

Simulation of four respiratory viruses and inference of epidemiological parameters

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ABSTRACT

While influenza has been simulated extensively to better understand its behavior and predict future outbreaks, most other respiratory viruses have seldom been simulated. In this study, we provide an overview of four common respiratory viral infections: respiratory syncytial virus (RSV), respiratory adenovirus, rhinovirus and parainfluenza, present specimen data collected 2004–2014, and simulate outbreaks in 19 overlapping regions in the United States. Pairing a compartmental model and data assimilation methods, we infer key epidemiological parameters governing transmission: the basic reproductive number R_0 and length of infection D . RSV had been previously simulated, and our mean estimate of D and R_0 of 5.2 days and 2.8, respectively, are within published clinical and modeling estimates. Among the four virus groupings, mean estimates of R_0 range from 2.3 to 3.0, with a lower and upper quartile range of 2.0–2.8 and 2.6–3.2, respectively. As rapid PCR testing becomes more common, estimates of the observed virulence and duration of infection for these viruses could inform decision making by clinicians and officials for managing patient treatment and response.

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1. Introduction

Respiratory viruses target particular host cells from the sinus cavity to the alveolar ducts and cause a variety of ailments. These ailments, including influenza-like illness (ILI), defined by the symptoms of fever, cough, and a runny nose, can only be reliably distinguished through laboratory testing (Ebell & Afonso, 2011). In addition to being clinically indistinguishable, co-infection with multiple viruses is not uncommon; one study found 23% of patients with ILI were co-infected with at least two pathogens (Pavia, 2011). In the U.S., acute lower respiratory infection accounts for 14% of mortality among children under 5 years old (Black et al., 2010), and about half of children visits to a primary care doctor or hospital (Schluger, 2010). Globally, acute respiratory infections are a leading cause of death in children (Lozano et al., 2012; Mayor, 2010; Williams, Gouws, Boschi-Pinto, Bryce, & Dye, 2002), in part due to indoor air pollution (Mishra, 2003; Smith, Samet, Romieu, Bruce) and under-nutrition (Black et al., 2010). Excluding influenza, other respiratory viruses (ORVs) can produce severe illness in children and the elderly; even in adults, ORVs can produce more hospitalizations than influenza (Gilca et al., 2014). In this

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paper, we simulate and estimate key epidemiological characteristics of four common respiratory viruses: respiratory syncytial virus, respiratory adenovirus, rhinovirus and parainfluenza. Table 1 summarizes the estimated contribution of each of these viruses to ILL.

1.1. Clinical description of the four respiratory viruses

Respiratory syncytial virus (RSV) infects the bronchiole tubes in the lungs, causing bronchiolitis. RSV is the most common respiratory ailment in infants under one year of age (Goldstein, Greene, Olson, Hanage, & Lipsitch, 2015; Hall, Douglas, & Geiman, 1976; Handforth, Friedland, & Sharland, 2000; Leader & Kohlhasse, 2003), and is also prevalent in older ages (Falsey, 1998; Falsey, Hennessey, Formica, Cox, & Walsh, 2005). RSV has been found to infect up to 29% of children with respiratory symptoms (Juvén et al., 2000). It has a very low asymptomatic rate among the very young (Jansen et al., 2011), but can manifest as mild ILL or be asymptomatic among adults (Munywoki et al., 2015). Table 2 provides estimates of key epidemiological characteristics for RSV, including duration of illness, D , and the basic reproductive number, R_0 , which were derived from clinical and challenge studies of healthy individuals. RSV is symptomatic for roughly a week. Modeling work has estimated the force of infection or R_0 within a range of 1.7–8.2, in part depending on the model structure and whether age stratification was included (Pitzer et al., 2015; Poletti et al., 2015; Reis & Shaman, 2016; Velasco-Hernández, Núñez-López, Comas-García, Cherpitel, & Ocampo, 2015; Weber, Weber, & Milligan, 2001; White et al., 2007).

Respiratory adenovirus (rAD) can cause bronchiolitis, croup, and pneumonia, and infects 70%–80% of children by age 5 (Aberle et al., 2003). Children have been found exposed to an average of 3.4 rAD serotypes by age two, with the highest incidence in infants aged 6–12 months (Pacini, Collier, & Henderson, 1987). Up to 14% of patients with ILL were rAD positive (Li et al., 2013). As listed in Table 2, untreated, rAD patients are infected for more than a week. A highly contagious strain, 7 h, can infect 55% of contacts (Palomino et al., 2000).

Rhinovirus, an enterovirus, is most associated with a mild upper respiratory tract infection, especially a runny nose (Garcia et al., 2013). Nearly half of acute respiratory infections in infants have rhinovirus (Kusel et al., 2007). Rhinovirus has a high asymptomatic rate, estimated between 15% and 30% in children (Jartti, Lehtinen, Vuorinen, Koskenvuo, & Ruuskanen, 2004; Johnston et al., 1993; van Bentem et al., 2003; van Gageldonk-Lafeber et al., 2005), and as much as 50% in adults (Peltola et al., 2008b). (Jansen et al., 2011). In temperate climates, rhinovirus outbreaks have been observed to peak in the fall and early spring (Gwaltney et al., 1967; Jacobs, Lamson, St George, & Walsh, 2013). All three serotypes have been found in each season, albeit sometimes on an alternating basis (Jacobs et al., 2013; Kaida et al., 2011; Miller et al., 2011; Savolainen-Kopra et al., 2009). Investigations continue to tease apart the contribution of each serotype to the seasonal pattern of rhinovirus (Kaida et al., 2011). Rhinovirus infections can last up to two weeks, and are easily spread among family members (Table 2).

