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The transmission dynamics of groups A and B human respiratory syncytial virus (hRSV) in England & Wales and Finland: seasonality and cross-protection

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SUMMARY

Human respiratory syncytial virus (hRSV) transmission dynamics are inherently cyclical, and the observed genetic diversity (between groups A and B) also appears to have a repeating pattern. A key unknown is the extent to which genetic variants interact immunologically, and thus impact on epidemiology. We developed a novel mathematical model for hRSV transmission including seasonal forcing of incidence and temporary intra- and inter-group partial immunity. Simultaneous model fits to data from two locations (England & Wales, UK, and Turku, Finland) successfully reproduced the contrasting infection dynamics and group A/B dominance patterns. Parameter estimates are consistent with direct estimates. Differences in the magnitude and seasonal variation in contact rate between the two populations alone could account for the variation in dynamics between these populations. The A/B group dominance patterns are explained by reductions in susceptibility to and infectiousness of secondary homologous and heterologous infections. The consequences of the observed dynamic complexity are discussed.

INTRODUCTION

Respiratory syncytial virus infection in humans (hRSV) is ubiquitous, the major viral cause of severe acute respiratory infection in childhood worldwide, and estimated to be responsible for 160 000 deaths per year [1]. The virus exhibits considerable genetic variability, primarily in the attachment (G) glycoprotein [2]. This variability is reflected antigenically, and hRSV can be divided into two groups (A and B) on the basis of reactions with panels of monoclonal antibodies [3, 4]. Children usually experience their first infection before the age of 2 years, and re-infection is a common occurrence in older children and also in adults [5–9]. Disease resulting from infection occurs principally in young children, particularly following primary infection [5, 10, 11] but is also observed in vulnerable adults. The reduced severity, with increasing age, is presumably in part a result of developing immunity to disease, but also in part physiological, i.e. older children have larger airways [12]. Clearly immunity is not necessarily protective against re-infection, but it is unclear to what extent immunity to disease or re-infection is group specific [2, 13].

The epidemiology of hRSV disease is characterized by marked seasonal patterns. In the United Kingdom, the annual epidemic peaks between late December

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and early January, and a cyclic, triennial pattern in genetic variation in groups A and B has been observed in Birmingham, UK [2, 14]. The transmission of hRSV in Turku, Finland has followed a distinctive quadrennial pattern for the past 20 years [15]: every 2 years there is a minor peak in April followed by a major peak in December. The group dominance alternates every 2 years. These observations taken together suggest that there is a potentially complex relationship between viral genetic variation, infection/disease and transmission dynamics. The consistency of the patterns is suggestive of an underlying mechanism that we attempt to understand better.

The characteristic recurrent epidemics of hRSV are, on the whole, observed through hospital surveillance, with cases consisting predominantly of young children experiencing severe disease from their primary infection [2]. Epidemics have been recorded in community and family study settings, and the link between elder school siblings and primary infant cases is strong [6, 16, 17]. However, the exact role of re-infection in the maintenance of hRSV transmission in communities, and hence the relationship between (observed) epidemics of primary infections and (unobserved) seasonal epidemics of re-infection in the general population is not clear.

The fact that, globally, the observed period of hRSV epidemic behaviour is a natural number (i.e. positive integer) suggests annual forcing. That is, having taken account of the number of infectious individuals, the remaining component of the risk of infection would vary throughout the year based on annually varying factors. The alternative explanation would be that transmission dynamics (created by interplay between susceptibility and infection) have sustained oscillations of period n years. However, sustained oscillations are rarely obtained from epidemiological models without seasonal forcing [18]. Models including the interaction between strains (i.e. cross-immunity between types) can produce sustained oscillations [19, 20] with the frequency of the oscillations defined by the parameters of the model. It is highly unlikely that these values would combine to give a period of precisely n years (n being a natural number), especially where n varies between regions.

Previous epidemiological models including seasonal forcing have reproduced observed hRSV dynamics [21] for both regular and irregular general periodic behaviour [18]. Models have also been used to consider the interaction between multiple strains or species and its effect on the behaviour of the whole biological system [22, 23]. We consider a model with seasonal forcing as implemented previously [21], but extended to include groups A and B and their influence on each other via re-infection and cross-immunity.

As far as we are aware, this is a first attempt to fit a seasonally forced, multiple strain model to specific data. We do so with the objectives of understanding the roles of interaction and transmission seasonality in determining the observed epidemics of disease, and developing hypotheses for further study.

