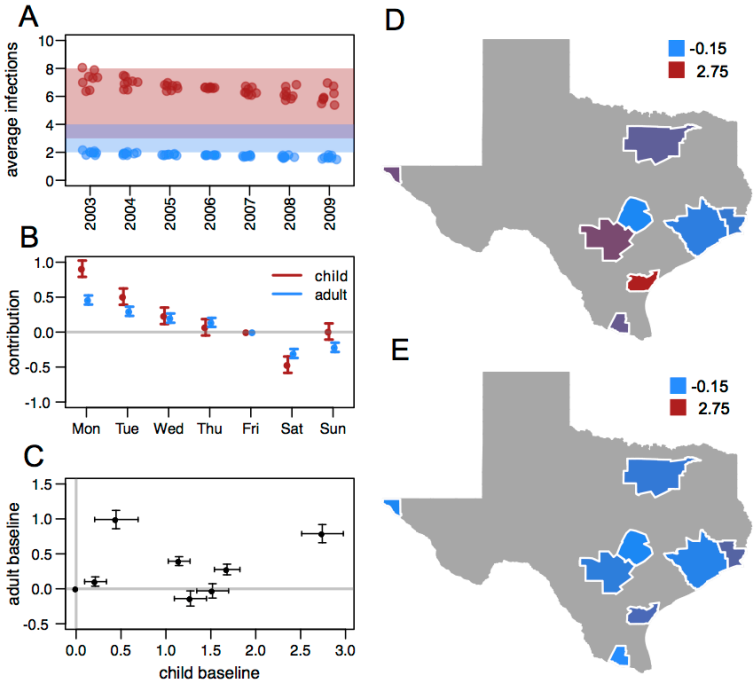
| Data | Source | Description | Included in best model |
|---|---|---|---|
| Common Cold | SIRS transmission model | 4-day aggregated common cold prevalence | * |
| Influenza prevalence | Hospitalization records | Daily state level hospitalizations per million due to influenza, in adults and children. Spline-smoothed | * |
| Day of week | Calendar | | * |
| Time trend | Daily index value | | * |
| Local Intercept | Metropolitan boundary | Geographic variation in baseline hospitalization rate | * |
| Low temperature | CDC Wonder | Daily minimum temperature in counties in the metropolitan area. Celsius. | * |
| Ozone | AIRS | Daily ozone. Air Quality Index value. | |
| PM 2.5 | CDC Wonder | Maximum daily PM 2.5 for counties in the metropolitan area. $\mu g/m^3$ | |

| Parameter | Symbol | Mean | 95% CI lower | 95% CI upper |
|---|---|---|---|---|
| Transmissibility | $\beta_0$ | 0.74 | 0.68 | 0.79 |
| Adult-Child Scaling | $\alpha_{AC}$ | 2.54% | 1.39% | 4.24% |
| Adult-Adult Scaling | $\alpha_{AA}$ | 41.6% | 34.6% | 48.3% |
| Vacation effect | $\sigma_t$ | 45.1% | 41.0% | 49.0% |
| Duration of cross-immunity | $\omega^{-1}$ | 19.3 days | 17.7 days | 21.1 days |
| Duration of infection | $\gamma^{-1}$ | 3.01 days | 2.64 days | 3.45 days |


A
B
hospitalizations
0
10
20
30
40
Aug
Sep
Oct
Nov
Dec
Jan
Feb
Mar
Apr
May
Jun
Jul


A
transmission
recovery
$S_{child}$
$\beta_{C,t}$
$I_{child}$
$\gamma$
$R_{child}$
$\omega$
loss of protection
transmission
recovery
$S_{adult}$
$\beta_A$
$I_{adult}$
$\gamma$
$R_{adult}$
$\omega$
loss of protection
B
prevalence per 1,000
250
200
150
100
50
40
35
30
25
20
15
10
1–Aug
1–Sep
1–Oct
1–Nov
1–Dec
1–Jan
1–Feb
1–Mar
1–Apr
1–May
1–Jun
1–Jul


A
B
C
D
E
hospitalizations (7-day mean)
contribution
0
10
20
30
0
1
2
3
2003
2004
2005
2006
2007
2008
2009
2010
Baseline
Day of Week
Low Temp
Common Cold
Influenza


A
average infections
10
8
6
4
2
0
2003
2004
2005
2006
2007
2008
2009
B
contribution
1.0
0.5
0.0
-0.5
-1.0
child
adult
Mon
Tue
Wed
Thu
Fri
Sat
Sun
C
adult baseline
1.5
1.0
0.5
0.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
child baseline
D
-0.15
2.75
E
-0.15
2.75