Parainfluenza virus (PIV) serotypes 1 and 2 cause croup symptoms (seal barking cough caused by infection of vocal cords) and infect most children by age five. PIV types 1 and 2 are responsible for an estimated 250,000 hospital visits and 70,000 hospitalizations (Henrickson, Kuhn, & Savatski, 1994). PIV type 3 is the second most common cause of acute respiratory infection after RSV, and also causes bronchiolitis and pneumonia; most children get PIV-3 by age two (Glezen, Frank, Taber, & Kasel, 1984). PIV type 4 is detected less frequently in sick patients (Fry et al., 2006), although serological data show that PIV-4 circulates widely (Henrickson, 2003). PIV also infects older generations and those with a weakened immune system (Fry et al., 2006). PIV-3 infections tend to last longer than a week, whereas PIV 1–2 infections usually clear within a week (Table 2). We were unable to find estimates of R_0 for any PIV subtypes.

1.2. Modeling work and aims

Of the four respiratory viruses to be examined here (Table 1), most prior studies have simulated RSV, using either a compartmental structure or more complicated model form (Pitzer et al., 2015; Reis & Shaman, 2016; Weber et al., 2001; White et al., 2007). Most likely, the work on RSV has been driven by its severity in infants and seasonal regularity. Recently Levy et al. (Levy et al., 2018) used a compartmental model in conjunction with twitter data, viral specimen data, and a matching pursuit decomposition approach to simulate nine respiratory pathogens producing ILL signal in England. In this paper, we use a compartmental model, data assimilation methods, and specimen data to simulate RSV, rAD, rhinovirus, and

Table 1
Contribution of ORVs to ILL.

Respiratory Virus	Estimated percent of ILL
Respiratory syncytial virus	3–29% (Pavia, 2011); 16.6% (Li et al., 2013); 19.6% in adults (Bellei et al., 2008); 31% among ≤ 6 yrs (Jansen et al., 2011)
Respiratory adenovirus	0.4–4% (Williams et al., 2002); 4.7 (Aberle et al., 2003); 7–8% (Brandt et al., 1969; Munoz, Piedra, & Demmler, 1998; Osiowy, 1998); 7–12% (Pavia, 2011); 14.11% (Li et al., 2013)
Rhinovirus	3–45% any season (Pavia, 2011); 25% among ≤ 6 yrs (Jansen et al., 2011)
Parainfluenza virus	PIV 8–13% (Pavia, 2011); PIV 1–3: 5% (Miller et al., 2013); PIV 1: 2.6–18.5% (Henrickson, 2003); PIV 1–2: 3.6–21% (Henrickson, 2003) PIV 1: 56% (Hall, Geiman, Breese, & Douglas, 1977); PIV 1–3: 9.25% (Li et al., 2013)

Table 2

Summary of clinical studies of each respiratory virus and estimates of the epidemiological parameters D and R_0 . We were unable to find an estimate of R_0 for respiratory adenovirus. Where data were available, we show the mean estimate from each paper.

	D (days)	R_0
Respiratory syncytial virus (RSV)	Mean: 7.3; 5–10 (Hall et al., 2009); 11.2 shedding detected by PCR (Munywoki et al., 2015); 4.5 by antibody detection (Okiro et al., 2010); 6 inferred by modeling (Reis & Shaman, 2016) Assumed in prior modeling studies: 10.14 (Weber et al., 2001); 5–10 with progressive immunity (Pitzer et al., 2015); 9 (White et al., 2007)	Mean: 4.5; 1.1–2.1 SIRS model (Weber et al., 2001) 8.9–9.2 SIRS model with age structures (Pitzer et al., 2015) 2.3–8.9 SIR model (Velasco-Hernández et al., 2015) 3.0 (Reis & Shaman, 2016) 2.18 (Poletti et al., 2015) 1.2–9.5 (White et al., 2007) depending on model structure 1.6 (Levy, Iv, & Yom-Tov, 2018)
Respiratory adenovirus (rAD)	Mean: 7.7; With treatment: 5.5 (Larrañaga, Kajon, Villagra, & Avendaño, 1988–1996); 10.6 (Hong et al., 2001); 7 (Aberle et al., 2003)	Cross-infection with adenovirus 7 h type: 55% (Palomino, Larrañaga, & Avendaño, 2000)
Rhinovirus	Mean: 7.7; 3 (Corne et al., 2002); 7.4 (Gwaltney, Hendley, Simon, & Jordan, 1967) 10 (Pappas, Hendley, Hayden, & Winther, 2008); ill 7–9, shedding > 10 (Douglas, Cate, Gerone, & Couch, 1966)	1.5 family members infected (Peltola et al., 2008a); 36% volunteers infected (small sample) (Hendley, Gwaltney, & Jordan, 1969); 95% infected, 74% developed a cold (Gwaltney, 2002); 74–90% volunteers developed a cold (Cohen, Tyrrell, & Smith, 1991); 1.2 from simulation (Levy et al., 2018) 2.7 from simulation (Levy et al., 2018)
Parainfluenza virus (PIV)	Mean: 9.8; All subtypes: 3–17 d (Henrickson, 2003); PIV1: 4 d PIV2, PIV4: 6–13 d (Henrickson, 2003); PIV3: 9–10 d (Frank et al., 1981); 16 d to zero shedding after given vaccine (Belshe et al., 2004)	

PIV subtypes and estimate epidemiological transmission parameters for each of these four viruses. Among the four viruses, outbreaks range from those that occur with regular, highly seasonal epidemic curves (e.g. RSV) to those with highly unstructured chains of transmission (e.g. rAD), where patterns only emerge at coarser temporal or geographical resolution.

