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

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

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30 exacerbations

31 **Abstract**

32

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

37 We jointly fit a common cold transmission model and a model of biological and
38 environmental exacerbation triggers to estimate effects on hospitalization risk.

39 Asthma hospitalization rate, influenza prevalence and air quality measures are
40 available, but common cold circulation is not, therefore we generate estimates of viral
41 prevalence using a transmission model. Our deterministic multi-virus transmission
42 model includes transmission rates that vary when school is closed. We jointly fit the
43 two models to seven years of daily asthma hospitalizations in adults and children
44 (66000 events) in eight metropolitan areas.

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

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

57

58 **Significance Statement**

59

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

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

71

72 \body

73 **Introduction**

74 Asthma is a chronic airway condition with increasing prevalence in many countries
75 (1,2). Exacerbations, the worsening of asthma symptoms, are a growing public health
76 concern, resulting in millions of missed work and school days, and \$50 billion in
77 direct healthcare costs in the USA each year (3–5). Prior studies have examined
78 environmental correlates of asthma exacerbations, including air quality measures (6–
79 8), while others have considered the role of respiratory virus infections in triggering
80 asthma exacerbation (9–13). However, none have simultaneously considered both
81 infectious and non-infectious factors that potentially influence the large-scale
82 spatiotemporal dynamics of asthma exacerbations.

83 Asthma-related hospitalizations exhibit an extraordinarily consistent seasonal pattern
84 from year to year (14). In children, this pattern strongly reflects the school calendar
85 (15–17). A wave of asthma exacerbations in children ensues shortly after the return to
86 school after summer break, shown in Fig 1 in Texas in mid-August. The return-to-
87 school peak has been termed the “September epidemic of asthma” (14) and has been
88 noted in the UK (18), Canada (17,19) and elsewhere (20). Asthma hospitalizations
89 also appear to rise following the two-week winter holiday (late December through
90 early January) and one-week spring break (late March) (Fig 1).

91 Respiratory virus infections, including those responsible for the common cold, are
92 known to cause exacerbations in asthmatic children and, to a lesser extent, in adults
93 suffering from respiratory diseases (11,21,22). In particular, rhinovirus has been
94 widely implicated in asthma exacerbations and wheezing-related hospitalizations
95 (13,16,23–29). Although asthma is not infectious, these aggravating viruses are.
96 Consequently, the dynamics of asthma hospitalizations can appear as if children are
97 serving as transmission vectors for exacerbations (19). Data on the prevalence of
98 these common viruses is infrequently available, and is never available for large
99 sample sizes.

100 Common cold viruses spread rampantly—typically causing two to four relatively mild
101 infections in adults and three to eight infections in children annually (30,31).

102 Although asthmatics tend to experience more severe and prolonged illness upon
103 infection, studies suggest that the frequency of infection is similar for asthmatics and
104 non-asthmatics (21). Yet, little is known about the transmission dynamics of these

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

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

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

126

127 **Results**

128 **Predictors of asthma hospitalizations**

129 We tested models with different combinations of predictive variables and determined
130 which explained the hospitalization data best. The variables tested are shown in Table
131 1 and the components of the best fitting model are indicated in the right-most column.
132 The best fitting model from our study included common cold prevalence, influenza
133 prevalence, daily low temperature, a baseline hospitalization rate specific to each city,
134 a term modifying the baseline rate on each day of the week, and a long-term temporal
135 trend in hospitalization rates. Fitted values for this model are shown in Fig. 3 for
136 children and adults, and coefficients for each parameter of the best fitting model are
137 given in SI Appendix Table S2. Bayesian model selection procedures excluded ozone

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

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

147 **Temporal variation in exacerbation triggers**

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

163 **Common cold transmission rates**

164 The common cold SIRS transmission model has six estimated parameters (Table 2).
165 The posterior mean and 95% credible intervals suggest that children infect each other
166 much more than do other combinations of age groups. Specifically, the estimated
167 adult-to-child and adult-to-adult transmission rates are 2.5% (1.4–4.2%) and 42%
168 (35–48%) of the child-to-child rate, respectively. We estimate that when schools close

169 for weekends and holidays, transmission rates between children decrease by 45%
170 (41–49%). Furthermore, we estimate that the common cold has an average infectious
171 period of 3.0 days (2.6–3.5 days), and following recovery, cross-protective immunity
172 lasts an average of 19 days (18–21 days).