Model structure

A schematic representation of the deterministic compartmental mathematical model or the transmission of the two groups A and B structure is shown in Figure 1, and written as a set of differential equations:

$$\left.\begin{aligned}
&\dot{X} = \mu - (\lambda_A + \lambda_B + \mu)X + \omega(X_A + X_B)\\
&\dot{P}_i = \lambda_i X - (\nu + \mu)P_i\\
&\dot{X}_i = \nu(P_i + Y_i) - (\sigma_{ho}\lambda_i + \sigma_{he}\lambda_j + \omega + \mu)X_i\\
&\qquad + \omega X_{AB}\\
&\dot{P}_{ji} = \sigma_{he}\lambda_i X_j - (\nu + \mu)P_{ji}\\
&\dot{Y}_i = \sigma_{ho}\lambda_i X_i - (\nu + \mu)Y_i\\
&\dot{X}_{AB} = \nu(P_{ij} + P_{ji} + Y_{ij} + Y_{ji})\\
&\qquad - (\sigma_{he}\sigma_{ho}(\lambda_A + \lambda_B) + 2\omega + \mu)X_{AB}\\
&\dot{Y}_{ji} = \sigma_{he}\sigma_{ho}\lambda_i X_{AB} - (\nu + \mu)Y_{ji}\\
&\lambda_i = \beta_i(P_i + \eta(P_{ji} + Y_i + Y_{ji}))\\
&\beta_A = b_A(a\cos(2\pi(t - \phi)) + 1)\\
&\beta_B = r\beta_A\\
&(i,j) \in \{(A,B),(B,A)\}
\end{aligned}\right\} \quad (1)$$

The symbol i is used to represent the groups A and B, and where i and j occur in the same equation they represent the two different groups. Tables 1 and 2 summarize the definitions of the variables and parameters respectively of the system.

The model describes infection and re-infection of the two main groups (or subtypes) of RSV, A and B, with duration of subsequent infection equal to duration of primary infection. The role of maternal antibodies in the transmission of hRSV at the population level is uncertain. It has been shown that higher levels of maternal antibodies are associated with increased protection from clinical infection [24], but this association is partial and probably short term (maternal antibodies are only present for 3–6 months [25]). For the purposes of the model presented, it is assumed that maternal antibodies have negligible effect on the transmission of the virus in the whole population. To keep the population size constant, children are born into the susceptible class, X at a rate equal to the