2. Methods

2.1. Data

Specimen data, sampled using antigen detection, viral culture, and PCR testing, were provided by the Centers for Disease Control and Prevention (CDC), as reported through the National Respiratory and Enteric Virus Surveillance System (NREVSS).

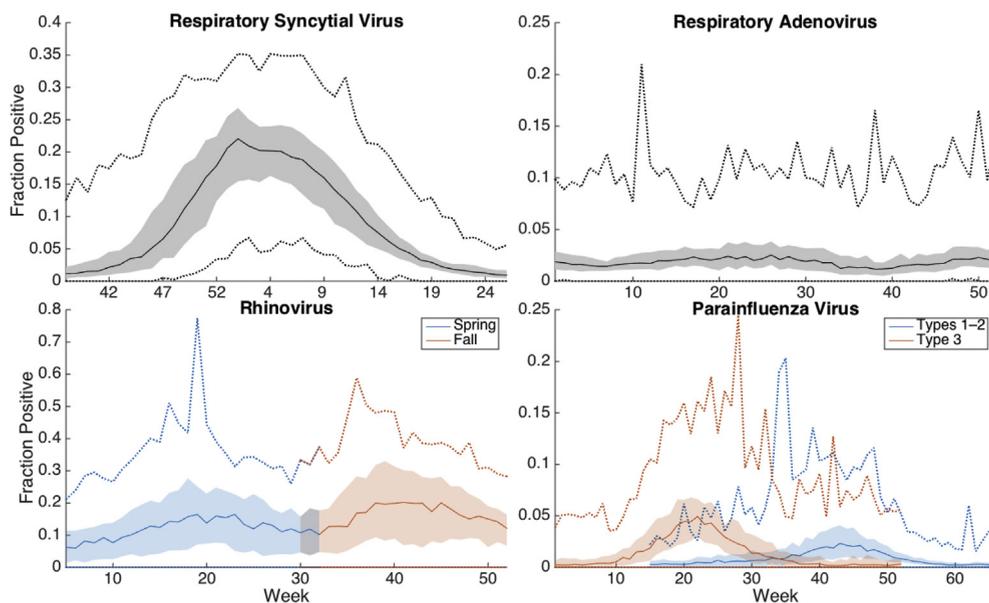


Fig. 1. The mean outbreak across each Census Division and HHS region and year from 2004 to 2015 (rhinovirus dates: 2009–2015). The shaded region shows the data quartiles, and the dotted lines show the extremes.

Table 3

Julian calendar weeks simulated for each virus.

Respiratory Virus	RSV	Adenovirus	Rhinovirus winter	Rhinovirus fall	PIV1-2	PIV3
Weeks simulated	37–26	1–52	5–32	30–52	15–14	1–52

Table 4

The range of initial state variables for the SIR model for each virus.

Variable or parameter	Initialized Range	Distribution
Susceptible, S	$1.1 \times 10^5 - 3.9 \times 10^5$ people; $\mu = 23.6 \times 10^4$; $\sigma = 5.7 \times 10^4$	Normal
Infectious, I	One to 1.5×10^3 people; $\mu = 14.8$	Exponential
Initial $D \pm$ range	3–8 days	Uniform
Initial R_0 range	1.3–4	Uniform

Data were available from 2004 to 2014 at the Census Division and Health and Human Services geographic regions in the United States. Rhinovirus samples were mainly tested using PCR-assay, and were only available in adequate volume since 2009 (i.e. at least ten tests per week). In this paper, we study positive specimen tests divided by the total number of tests performed each week in each region. The age structure of those tested was not available. Fig. 1 shows the mean outbreak for all each regional groupings and years. The shaded region indicates fraction positive data within 25–75% percentiles.

For each virus type or subtype, we simulated each individual seasonal outbreak; thus, we modeled 19 overlapping geographical areas and 10 outbreak seasons for RSV, rAD, and PIV, and five seasons for rhinovirus. We simulated outbreaks of rhinovirus beginning in the fall and winter separately. We also grouped PIV types 1 and 2, and simulated PIV type 3 separately, due to PIV's marked seasonal variation by subtype; we did not include PIV type 4 due to a low number of positive tests (S1 Fig). Table 3 shows the Julian calendar weeks used to define the period of simulation for each virus. As shown in Fig. 1, mean outbreak structure differs among the viruses, ranging from regular outbreaks of RSV to highly irregular incidence of rAD. By separately simulating these four virus types, we can estimate the epidemiological characteristics of each, including the force of transmission.

2.2. Compartmental model

We used a susceptible–infected–recovered (SIR) compartmental model to represent transmission dynamics. As previously described for simulation of RSV outbreaks (Reis & Shaman, 2016), the SIR model structure is as follows:

$$\frac{dS}{dt} = -\frac{R_0 IS}{DN} \quad (1)$$

$$\frac{dI}{dt} = \frac{R_0 IS}{DN} - \frac{I}{D} \quad (2)$$

where S is the susceptible population, I is the number of infected, R_0 is the basic reproductive number, D is the mean infection period, and N is the size of the population. N was held constant at an arbitrary size of 500,000 people.

