# Cross-immunity between strains explains the dynamical pattern of paramyxoviruses

Samit Bhattacharyya[a,b,1], Per H. Gesteland[c,d], Kent Korgenski[c,e], Ottar N. Bjørnstad[a,f], and Frederick R. Adler[b,g]

[a]Center for Infectious Disease Dynamics, Pennsylvania State University, University Park, PA 16802; [b]Department of Biology, University of Utah, Salt Lake City, UT 84112; [c]Department of Pediatrics, School of Medicine, University of Utah, Salt Lake City, UT 84112; [d]Department of Biomedical Informatics, University of Utah, Salt Lake City, UT 84112; [e]Pediatric Clinical Program, Intermountain Healthcare, Salt Lake City, UT 84111; [f]Fogarty International Center, National Institutes of Health, Bethesda, MD 20892; and [g]Department of Mathematics, University of Utah, Salt Lake City, UT 84112

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**Viral respiratory tract diseases pose serious public health problems. Our ability to predict and thus, be able to prepare for outbreaks is strained by the complex factors driving the prevalence and severity of these diseases. The abundance of diseases and transmission dynamics of strains are not only affected by external factors, such as weather, but also driven by interactions among viruses mediated by human behavior and immunity. To untangle the complex out-of-phase annual and biennial pattern of three common paramyxoviruses, Respiratory Syncytial Virus (RSV), Human Parainfluenza Virus (HPIV), and Human Metapneumovirus (hMPV), we adopt a theoretical approach that integrates ecological and immunological mechanisms of disease interactions. By estimating parameters from multiyear time series of laboratory-confirmed cases from the intermountain west region of the United States and using statistical inference, we show that models of immune-mediated interactions better explain the data than those based on ecological competition by convalescence. The strength of cross-protective immunity among viruses is correlated with their genetic distance in the phylogenetic tree of the paramyxovirus family.**

paramyxoviruses | respiratory syncytial viruses | human parainfluenza | pathogen interactions | cross-immunity

Respiratory Syncytial Virus (RSV) and Human Parainfluenza Virus (HPIV), two important closely related members in the *Paramyxovirus* family (1), are leading causes of hospitalization in young children with community-acquired respiratory disease (2–13). Each year, they impose a huge burden on public health by demanding substantial healthcare system resources (14). Human Metapneumovirus (hMPV), a relatively recently identified member of the same *Paramyxovirus* family, causes upper and lower respiratory tract infections in young children. These viruses are now recognized as important pathogens in adults as well (15–17) but poorly characterized, because they present less distinctive clinical findings than in children and are clinically similar to other viral infections, such as influenza.

The consistent annual outbreaks of these agents and the frequency of reinfection suggest that they impose a considerable disease burden throughout life. Despite several decades of effort, there are no effective means to control RSV and HPIV infections. The development of successful vaccines has been confounded by the lack of durable immunity (18), even after natural infection, and the diversity and ubiquity of populations at risk for infection (19, 20).

Both extrinsic factors, such as weather (21–23) and pollution (24, 25), and intrinsic factors, such as host heterogeneity (26–28), could drive the cyclic dynamics of these viruses.

In the United States, most RSV infections occur during a period of about 22 wk from November to May (3, 29, 30). The peak activity in most of the country is usually in January or February, although slightly earlier in the southeast. In contrast, the seasonal patterns of serotypes 1, 2, and 3 of HPIV are curiously interactive (3, 30, 31). Data on HPIV hospitalizations in Utah show HPIV-1 causing the largest and most clearly defined outbreaks, marked by sharp biennial rises in cases of croup in the autumn of odd-numbered years (Fig. 1). Outbreaks of infection with HPIV-2, although more erratic, are also biennial but occur in even years. Outbreaks of HPIV-3 occur yearly, mainly in spring and summer, and last longer than outbreaks of types 1 and 2. HPIV-4 is infrequently isolated (32).

The timing of these respiratory pathogen outbreaks may be driven by external forces, such as weather (33), or interactions between pathogens (34) that drive out of phase dynamics. Because these pathogens belong to same RNA virus family *Paramyxovirus* and are responsible for respiratory disease in mostly children and adults of similar ages, we investigate whether interactions (either immunological or ecological) among them are the primary drivers of their epidemic patterns. In fact, there are previous theoretical and empirical studies that discuss interactions among these respiratory viruses (35, 36). Understanding the factors that regulate epidemiological patterns and predicting the seasonal abundance of these viruses are central to their effective management.