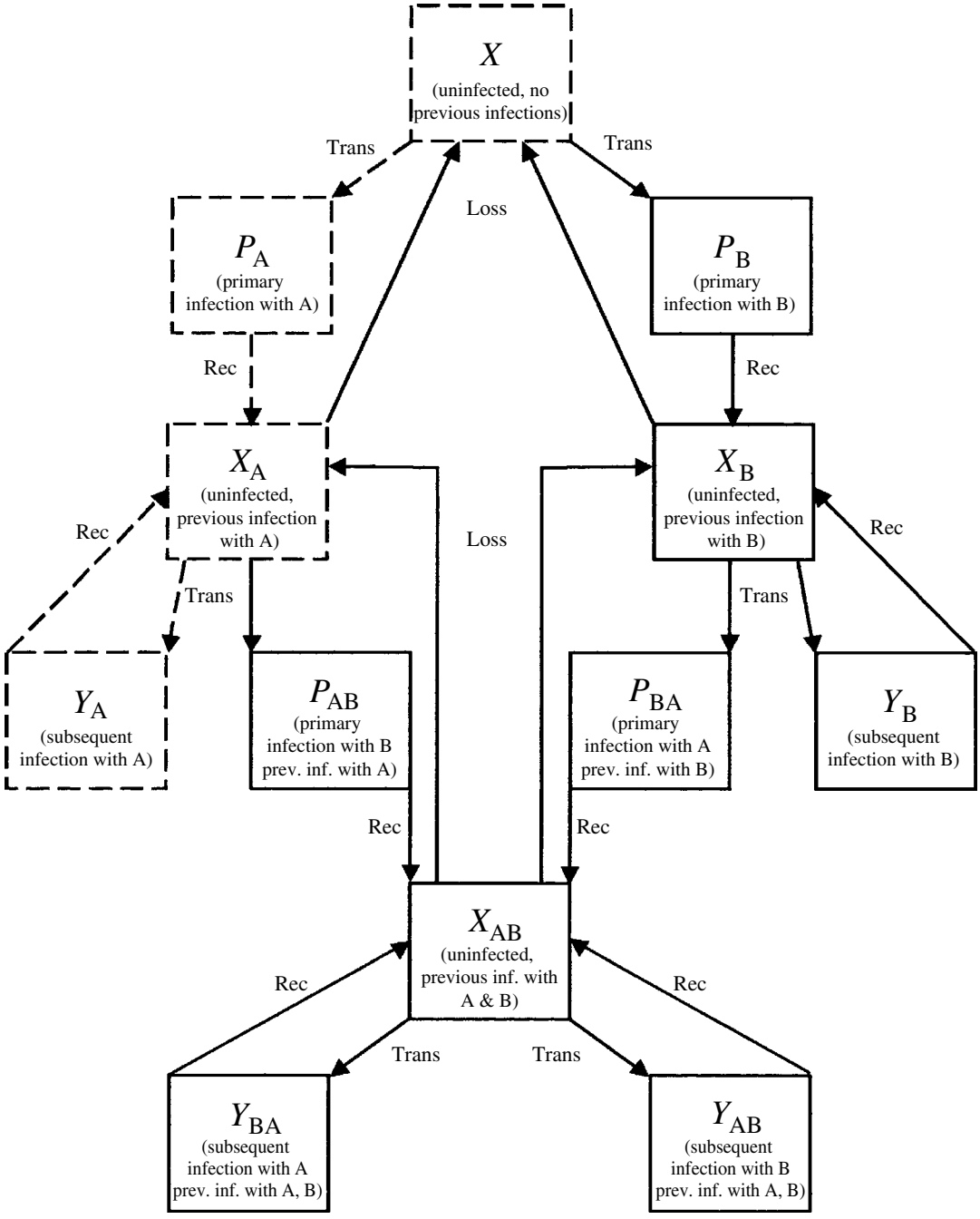

Fig. 1. The transmission model structure as defined in eqn (1) and Tables 1 and 2. The underlying single group model is dashed (see text). The boxes represent the state variables and the arrows represent the transitions between the states, labelled as: Trans = transmission; Rec = loss of infection (recovery); Loss = loss of immunity.

inverse of the average life expectancy for the population. They are then susceptible to a primary infection with group A or B hRSV. If infected they enter the primary infected class, e.g. P_A, and recover at rate ν into a class of individuals previously infected with one group, e.g. X_A. The duration of infection is fixed (i.e. not estimated) at 9 days [21].

Susceptible individuals who have experienced a primary infection may be re-infected with the same group (e.g. entry into class Y_A) or undergo a primary infection with the alternative group (e.g. entry into class P_{BA}). If the individual is re-infected with the same group, when they recover they re-enter the class of those previously infected with one group, e.g. X_A.

Table 1. *Model variables*

Variable	Definition
X	Proportion of hosts uninfected with no previous hRSV infection
X_A	Proportion of hosts uninfected with a previous infection with group A
X_B	Proportion of hosts uninfected with a previous infection with group B
X_{AB}	Proportion of hosts uninfected with previous infections with both groups A and B (order not considered)
P_A	Proportion of hosts infected with group A and no previous infection
P_B	Proportion of hosts infected with group B and no previous infection
P_{BA}	Proportion of hosts infected with group A and a previous infection with group B
P_{AB}	Proportion of hosts infected with group B and a previous infection with group A
Y_A	Proportion of hosts infected with group A and a previous infection with group A
Y_B	Proportion of hosts infected with group B and a previous infection with group B
Y_{BA}	Proportion of hosts infected with group A and previous infections with groups A and B
Y_{AB}	Proportion of hosts infected with group B and previous infections with groups A and B
λ_A	Force of infection of group A acting on naive hosts
λ_B	Force of infection of group B acting on naive hosts
β_A	Seasonally varying transmission coefficient for group A
β_B	Seasonally varying transmission coefficient for group B

Table 2. *Model parameters*

Parameter	Definition	Location	Estimate
Global parameters (fixed between locations)			
r	Group B average transmission coefficient relative to b_A		0·9159
η	Altered infectiousness factor		0·4126
σ_{ho}	Altered susceptibility to homologous secondary infection		0·3569
σ_{het}	Altered susceptibility to heterologous secondary infection		0·8426
ν	Recovery rate*		40·56 yr^{-1}
ω	Rate of loss of partial immunity		0·51 yr^{-1}
Local parameters (variable between locations)			
b_A	Group A average transmission coefficient	E&W	113·99 $capita^{-1}$ yr^{-1}
		Finland	99·51 $capita^{-1}$ yr^{-1}
μ	Birth rate*	E&W	0·014 yr^{-1}
		Finland	0·012 yr^{-1}
ϕ	Point in the year of peak transmission coefficient	E&W	0·929
		Finland	0·97
a	Amplitude of transmission coefficient	E&W	0·815
		Finland	0·347
s_f	Scaling factor†	E&W	397·3
		Finland	6·638

* Not estimated from the model fit but from another source (see text).
† Restricted to within limits (see text).