2.3. Mapping fraction positive to number infected in the population

To estimate the incidence in a population of arbitrary size N , the positive fraction of specimen tests were multiplied by both N and a scalar γ . Generally, γ scales N to the actual population sampled in NREVSS regional ‘catchments’, including the number of reporting NREVSS laboratories and the population served by each laboratory. We found γ ranging from 0.02 to 0.05 produced posterior outbreaks with lowest RMSE for the six outbreak types, and $\gamma = 0.02$ produced the lowest RMSE summed across all six viruses.

2.4. Inference of parameter and state variables

We used the ensemble adjustment Kalman filter (EAKF) to infer parameter and state variables during model integration (Anderson, 2001; Karspeck & Anderson, 2007a, 2007b; Reis & Shaman, 2016; Shaman & Karspeck, 2012; Shaman, Karspeck, Yang, Tamerius, & Lipsitch, 2013). The EAKF generates posterior distributions by taking a weighted average of the prior distribution and observations, weighting the two estimates based on the variance of the observed model variable (here incidence), estimated directly from the ensemble of simulations, and the error variance of the observational data stream (OEV), estimated as:

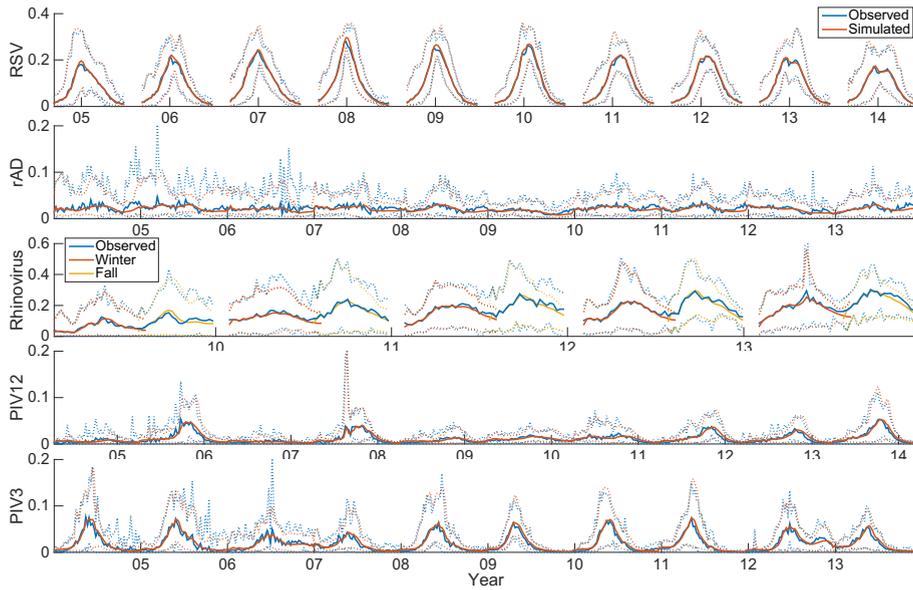


Fig. 2. Observed outbreaks of each virus shown as a mean across the 19 overlapping U.S. regional data. Each season was simulated independently. Rhinovirus winter and fall outbreaks were each simulated independently. The dotted lines show the 5th and 95th percentile across all regions.

$$OEV = OEV_0 + \frac{\overline{OBS}^2}{a} \tag{3}$$

The initial OEV (OEV_0) was assumed to be 10^5 and the constant a was set to 50, values selected during prior work developing an SIR-EAKF model for RSV (Reis & Shaman, 2016). The observed infections are taken as a running mean of the prior 3 weeks (\overline{OBS}), allowing OEV to rise and fall with observed incidence.

To utilize the EAKF, an ensemble of model realizations is required. Here we used 300 ensemble members for each outbreak simulation, where each ensemble member was initialized independently from a wide range of initial state variable and parameter conditions (Table 4), as previously described (Reis & Shaman, 2016). We further ran each 300-member simulation five times to account for any stochastic effects during initialization. As our principal aim was to estimate D and R_0 , we ran a series of estimation tests using the SIR-EAKF and ‘synthetic’ (i.e. model-generated) data that resembled different viral outbreaks (see SI). These synthetic tests demonstrated the ability of our SIR-EAKF to adequately converge to the parameters used to generate the synthetic data.

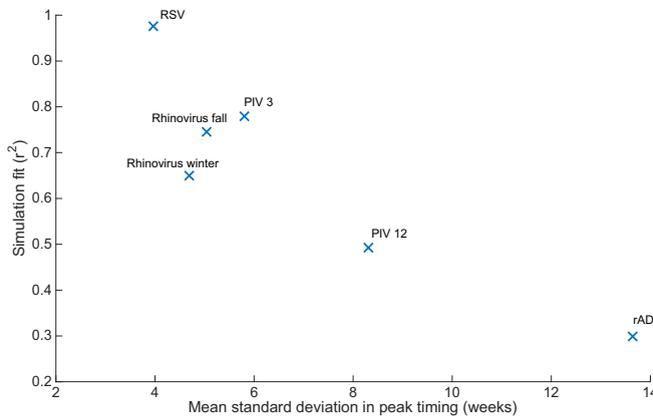


Fig. 3. The model fit (r^2) is negatively correlated with observed standard deviation of observed peak timing (weeks).