We confront a seasonally forced mechanistic transmission model with incidence reports of RSV, serotypes 1–3 of HPIV, and hMPV. Using statistical likelihoods, we compare two hypothetical mechanisms of interaction between diseases: cross-immunity (immune-mediated interaction) (37–42) and convalescence (ecological interaction) (43, 44). Accurate assessment of the nature of interaction among these viruses has important potential public health consequences for prediction of outbreaks and control of disease by targeting and timing of control strategies.

## Significance

**Pathogens that invoke an immune response immediately after infection can also provide partial cross-protection against other strains of the same or closely related pathogens. This cross-protection can shape the epidemiological dynamics of multi-strain pathogens when an epidemic of one strain temporarily suppresses the transmission of another. Identifying these interactions from time series of epidemiological data is difficult, particularly when prevalence oscillates seasonally. We use long-term incidence data on Respiratory Syncytial Virus (RSV), three serotypes of Human Parainfluenza Virus (HPIV), and Human Metapneumovirus to study mathematical models of different mechanisms of pathogen interaction. Our results show a strong signal of cross-protection from RSV in controlling the timing and magnitude of HPIV outbreaks, and a stronger interaction with more closely related serotypes.**

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[1]To whom correspondence should be addressed. Email: szb16@psu.edu.

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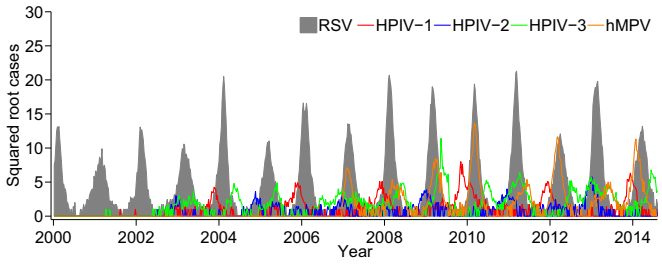


**Fig. 1.** Weekly observed case reports (square root) for all five pathogens: RSV (gray), HPIV-1 (red), HPIV-2 (blue), and HPIV-3 (green) from 2000 to 2014 and hMPV case reports for the relatively shorter period from 2007 to 2014 (yellow).

## Results

**Data Analysis.** We perform wavelet decomposition of all time series from the years 2002 to 2014 to analyze the data in time–frequency domain. The continuous wavelet transformations of the RSV and HPIV time series are shown in *SI Appendix*, Fig. S2. The significant peaks of RSV periodicity are around the 52-wk band, whereas peaks of HPIV-1 and HPIV-2 activity are around the 104-wk band. However, there is high power for HPIV-2 around the 52-wk band in the period from 2010 to 2013. In contrast, HPIV-3 does not exhibit any consistent period, although there is significant high power around 52 and 104 wk in the periods of 2008–2010 and 2010–2012, respectively.

The wavelet coherence (WC) (*SI Appendix*, Fig. S3) and cross-wavelet transformation (XWT) (*SI Appendix*, Fig. S4) between pairs of strains reveal how strongly they are correlated in the time and frequency domain. Both XWT and WC of RSV with HPIV serotypes 1 and 2 (*SI Appendix*, Fig. S3 *A* and *B*) indicate that HPIV serotypes 1 and 2 are strongly correlated with RSV in the 52-wk band and lead RSV throughout the entire period. In contrast, the WC between RSV and HPIV-3 (*SI Appendix*, Fig. S3*C*) shows several significant spots of correlation along the 52-wk band with RSV leading HPIV-3. WC between HPIV-1 and HPIV-2 (*SI Appendix*, Fig. S3*D*) shows consistent significant power in the 104-wk band in a perfect antiphase relation. The wavelet analysis of hMPV data also shows high power in the 52-wk band, and cross-wavelet analysis with RSV exhibits in-phase relation in the 52-wk band. Thus, XWT and WC between RSV and HPIV serotypes are strong preliminary indicators of interactions among these pathogens.