If the individual is infected with the alternative group, when they recover they enter the class of individuals previously infected with both groups, X_{AB}, where they are susceptible to re-infections with either group.

Individuals in the classes X_A and X_B are subject to proportionally altered forces of infection from homologous (proportion σ_{ho}) and heterologous (proportion σ_{he}) viruses. This partial immunity is also temporary since we assume that this effect lasts on average for the inverse of the rate ω, i.e. the rate of waning specific and cross-reacting immunity is equal and group independent. A similar situation exists for those individuals in class X_{AB}: since they have experienced both groups they are subject to a reduced force of infection by the proportion $\sigma_{he}\sigma_{ho}$ and lose the immunity of previous infection by each group independently at the rate ω (i.e. the total rate of loss of immunity is 2ω). Finally, individuals undergoing

re-infection, e.g. Y_A, P_{AB} and Y_{AB}, have a uniformly modified (lower) infectiousness, by factor η.

In summary, the model includes four aspects of immunity: altered susceptibility to homologous infections (infections of the same group as previous infection); altered susceptibility to heterologous infections (infections of the different group from previous infection); altered infectiousness of secondary infection with the virus (not group specific); waning of the previous three effects. It should be noted that the model describes what is in effect a 'memory' of past infections that, in time, wanes. As such, individuals can re-enter the susceptible class, X, in which all 'memory' of past exposures has been lost, and can again experience a 'primary' infection.

The group-specific force of infection, λ_i, is dependent on the proportions of individuals infected, with primary infected individuals (P_A and P_B) making a higher contribution than those undergoing re-infections (Y_A, Y_B, P_{AB}, P_{BA}, Y_{AB} and Y_{BA}) as determined by parameter η. The force of infection is also dependent upon some measure of the potential for transmission that is dependent upon time, and is captured in the term, β. This transmission coefficient varies seasonally, with the timing of the peak determined by ϕ varying between 0 (=1 January) and 1 (=31 December), and amplitude determined by a varying between 0 (=constant throughout year) and 1 (=transmission coefficient in the trough being 0). The seasonality component is assumed to influence both groups equally. We allow the transmission term to be group specific (i.e. β_i) due to variation in infectivity, and estimate the relative infectiousness of group B to group A with the parameter r. The basic reproduction number of the primary infection with group A is given as:

$$\bar{Q}_A = \frac{b_A}{(\nu+\mu)}. \tag{2}$$

We are also interested in the role of primary infections, and so define the following quantities:

$$u_i(t) = \frac{P_i}{P_i + P_{ji} + Y_i + Y_{ji}} \tag{3}$$

and

$$V(t) = \frac{\beta_A P_A + \beta_B P_B}{\lambda_A + \lambda_B}. \tag{4}$$

The proportion of prevalent group A infections at time t that are primary infections (i.e. that are infected individuals without immunity) is given by $u_A(t)$. The proportion of incident hRSV infections that arise from primary infections is given by $V(t)$.

Data

Time-series data of hRSV hospitalizations come from two countries, the United Kingdom and Finland. For each the data are the weekly number of reported cases, and the proportion of samples that are group A. The UK data comprise (i) hRSV hospitalizations for England & Wales, reported weekly to the Communicable Disease Surveillance Centre over the period 1991–2000, and (ii) the annual proportion of samples taken from Birmingham Heartlands Hospital (a subset of the total) that are group A between 1989 and 2001 [14]. The Finnish data comprise (i) weekly hRSV hospitalizations for the Turku region from 1980 to 2001, and (ii) the proportion of monthly samples taken from the same region that are group A for the time periods surrounding the major and minor peaks from 1980 to 2000 [15].

Data scaling and model fitting

Since the weekly incidence data are hospitalizations, and assumed to be predominantly primary cases, we use a scaling factor to multiply the predicted primary incidence of hRSV from the model $[(\lambda_1+\lambda_2)X]$ to compare with observation. The scaling factor, s_f, is given as:

$$s_f = \mu N c A \Delta t, \tag{5}$$

The components of s_f are defined and evaluated as follows. The inverse of the average life expectancy, μ, is obtained from the life expectancy for each country [26]. The population size, N, from which the data originates is $7{\cdot}5 \times 10^5$ for Finland [27] and $5{\cdot}6 \times 10^7$ for England & Wales (ONS, Population Estimates Unit). The percentage of primary hRSV cases that are hospitalized, c, is taken to be 2·45 [21]. The time between samples in years, Δt, is 1/52. If the maximum age of hospitalized children is given by A (between 1 and 2 years) then the scaling factor would be between 4·2 and 8·4 for Finland and 350 and 700 for England & Wales. Simultaneously, the predicted proportion of group A incidence $[\lambda_1/(\lambda_1+\lambda_2)]$ was fitted to the proportion of samples of group A.