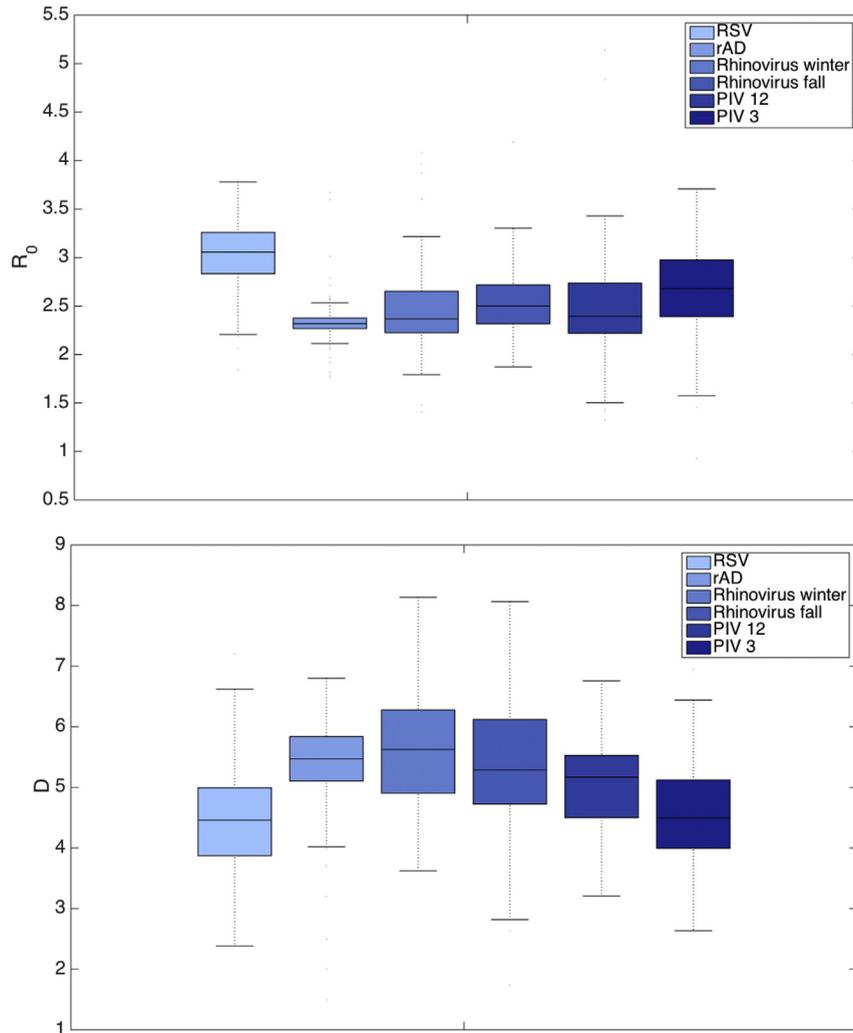


Fig. 4. Estimates of R_0 (top plot) and D (bottom plot) for each virus shown as a boxplot. Estimates were obtained on the last week of outbreak simulation.

3. Results

3.1. Simulation

The observed and simulated outbreaks, taken as an average over each of the 19 regions, again reveal differences among the epidemic curves of the different respiratory viruses (Fig. 2). RSV is the most regular and rAD is the least regular of the simulated viruses. Simulation of highly regular outbreaks such as RSV had a high correlation with observed data ($r^2 = 0.98$), whereas simulation of irregular outbreaks, such as rAD, had low correlations ($r^2 = 0.30$, S1 Table). The fraction of observations that falls within the 90% and 50% credible intervals of all posterior ensemble ranges between 0.70–0.86 and 0.55–0.66, respectively, depending on the virus (see S1 Table). These ranges indicate that the ensemble-estimated credible intervals are slightly too narrow.

We quantified the variability of four epidemic characteristics: value of peak intensity, timing of peak intensity, mean cases (percentage of positive tests per week), and onset of the epidemic. The CDC defines an onset threshold for RSV as 10% positivity, but does not specify an onset threshold for the other viruses we simulate. Here, we define onset threshold as the mean level for each virus over all locations and epidemic weeks simulated, e.g. the RSV data on average were 9.4% positive. Based on quantification of these four characteristics, RSV outbreaks are the least variable, whereas the other viruses show considerably more variability (S2 Fig). Of the four epidemic characteristics, the strongest predictor of simulation fit was variability in peak timing. Fig. 3 shows that model fit, as measured by r^2 , has a strong negative correlation with the observed variability of the timing of peak intensity. Fig. 3 suggests that a compartmental model will yield an $r^2 \geq 0.5$ with a mean observed standard deviation of peak timing of eight weeks or fewer.

Table 5

Mean estimates of parameters R_0 and D at the week of peak intensity and on the last week of outbreak simulation.