**Cross-Immunity and Competition Models of Disease Interactions.** We extend the susceptible–infected–recovered (SIR) compartmental model (45) to include two different disease interaction mechanisms: cross-immunity and convalescence (detailed descriptions are given in *Materials and Methods* and *SI Appendix*). Cross-immunity acts by reducing the rate at which a host that has recently recovered from one pathogen may become infected with another (38). Convalescence acts by temporarily removing individuals after infection because of behavioral modification and thus, transiently reducing the susceptible pools of the infections (43). Our models include seasonally forced transmission dynamics and temporary immunity of acquired infection. Studies suggest that reinfection by RSV and HPIV is likely in infants and the elderly, although it remains largely undetected in the latter (19, 20). A detailed description and schematic (*SI Appendix*, Fig. S1) of the models are given in *SI Appendix*.

Both models can exhibit a variety of dynamics depending on the strength of interactions (46). For example, when the two viruses are in a similar parameter regime with no interaction, they often have annual and in-phase oscillations. Increasing the strength of cross-protection can induce oscillations with higher-order cycles and out of phase dynamics (*SI Appendix*, Fig. S5). Generally, either cross-immunity or convalescence has little influence on the interepidemic period (*SI Appendix*, Fig. S6). These theoretical results indicate that both mechanisms may generate broad dynamical features of our paramyxovirus case studies. In the next section, along with the no interaction model (as "null model"), we fit these two models to the time series of case reports to select the most parsimonious model to explain RSV, HPIV, and hMPV dynamics.

**Parameter Estimation and Model Selection.** We begin parameter estimation by fitting the single-disease seasonally forced SIR model (i.e., no interaction model) for each strain separately [a detailed discussion of the observation model, baseline parameter values (*SI Appendix*, Table S1), parameter estimation, and model selection methodology is given in *Materials and Methods* and *SI Appendix*]. The single-disease SIR model gives a good fit to timing and size of RSV peaks, a poor fit to the biennial dynamics of HPIV-1 and HPIV-2 (the goodness of fit being negative), a moderately accurate fit for HPIV-3 (*SI Appendix*, Fig. S7 and Table S2), and good predictive power for hMPV (results in *SI Appendix*).

The two-disease cross-immunity model fits well to the paired datasets with RSV and each serotype of HPIV (Fig. 2), describing the high annual peak of RSV and the relatively small biennial peaks of HPIV (Fig. 2 *A* and *B*). The estimated strength of cross-protection (*SI Appendix*, Table S2) suggests that strong cross-protective immunity created by RSV on HPIV serotypes 1 and 2 shapes the biennial abundance pattern in these serotypes. The model also captures the behavior of the pair of RSV and HPIV-3, describing relatively lower annual peaks of HPIV-3. The cross-immunity model also captured the dynamics of the paired dataset of RSV and hMPV (*SI Appendix*, Fig. S9).

The two-disease convalescence model, in contrast, broadly fails to simultaneously explain the dynamics of RSV and serotypes of HPIV (*SI Appendix*, Fig. S8), although it exhibits a biennial oscillation at low convalescence rate and the annual peaks of HPIV-3 at a higher convalescence rate (*SI Appendix*, Table S2). This model does provide a relatively better fit for the hMPV data. However, the error profile of the convalescent parameter θ for all three estimations in *SI Appendix*, Fig. S13 indicates that the convalescence mechanism has less influence in explaining the paired RSV–HPIV datasets.

Altogether, the data suggest that the dynamics are shaped, in part, by interactions among strains and the cross-immunity hypothesis (*SI Appendix*, Table S2). Confidence intervals, best-