The model was fitted with parameters including 'social' processes made specific to the location, and those including biological processes not location specific (referred to as local and global parameters

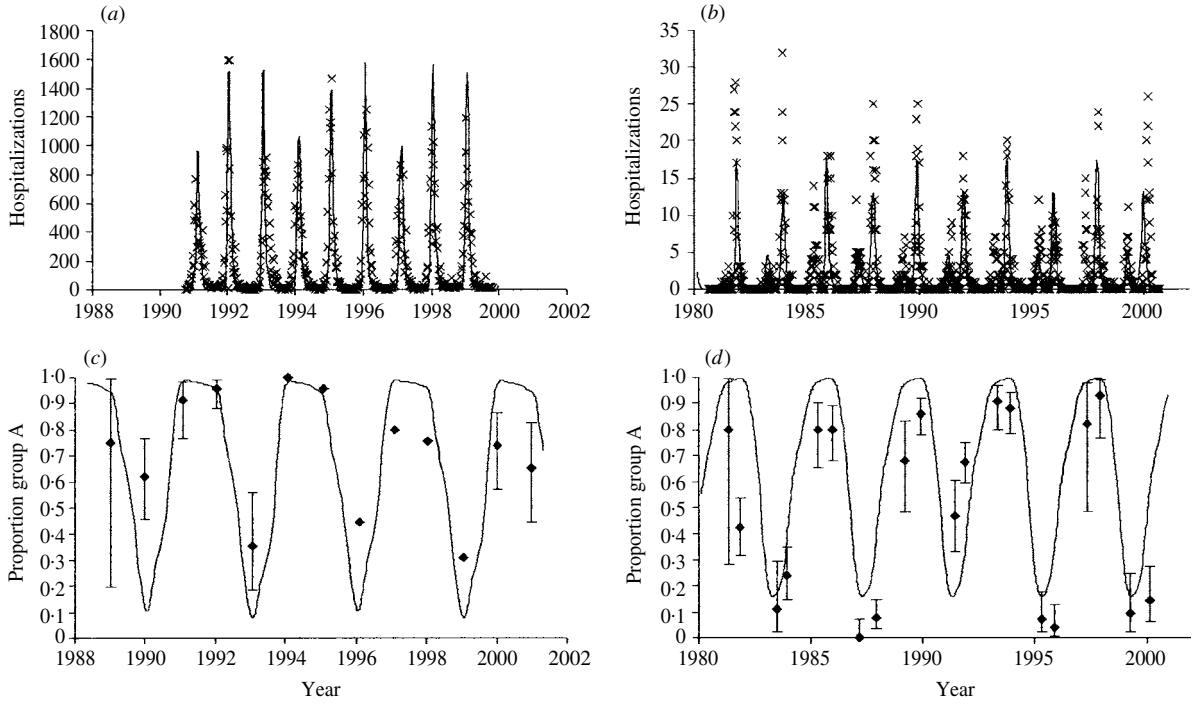

Fig. 2. Graphs of the model fit to the time-series data on hRSV hospitalizations for two country locations. The weekly hospitalizations (shown as crosses) in England & Wales (*a*) and Turku (*b*) with the model predictions (solid line). The proportion of typed samples that were group A in England & Wales (*c*) and Turku (*d*), shown as solid diamonds (with exact binomial 95% confidence interval where possible) and the corresponding predicted proportion from the model (solid line).

respectively in Table 2). The model was fitted using Berkely Madonna [28], which minimizes the root mean square deviation (RMSD) of the model prediction from the data using the simplex method [29]. Numerical algorithms were validated in MatLab [30]. We present stable limit cycle results, thus avoiding the complication of estimating unknown initial conditions since, because the equations are seasonally forced, the seasonal patterns are repeated.

RESULTS

The parameter estimates are given in Table 2, and the graphs in Figure 2 show the best fit to the datasets. Generally, the model reproduces both the epidemic patterns and the group A dominance time series in both locations.