Respiratory Virus	RSV	rAD	Rhinovirus winter	Rhinovirus fall	PIV1-2	PIV3
R_0 at peak timing	2.82	2.34	2.60	2.71	2.31	2.53
D at peak timing	5.16	5.49	5.24	5.24	5.53	5.29
R_0 on last week	3.02	2.33	2.46	2.52	2.49	2.69
D on last week	4.44	5.39	5.64	5.35	4.99	4.58

3.2. Parameter estimation

Fig. 4 presents boxplots of the basic reproductive number, R_0 , and the infection period, D , estimated on the last week of simulation for each outbreak. Across the six different viral groupings, the mean estimate of R_0 range is 2.3–3.0, with a lower and upper quartile range of 2.0–2.8 and 2.6–3.2, respectively. Synthetic tests show that estimation R_0 but not R_E depend on the initialization of S , and median estimates of R_E are shown in S5 Fig. The mean length of infection D varies 4.4–5.6 days, with the upper and lower interquartile ranges varying 3.7–4.9 and 5.1–6.3, respectively. As discussed, rAD has a relatively irregular seasonality and is unstructured, and this irregular shape may account for its relatively low R_0 and high D . Table 5 lists the mean estimates of the parameters at the week of outbreak peak intensity and on the last week of simulation. RSV has the highest R_0 (2.8 at peak) and the lowest length of infection, D , (5.2 days). Conversely, rAD and PIV types 1–2 had the lowest R_0 (2.3 each at peak timing) and greatest value of D (5.5 each).

Figs. 5 and 6 show the median parameter estimates of R_0 and D as a time series throughout the simulation over each region. The shaded region shows the 25–75% ensemble result and the dotted lines show the minimum and maximum. We performed sensitivity analysis for the above estimates by shifting the initial prior range of D and repeating the simulation and parameter estimation. S3 and S4 Figures show R_0 and D , respectively, over the simulation period when D is initialized with an initial prior range shifted ± 4 days above or below the values listed in Table 4 (for convenience this simulation will be referred to as the baseline). As shown, the values of D are sensitive to the initial prior. The value of R_0 converges to the baseline value for rAD and rhinovirus, but the change in initialization has a greater impact on the final value of R_0 for RSV and PIV, although these values vary by less than one, suggesting that R_0 is not overly sensitive to changes in the simulation initialization. The effective reproductive number, R_E , moreover, converges within the simulation period (S5 Fig.). We also provide estimates of R_E and β (R_0/D) for the baseline simulation (S6 Fig.).

3.3. Geographical variation of parameter estimates

Figs. 7 and 8 map the values of R_0 and D , respectively, in the continental U.S., showing the mean parameter values, from weeks 7 to the end of the simulation, in each state as an average of the corresponding CD and HHS regions. RSV has a lower R_0 in Florida and the southeast than in other states, which may be a reflection of the type of data simulated here, percent

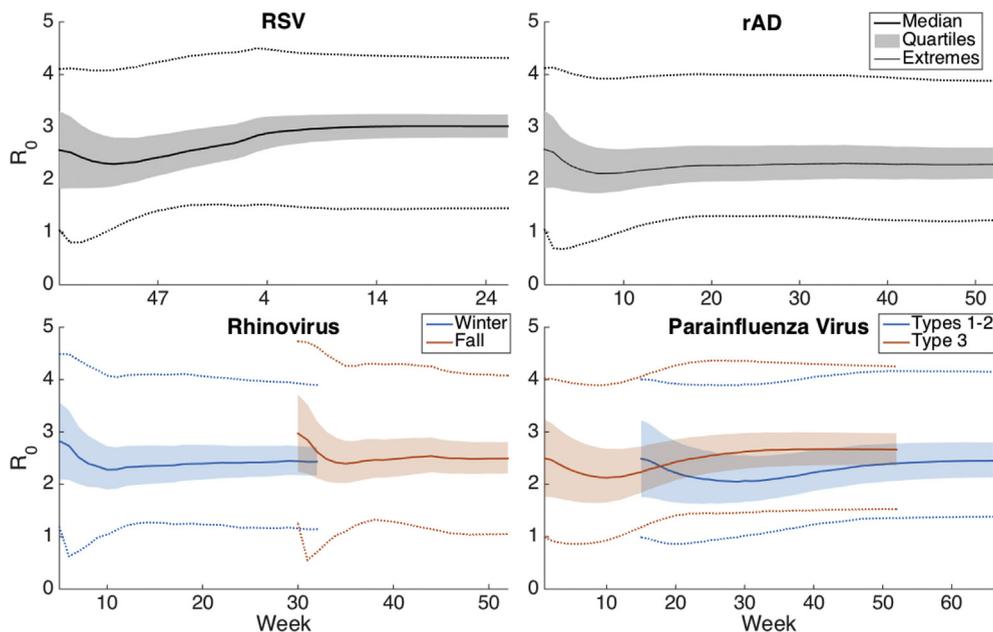


Fig. 5. Estimates of R_0 as an average time series for each virus. The shaded region shows the 25–75% interval. Dotted lines show the minimum and maximum ensemble values.