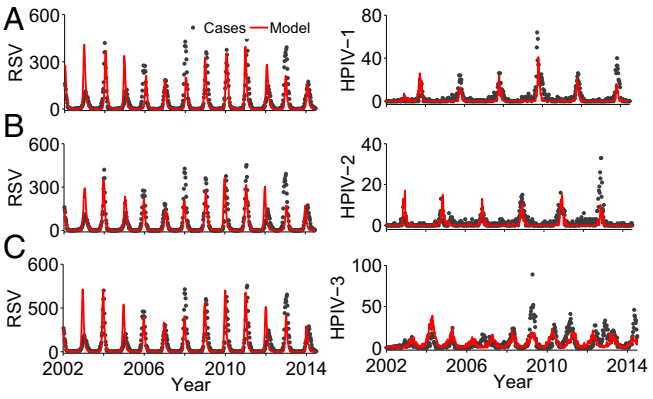


**Fig. 2.** Dynamics with best-fit parameters of the two-disease cross-immunity model showing pairwise (*Left*) RSV and (*Right*) HPIV serotypes: (*A*) RSV and HPIV-1, (*B*) RSV and HPIV-2, and (*C*) RSV and HPIV-3. The model captures the timing and peak of all pairs of datasets, including the biennial pattern of HPIV-1 and HPIV-2.

fitting parameter values, and AIC index for all models are given in *SI Appendix*, Figs. S15–S18 and Tables S2 and S5.

Although HPIV-1 and HPIV-2 are less common among hospitalized cases, they could have a strong interaction among the potentially many more less severe cases. The outbreaks of these two serotypes are separated by the outbreak of RSV in alternate years. Therefore, we further extended the SIR model to a three-strain model to check if including the full web of potential interactions better explains the dynamics of these three pathogens. However, the three-disease model does not explain the data better than the two-disease cross-immunity model (*SI Appendix*, Table S3), perhaps because the resultant model has many parameters relative to the total amount of data available.

To investigate further statistical limitations on inference, we compute the correlation matrix among parameters (obtained from inverting the Hessian matrix) (*SI Appendix*, Fig. S11). We also represent the two-parameter profile ($\varepsilon_P - \varepsilon_R$) of normalized error from each paired dataset (*SI Appendix*, Fig. S12). As is to be expected from this type of mechanistic model, there is substantial multicollinearity among parameters.

## Discussion

Understanding the dynamics of multiple infections that cocirculate in a community helps to forecast disease outbreaks and aids disease management. Respiratory pathogens that cocirculate in a population or co-occur within individual hosts may serve as cofactors that shape outbreaks and modulate attack rates (30). Despite their high prevalence, detecting interactions among respiratory pathogens remains a challenge to public health programs and disease management.

This study focuses on the common respiratory pathogens RSV, HPIV, and hMPV, all members of the paramyxovirus family, that cocirculate in the greater Salt Lake City area of Utah [including other Intermountain Healthcare (IHC) facilities] and explores possible interaction among them. We fit a hierarchy of multistrain disease models to the time series of incidence data to evaluate mechanisms that shape their dynamics. Our results indicate that seasonality in transmission is an important driver of intraannual variation in weekly incidence. The no interaction model (null model) cannot explain the pattern of HPIV serotypes in our data, although the seasonally forced SIR model does exhibit biennial oscillation in a different parameter regime (such as that governing the dynamics of measles) (47).

The immunity from natural infection is transient in these infections (lasting for around 1 y), which has a significant influence on the possible dynamics of the no interaction model. Allowing greater statistical flexibility by freely estimating the duration of immunity from the data permits biennial dynamics (*SI Appendix*, Fig. S14). However, the required estimated periods of immunity for HPIV-1 and HPIV-2 are 8.74 and 5.82 y, respectively (*SI Appendix*, Table S4), which are inconsistently long compared with available clinical data. We, therefore, base our general analysis on a shorter duration of immunity as consistent with previous models of these respiratory viruses (19, 20).

Among the mechanisms of disease interaction considered, we find the strongest support for transient cross-immunity among strains. Ecological interference through convalescence can affect phase differences in the dynamics of interacting pathogens but generally does not alter pathogen outbreak periodicities (46). We find that the cross-protective mechanism can modulate both peak size and timing of RSV (annual) and HPIV-1 and HPIV-2 (biennial) outbreaks, indicating that phase association is the key dynamical signature of interaction. This immunological interaction has also been observed for other multistrain pathogens, like dengue (37, 48, 49).