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

182 **Robustness of common cold model**

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

193

194 **Discussion**

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

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

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

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

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

230 Understanding the impact of school closures on the transmission of respiratory viral
231 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 distills 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**

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

269 **Hospitalization data**

270 To calculate the daily hospitalization rate per million, we use daily hospitalization
 271 records which have principal admission code indicating asthma (ICD-9 code 493.XX)
 272 in each of the eight largest metropolitan areas of Texas from January 1, 2003 to
 273 December 30, 2009. There were 66,000 hospitalizations, stratified into school-aged
 274 children (5–18 years, 27,000 hospitalizations) and non-elderly adults (19–55 years,
 275 39,000 hospitalizations). We excluded age groups over 55 years, due to overlapping
 276 effects and diagnoses of chronic obstructive pulmonary disease. The eight focal
 277 populations totaled 14.8 million people in 2009, which is approximately 59% of the
 278 state population. Further details of the data are provided in SI Appendix Sections 1-5.

279 **Common Cold Transmission Model**

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

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

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

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

$$287 \quad \beta_A = \beta_0 \left(\alpha_{AC} \left(\frac{I_C}{N_C} \right) + \alpha_{AA} \left(\frac{I_A}{N_A} \right) \right)$$

288 where β_0 is the baseline child-to-child transmission rate, the α_{ij} terms are scaling
 289 factors for transmission rates between age groups, where α_{AC} and α_{CA} are assumed to
 290 be equal. σ_t is time dependent and represents the decrease in child-to-child

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

295

296 Multiple co-circulating viruses cause common colds, and recovery from one virus
297 does not provide lasting immunity against other viruses. Thus, the Recovered class
298 models short-term broad-spectrum immunity against all common cold viruses.

299 Though not fully understood, broad cross-protection following infection has been
300 noted for other respiratory viruses (47,48) and may be mediated by innate immune
301 mechanisms (49,50). Individuals return to the Susceptible class after a period of
302 protection, which has duration ω^{-1} .

303

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

311

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

316

317 **Hospitalization model**

318 We developed a linear regression model to fit the daily hospitalization rate per million
319 adults and children in each metropolitan area using potential predictors of variation in
320 asthma hospitalization rate (see SI Appendix). The variables included in model
321 selection were common cold prevalence, influenza prevalence, particulate matter
322 ($2.5\mu\text{m}$), ozone, low temperature, city-specific difference in hospitalization rate, day-
323 of-the-week variation, and secular trend in hospitalization rate (Table 1). For common

324 cold, we used the SIRS model to generate daily prevalence; for influenza, we
325 estimated daily prevalence directly from hospitalization records and did not explicitly
326 model transmission dynamics; for all other variables, daily measurements were
327 obtained from publicly available sources (see SI Appendix Sections 2-3). Model
328 components were compared extensively using the DIC, where $DIC = \bar{D} + p_v$, and p_v
329 $= 0.5var(\bar{D})$ (46,54). Lower values indicate a better fit of model to data, and a
330 difference of five units is the customary threshold for distinguishing model variants.

331

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

337

338

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344

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510

511 **Figure Legends**

512 **Fig 1. Daily number of asthma hospitalizations.** Total hospitalizations in the eight largest
513 metropolitan areas in Texas from August 2004 through August 2005, where markers indicate the 1st of
514 the month. Daily count values (light grey) and a spline-smoothed value (dark grey) in (A) children
515 aged 5 to 18 and (B) adults aged 19 to 55. In 2004, most Texas schools started in mid-August, took a
516 two-week winter break in late December to early January, and a one week spring break in late March.
517

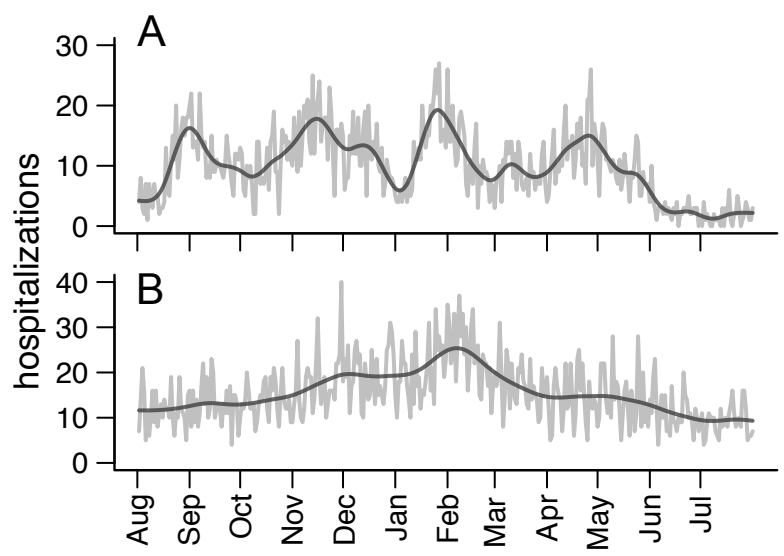
518 **Fig 2. The Susceptible-Infectious-Recovered-Susceptible (SIRS) dynamic transmission model of**
519 **common cold circulation.** (A) The child and adult populations are each divided into three infection
520 classes: Susceptible, Infectious and Recovered. The recovered class is immune to infection. Transitions
521 between compartments are governed by the rate parameters indicated. (B) Example model output for
522 children (red) and adults (blue). Weekends and vacations for the Dallas-Fort Worth-Arlington
523 metropolitan area in 2003-4 are shown as grey areas. On those days, the transmission rate of children is
524 decreased by σ . The prevalence of common cold infections in children more directly reflects the school
525 calendar (i.e. weekends and holidays). Variation in adults is driven by changes in prevalence in
526 children in the model. The estimated prevalences are incorporated into an asthma hospitalization risk
527 model to assess the relative impact of viral transmission on asthma exacerbation rates.
528