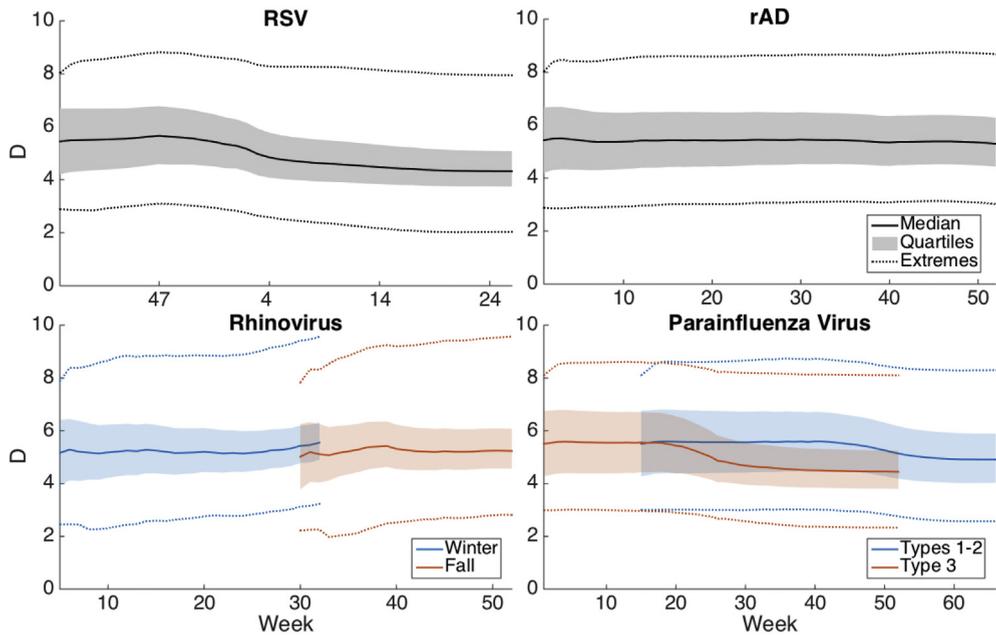


Fig. 6. Estimates of D as an average time series for each virus. The shaded region shows the 25–75% interval, with dotted lines indicating the maximum and minimum.

positive, versus the number of hospitalizations that has been used in previous work (Pitzer et al., 2015). Overall, R_0 was the highest for RSV outbreaks and the lowest for outbreaks of parainfluenza virus types 1–2 in northern states. These maps show a greater spatial variation in D than in R_0 .

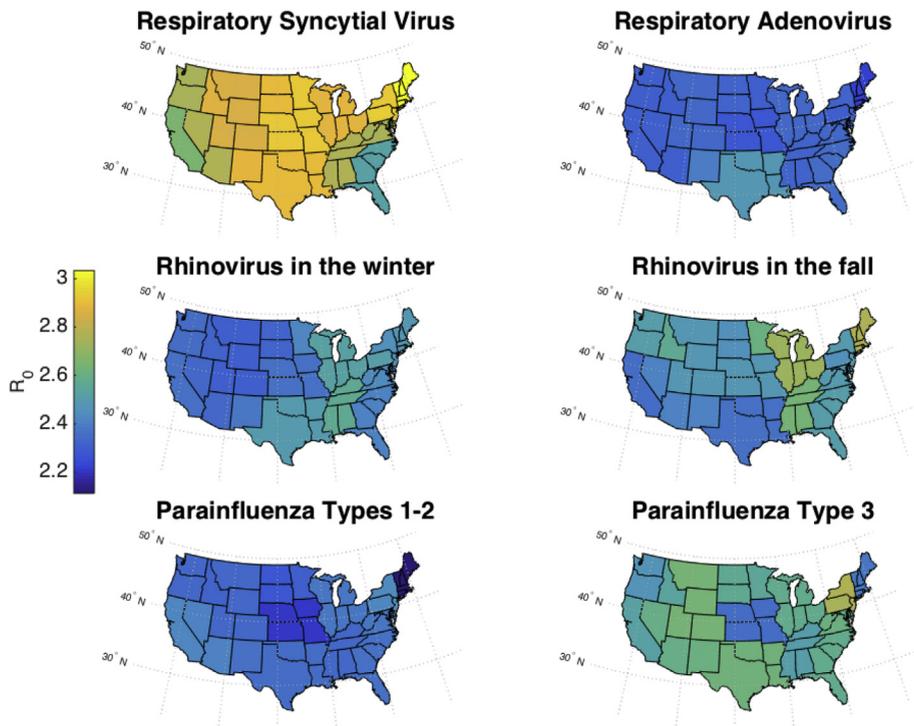


Fig. 7. Estimates of mean R_0 plotted in the continental U.S. Because Census Divisions and HHS regions overlap, the mean estimate from both regional groupings was taken for each state.