We find that RSV infection generates pronounced cross-protective immunity on each HPIV serotype and hMPV, although the reciprocal effects on RSV appear much smaller. These interactions combined with seasonality point toward a dynamic regime, where RSV dynamics may be largely autonomous with clear annual peaks that then drive or modulate the dynamics of the other viruses. Our best models could not capture the higher peak in 2009, which is especially pronounced in the hMPV data (*SI Appendix*, Fig. S9). The higher peak size in 2009 is likely, at least in part, the result of increased surveillance because of the pandemic H1N1 influenza (swine flu) outbreak in that year (50).

We checked the identifiability of important interaction parameters in the two-disease cross-immunity model by relaxing the assumption regarding reporting probabilities. We found that undernotification does not significantly impact the key signature in the pattern of temporal dynamics of these pathogens, except outbreak size. Our results indicate that pathogen interactions remain identifiable in the incidence data, even when the extent of underreporting is not known and must be estimated along with other parameters.

Interestingly, our cross-immunity estimates correlate broadly with the distribution of these viruses within their phylogenetic tree (ref. 1, p. 242). RSV belongs to the subfamily *Pneumovirus*, most distant from the subfamily *Rubulavirus* that includes HPIV-2. In contrast, hMPV belongs to the subfamily *Metapneumovirus*, and HPIV-1 and HPIV-3 belong to the subfamily *Respirovirus*, both closer to *Pneumovirus*. Our estimates mirror this pattern of taxonomic proximity. The estimated cross-protective immunity of RSV on HPIV-2 is lowest and higher for more closely related pathogens, such as HPIV-1, HPIV-3, and hMPV (Fig. 3). The estimated strengths of cross-immunity on RSV are weaker and do not clearly follow this pattern, perhaps because of lower power to estimate these effects or epidemiological dominance of RSV.

Although we suspect that other two-way interactions, such as those between HPIV-1 and HPIV-2, could be important, our time series are likely too short for these less commonly reported infections to provide accurate inference. Similarly, models involving more complex interactions among more than two viruses proved less accurate, again perhaps because of the limitations of the data. In addition, as always with mechanistic ecological models, correlation among certain parameters causes identifiability issues.

Stochasticity could provide another reason for the better parameter estimates involving HPIV (51). Our deterministic models of unbroken chains of transmission better fit RSV incidence during annual outbreaks, whereas HPIV spends a significant fraction of time in the stochastic regime with low numbers of infections or fluctuations in reporting (7). With appropriate assumptions, a fully

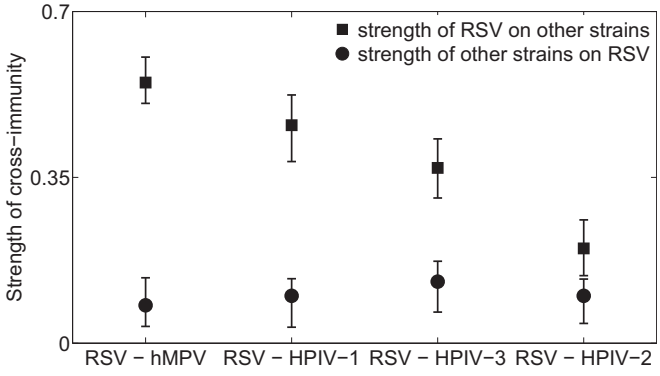


**Fig. 3.** Strength of cross-protective immunity showing $1 - \varepsilon_P$ and $1 - \varepsilon_R$ from the two-disease cross-immunity model with RSV and each serotype of HPIV and with hMPV. The viruses are arrayed from left to right in order of increasing distance from RSV in the phylogenetic tree (1). The cross-protection from the other virus on RSV is low and similar. The error bars indicate uncertainty in the estimates of cross-protection parameters.

stochastic model could be better fit to these same data to perhaps allow better estimations of parameters.

Biologically, we make several restrictive assumptions. Our two-disease cross-immunity model is deliberately simple, and we focus on interactions that only modulate host susceptibility, although it can act in other ways, such as reducing infectiousness. We also treat each virus as a single entity, although they have substantial genetic variability and potentially, multiple serotypes (52). Furthermore, concurrent or prior infection with heterotypic pathogens may modify host susceptibility, transmissibility, virulence, and infection duration, with concomitant impacts on epidemiology.

Previous studies have indicated that epidemiological interference can potentially have important consequences for the design of effective immunization schemes (53). Currently, there are no vaccines for RSV or HPIV, although research is underway (18, 54, 55). Our work could aid in timing vaccination to make optimal use of interference.