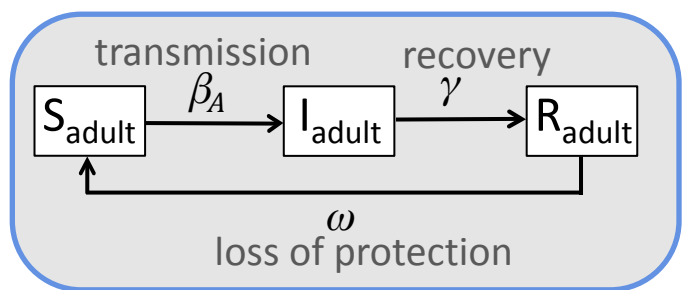
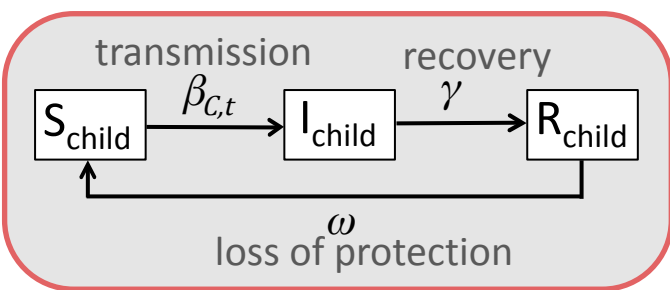
529 **Fig 3. Fit of the best model in children and adults.** Seven-day rolling mean of observed
530 hospitalizations in all cities (black) and simulations from the best fitting model (red). We sampled
531 twenty parameter sets from the joint posterior distribution, and generated five non-homogeneous
532 Poisson simulations for each set. Hospitalizations shown for (A) children aged 5 to 18 and (B) adults
533 aged 19 to 55. Contribution of each factor to the predicted hospitalization rate in children for (C)
534 Monday, August 11, 2003, (D) Monday, September 1, 2003, and, (E) Monday, December 29, 2003 in
535 the Dallas-Fort Worth-Arlington area (Metropolitan code 19100). The heights of the bars in each figure
536 sum to the fitted total asthma hospitalization rate on those days.
537

538 **Fig 4. Results from the best fitting model.** (A) Average number of colds in children (red points) and
539 adults (blue points) for each of the eight metropolitan areas, predicted by the model for each year of the
540 study. The shaded windows indicate public health estimate of 3–8 colds per year for children and 2–4
541 per year for adults (30). (B) Estimated day of week coefficients in the hospitalization model. Variation
542 in these values captures, in part, variation in healthcare seeking behavior on different days of the week.
543 (C) Correlation of baseline hospitalization rate in adults and children for each of the eight metropolitan
544 areas in the study. (D and E) Baseline hospitalization rate in each metropolitan area for children (D)
545 and adults (E). Values represent the city-specific addition to baseline asthma hospitalization rate.
546 Positive values of this coefficient indicate higher baseline rate.
547

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. $\mu\text{g}/\text{m}^3$	

Parameter	Symbol	Mean	95% CI lower	95% CI upper
Transmissibility	β_0	0.74	0.68	0.79
Adult-Child Scaling	α_{AC}	2.54%	1.39%	4.24%
Adult-Adult Scaling	α_{AA}	41.6%	34.6%	48.3%
Vacation effect	σ_t	45.1%	41.0%	49.0%
Duration of cross-immunity	ω^{-1}	19.3 days	17.7 days	21.1 days
Duration of infection	γ^{-1}	3.01 days	2.64 days	3.45 days



A**B**