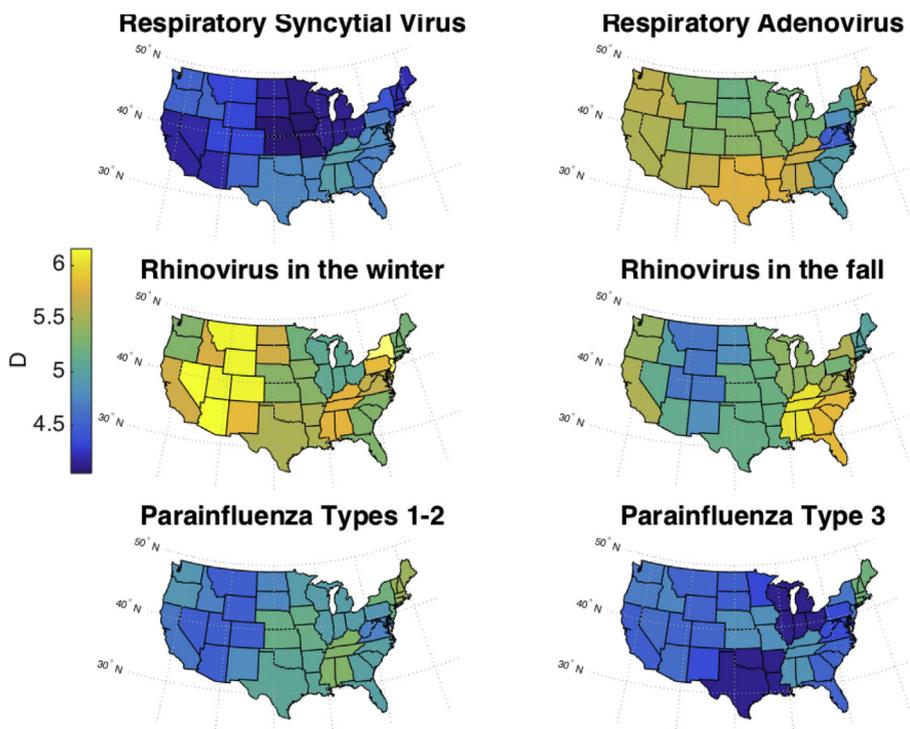


Fig. 8. Estimates of mean D plotted in the continental U.S. Because Census Divisions and HHS regions overlap, the mean estimate from both regional groupings was taken for each state.

4. Discussion

In this paper, we simulated outbreaks of four respiratory viruses that often present as ILL, including simulations of respiratory adenovirus, rhinovirus, and parainfluenza virus. Prior estimates of epidemiological parameters for these three viruses were derived mainly from clinical work (Table 2), but here we provide estimates of the reproductive number, R_0 , and the length of illness, D , using broad epidemiological surveillance data.

Model simulations were well correlated with observed infection rates for rhinovirus, RSV, and PIV. The simulations were less strongly correlated with rAd observations, whose irregularity may reflect co-circulation of multiple serotypes or sparse reporting due to high asymptomatic infection rates or more limited testing. Should more active surveillance and testing for rAd occur in the future, outbreaks may be better resolved and simulated. Alternatively, other model forms might be tested in the future and might improve simulation. For the other viruses, the high correlation of the modeled data to the observations suggests that the SIR compartmental model is a reasonable form for representing transmission dynamics. We deliberately chose this simple model form so that it could be applied to a wide variety of respiratory viral outbreaks.

For RSV, our mean estimate of D and R_0 of 5.2 days and 2.8, respectively, are within published clinical and modeling estimates (Table 2). Our estimate of the infection period, D , for rAd conforms to clinical observations, while our estimate of R_0 of 2.3 is lower than the attack rate of 55% observed for the virulent strain 7 h, which seems to be more prevalent in low-income countries (Hatherill et al., 2004; Palomino et al., 2000; Rodríguez-Martínez, Rodríguez, & Nino, 2015; Stralio, Siqueira, Machado, & Maia, 2004) but has also been found in the US and Canada (Erdman et al., 2002). The great diversity of rAd serotypes and their characteristics (Gray et al., 2007; Morris, Cooper, Barr, & Bailey, 1996) precludes identifying a single R_0 for all rAd species. Fall and winter outbreaks of rhinovirus, which we simulated separately, may be caused by different strains; however, the mean R_0 value of rhinovirus in the fall (2.7, September to December) was only slightly higher than it was for outbreaks beginning in the winter (2.6, February through July), but with a greater upper range (Fig. 8). Overall the R_0 we inferred was at the high end of the range estimated from observations of household viral spread (roughly 1.5–2.5) and higher than a previous modeling estimate (Levy et al., 2018). Even so, it is possible that the R_0 of rhinovirus is in fact still greater than here estimated due to the relatively mild symptoms expressed with rhinovirus infection that typically do not require medical attention. Clinical estimates of the infection period, D , for PIV subtypes vary widely from 3 days to two weeks (Belshe et al., 2004; Frank et al., 1981; Henrickson, 2003), and our estimates fall in the middle at slightly less than one week (5.5 and 5.3 days for PIV 1–2 and PIV 3, respectively), though our sensitivity analyses indicate that this parameter is not strongly constrained. Although a prior estimate found a higher estimate of R_0 for PIV (Levy et al., 2018), our inferred values (Table 5) are among the smallest of the four viruses simulated, suggesting a less contagious pattern of transmission than RSV or rhinovirus.

Here we inferred epidemiological parameters using the EAKF, which provides a probability distribution for each estimate. In this study, we initialized the model susceptible and infectious state variables and D and R_0 parameters from a random uniform range. To evaluate the sensitivity of the estimates, we varied the initialization of parameter $D \pm 4$ days from the values derived from clinical work (Table 4). S3–S5 Figs show that the impact on the estimate of R_0 and R_E was minor while the estimate of D was sensitive to initialization.

In the future, these four respiratory viruses could be further interrogated to identify factors affecting outbreak timing and intensity, such as events where vulnerable populations mix with other critical subpopulations, or geospatial or climatic associations with intensification of viral outbreaks (Pitzer et al., 2015; Shaman, Pitzer, Viboud, Grenfell, & Lipsitch, 2010). These viral outbreaks could be simulated to then explore scenarios that foster intense transmission, which could alert public health authorities to the most dangerous combination of risk factors. Similarly, computational experiments could be used to help evaluate potential interventions to limit infection, such as reduced contact with infected groups when infection rates are high or greater preparedness in hospitals and clinics for high volume of respiratory illnesses.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.idm.2018.03.006>.

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