The estimates of the global parameters relate primarily to the natural history of infection in the individual (Table 2, upper section). Immunity is temporary and lasts on average for approximately 2 years (i.e. temporary immunity wanes at the rate of 0·51 per person per year). During the period of immunity, individuals experience a reduction in the rate of infection by homologous group virus to 0·36 relative to uninfected individuals, i.e. a 64% reduction in the relative *per capita* incidence. This effect is less pronounced for heterologous re-infection, i.e. an individual infected with one group recovers to a partial immune state in which re-infection incidence with the heterologous group is reduced to 0·84 (a 16% reduction). Hence we estimate the effect of homologous (or group-specific) immunity to be four-fold greater than heterologous (or cross-) immunity. Infected individuals who have experienced at least one prior infection are predicted to be less infectious compared to primary infections by a factor of 0·4, i.e. on average they are 60% less infectious. There is little asymmetry in transmissibility between groups: group A is estimated to be 1·09 times more transmissible than group B.

The estimates of the local parameters reveal differences between the two populations (Table 2, lower section). The seasonally varying transmission coefficient showed a greater mean and variance in England & Wales (Fig. 3*a*, *b*). The estimates of the average basic reproduction numbers of primary group A infection are 2·81 (England & Wales) and 2·46 (Finland). However, the peak in the transmission coefficient was more similar, estimated to fall approximately on 5 and 20 December in England & Wales and Turku respectively.