## Materials and Methods

**Time Series Data.** The data presented in the paper (Fig. 1) are weekly case reports of respiratory virus results (RSV and serotypes of HPIV from 2000 to July of 2014 and hMPV from 2007 to July of 2014) from all IHC laboratories (22 hospitals and a medical group with more than 185 clinics) in the states of Utah and Idaho in the intermountain west with a population of ∼3 million in 2011 (56). During the study period, direct respiratory sampling (mainly saline-assisted nasopharyngeal aspiration) for respiratory viral testing was performed on children admitted in the clinic or hospitals with respiratory complaints. The test methods were enzyme immunoassay for RSV, direct fluorescent antibody strain, culture, and/or PCR. Test methods differ in sensitivity and turnaround time. Testing algorithms vary across IHC facilities, with some facilities using automatic reflex testing to more sensitive methods (e.g., direct fluorescent antibody to PCR), whereas other facilities require a clinician order for a more sensitive method to be performed. Results of testing are aggregated into a single patient encounter, even if multiple tests are performed. The RSV epidemic year was defined to be from July 1 of the year to June 30 of the following year. This time period was chosen to place the beginning date close to the middle of the interepidemic period, approximately 6 mo from the average historical peak of the seasonal epidemic. This study was reviewed by the Institutional Review Boards of IHC and the University of Utah and determined by both organizations to be exempt.

**Model.** The full set of equations and the descriptions of all three models (cross-immunity, convalescence, and no interaction) are given in *SI Appendix*. Here, we outline how the interaction mechanisms are implemented in the model framework.

**Cross-Immunity.** The precise immunological mechanisms of cross-protective immunity between strains of paramyxoviruses are not yet known. Our models incorporate a parameter to reflect the strength of cross-immunity between strains that is assumed to hold for the same duration as for the primary pathogen but with lesser effect. We also assume that partial cross-immunity acts as reducing susceptibility to other pathogens. Usually, the acquired immunity from infection protects the individual from original pathogen, but the same immunity may work for other antigenically related pathogens, and hence, the host will be rarely infected by such strains. Thus, two strains interact by conferring some protection to the host against other strains. Here, we assume that cross-protective immunity has the same duration for the related and original pathogens. In our main analysis, we follow clinical data that suggest that immunity lasts for around 1 y. However, in the analysis in *SI Appendix*, we allow this parameter to vary freely to be estimated from time series data.

**Convalescence.** This interaction between strains arises by competition for susceptible hosts and the temporary removal of individuals after infection because of quarantining or convalescence (43, 44, 53). In respiratory viral infections, such as RSV, child patients are often sent home or to the hospital until they are recovered or cured. We incorporate a parameter for the decreased likelihood of acquiring another infection during the convalescent period.

**Observation Model, Parameter Estimation, and Model Selection.** We estimate transmission rate, seasonality, interaction parameters, and reporting probability along with initial conditions for all different models using the time series data from the years 2002–2014. The reporting probability (i.e., observation model) is modeled in the following way: if $T_{i,t}$ is the total number of newly infected in week $t$ for pathogen $i$, and $f$ is the reporting probability, then weekly case notification is assumed to have been drawn from a Poisson distribution with mean $fT_{i,t}$. We estimate parameters of two-disease models using pairs of time series and parameters of three-disease models using data of RSV, HPIV-1, and HPIV-2. We minimize the negative of log likelihood to estimate on the best parameter values that describe the case data and use the Akaike Information Criterion (57) to evaluate the parsimony of competing models. Detailed descriptions of the likelihood function and model selection methodology are given in *SI Appendix*.

**Sensitivity Analysis.** We find confidence intervals of estimated parameters using generalized cross-validation (*SI Appendix*, refs. 8 and 9). In this case, we generate 100 samples by randomly partitioning the entire dataset into two subsets (training set and test set) and validate parameter estimates on the test set. Three different partitions (70%, 80%, and 90%) were used in each case. Details are in *SI Appendix*.

We also use rms error to calculate the mean deviance for error profile. We calculate rms error from 10 sample model fits and average these to calculate the mean deviance. Details are given in *SI Appendix*.

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