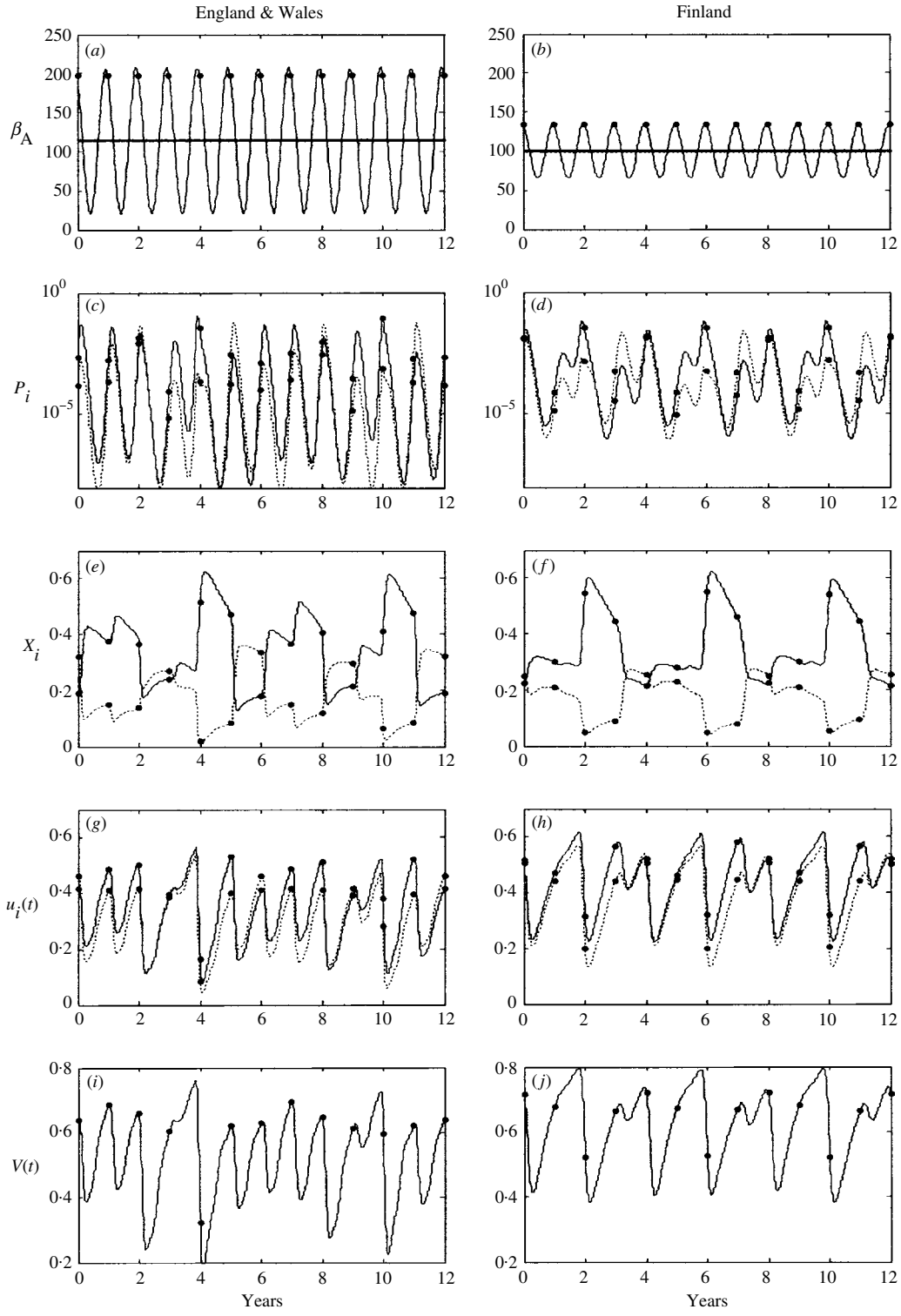

Fig. 3. Illustrations of the dynamics of the fitted models. Left-hand panels are for England & Wales, right-hand panels for Turku. In each panel the solid symbols (●) represent the start/end of each year, the peak in transmission occurs just before them, and the simulations are run over 12 years. (*a*, *b*) The seasonal transmission coefficient for group A (β_A). The horizontal line is the mean transmission coefficient. (*c*, *d*) The proportions of the population with primary infections with group A (——) and group B (·····), P_A and P_B respectively. (*e*, *f*) The proportions of the population with immunity to group A only (——) and group B only (·····), X_A and X_B respectively. (*g*, *h*) The proportion of group A infections that are primary infections (u_A, ——) and the proportion group B infections that are primary infections (u_B, ·····). (*i*, *j*) The proportion of hRSV infections derived from primary infections (V).

The transmission dynamics of the two groups in the two locations are illustrated in Figure 3. The interactions between seasonal forcing and cross-immunity create complicated, repeated patterns. In England & Wales, the combined effect is essentially a limit cycle with a 6-year period (i.e. the population returns to its original state every 6 years). However, careful inspection of Figure 3 (c, e, g) shows that the pattern generated is actually more complicated, i.e. a 12- or 18-year cycle. The dynamics in Finland are based on a 4-year period. However, these simulations are very sensitive to specific parameter values, and a small change in estimate (well within believable values) can produce a large effect in dynamic terms.

The effect of the increased amplitude of the transmission coefficient in England & Wales can be seen particularly in the troughs (between epidemics, in summer months), where the prevalence of primary infection reaches two orders of magnitude lower than in Finland (Fig. 3 c, d). The dynamic patterns are most clearly illustrated by considering the proportions of the population that are immune to one group only (Fig. 3 e, f). Note that these individuals can arise either from infection with one group only or from loss of immunity following infection with both virus types. The pattern clearly demonstrates the asymmetry, i.e. more individuals have been infected with group A only than group B only in 2–3 years (England & Wales) and 3–4 years (Turku). It also demonstrates the competition between groups in that the lines are highly negatively correlated (increasing X_A implies decreasing X_B and vice versa). Simulations with $r = 1$ (not shown) show complete symmetry, thus demonstrating that a relatively small difference in the transmission potential can have a large impact.

Generally, prevalent primary infection represents between 20% and 60% of the total prevalent infections by group (Fig. 3 g, h). Because primary infections are estimated to be more infectious, they are generally responsible for between 40% and 80% of all infections (Fig. 3 i, j). The lowest values tend to occur during the summer months, i.e. infection from non-primary infections appears to be responsible for maintaining infection during non-epidemic periods.

DISCUSSION

The combination of the effects of acquired immunity and seasonal transmission are able to reproduce the main features of hRSV epidemiology for two contrasting time series from two separate locations. The analysis provides the first estimates of the competitive relationship and cross-immunity between groups from population level data. Following infection, individuals gain transient immunity of average duration 2 years. This immunity is partial in its efficacy, and greater for homologous challenge (60%) than heterologous (16%). It is further predicted that group A hRSV is slightly more transmissible (8%) than group B.

Seasonal transmission varied between locations in magnitude (b_A), amplitude (a) and phase (ϕ) (timing of the peak). Alteration of the phase shifts the dynamics along the time axis; therefore, variation in phase between locations is not as significant as amplitude and magnitude when considering the dynamics. Different amplitude and magnitude were both necessary to replicate the dynamic behaviours in the two locations. The seasonality in transmission (Fig. 3 a, b) does not necessarily represent alterations in contact rate as is understood for measles [31, 32]. Exploratory fitting of a single group version of the model to the incidence data from Turku (not shown here) indicates that there is a correlation between the phase and temporary immunity, such that the timing of peak transmission (i.e. ϕ) in relation to peak incidence giving a best model fit to the observed data is dependent on the rate of waning of immunity. Consequently, direct, longitudinal estimates of immunity duration are required to specify the contact rate uniquely.

Model simulations suggest a key role for primary infections in hRSV transmission (Fig. 3 g–j), responsible for, on average, 40–80% of incidence, as a result of relatively high prevalence (20–40% of prevalent infection) and infectivity (Table 2). Within the model structure the origin of these primary infections is not only individuals who have never previously encountered hRSV from birth, but also those who have lost all 'memory' of previous exposure and returned to a 'naive' state. Together they comprise class X (Fig. 1) and are indistinguishable epidemiologically (i.e. equally susceptible to infection and equally infectious when infected), although the latter will have a much wider age distribution. Suitable data do not exist by which to validate the model structure. No explicit account is taken of the higher propensity for disease in those experiencing a first infection following birth, though implicitly this is accounted for in the scaling factor by which the model is fitted to hospitalization data. It follows from the above that the model results should not be regarded as suggesting a central role in hRSV epidemiology for young children

experiencing their first ever RSV infection; this remains an open question for further research.

Although we believe that these conclusions are robust, it is important to note that the model is merely one member of a large family of multistrain models [22], a subset of which may also fit the data equally well. Therefore, we cannot assume that a model that provides a fit to the data also provides a description of the underlying biological mechanism. Previous work has shown that several mechanistically distinct models for hRSV can reproduce observed transmission patterns equally well [21]. We suggest, however, that temporary intra- and inter-group immunity in some form would be common to the members of this subset, but we do not intend our simulations (Fig. 3) to be regarded as quantitative predictions.

Although not shown here, we attempted to fit the model with constraints on the parameters' values. The dynamics were successfully replicated when heterologous susceptibility was assumed unaltered ($\sigma_{he}=1$) where the interaction of the groups via altered duration of secondary infection and the increased transmissibility of group A compared to group B were enough to reproduce the dominance patterns. The dynamics of Finland could be replicated when groups A and B were assumed equally transmissible ($r=1$), but this constraint did not result in the replication of the dynamics in England & Wales. The complexity of the model prevented any more formal parameter estimation.

Perhaps the most robust result is the complexity of the dynamics illustrated in Fig. 3. Such complexity is caused by the combination of seasonality and multiple groups, both of which are logically required and necessary for providing a fit to the data. One of the consequences of the complexity is that epidemiological quantities (such as the average age at infection, or the average time between infections) vary considerably with time. The expected outcome of hRSV infection (e.g. age and type of first infection) will also vary for infants by birth season and birth year (in the epidemic cyclical pattern). We plan to explore this dynamic complexity.

We have made the simplest possible assumption regarding virus heterogeneity. The freedom of mathematical modelling in the production of 'n-strain' models [33] (where n can be any natural number) is constrained by the two pragmatic concerns of (1) data abundance/quality and (2) the appropriateness of a deterministic model. The number of types into which the samples can be realistically divided, within the confines of a longitudinal study of the type described in ref. [34], is limited and, therefore, limits the dimension of any useful model. A deterministic model is appropriate only for large population sizes. If the model is expressed in deterministic form, as n increases, the necessary size of a population to be modelled will also increase for a deterministic structure to remain appropriate. For example, a 20-strain model would have in the order of a million compartments and would, therefore, be unsuitable for England & Wales (population of approximately 53 million). Consequently, future attempts to model hRSV are likely to be stochastic and to include specific mechanisms of viral change and immune selection [35]. In the current framework, viral diversity is captured in the parameters σ_{ho} and σ_{he} and viral evolution in ω, assuming that waning immunity is as a result of viral change.

Vaccines providing protection against hRSV infection (or disease) are required and are being developed. Given the antigenic diversity of the virus, an important issue is which antigenic components should be included within a vaccine. Consequently, vaccine design will benefit from an understanding of the role the antigenic diversity of the pathogen plays in the natural history of the disease at both the individual and population levels. Recent work has indicated that groups are not linked to severity of infection, but a clade within group A is [36], although analysis of samples from The Netherlands found that the G protein variation did not correlate with disease severity [37]. Environmental and demographic factors can be strongly correlated with disease severity [38]. There clearly is potential for the antigenic variation in hRSV to interact with the transmission dynamics, although many issues remain to be resolved. For example, what features of population dynamics promote antigenic variation, and what effect does antigenic variation have on transmission dynamics? Further, once putative vaccines are developed, mathematical models can be used to assess the risk of strain replacement [33, 39]. There will probably be other questions such as timing of vaccination (related to seasonal dynamics), and frequency of vaccination (related to rate of drift of antigenic types and duration of immunity).

To obtain a biologically realistic multigroup model for hRSV the follow-up cohort data generated by studies such as described in ref. [34] are required to refine model representation of the natural history of the infection at the individual level. Such data, which

define the influence of prior infection on group and genotype-specific immunity, will allow the further compartmentalization of the virus into types within the groups and realistically parameterize homologous and heterologous type immunity.

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