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Models of contrasting strategies of rhinovirus immune manipulation

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HIGHLIGHTS

- ▶ We develop a detailed model of how rhinovirus interacts with the human immune system.
- ▶ We model the contrasting immunological effects of major and minor group rhinovirus.
- ▶ We predict similar courses of damage but different levels of immunity.
- ▶ Provides a framework for understanding rhinovirus symptoms and pathologies.

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ABSTRACT

Rhinoviruses, consisting of well over one hundred serotypes that cause a plurality of common colds, are completely cleared by the host immune system after causing minimal cell death, but often without inducing long-term immune memory. We develop mathematical models of two kinds of rhinoviruses, the major group and minor group, that use different receptors to enter target cells. Roughly the 90 serotypes in the major group bind to ICAM-1, a molecule that is upregulated on antigen-presenting cells, and alter the timing, location and type of the immune response. The 12 members of the minor group do not so modulate the response. Our model predicts similar virus dynamics for the major and minor groups but with quite different underlying mechanisms. Over a range of key parameters that quantify immune manipulation, disease outcomes lie within a triangle in the plane describing damage and memory, of which the major and minor group form two corners. This model of infection by a highly adapted and low virulence virus provides a starting point for understanding the development of asthma and other pathologies.

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1. Introduction

Rhinoviruses cause a plurality, and often a majority of upper respiratory tract infections in humans (Monto et al., 1987). Unlike infection by influenza or respiratory syncytial virus (RSV) which can be life-threatening in the very old or very young, rhinovirus is a mild and self-contained infection except in patients who are highly immunosuppressed (Heikkinen and Jarvinen, 2003).

Ciliated epithelial cells of the upper respiratory tract and other cell types in these tissues serve as the primary target cells for these viruses (Ghildyal et al., 2005; Winther et al., 1986). In contrast to influenza, which leaves few surviving target cells in its wake, rhinovirus creates relatively little cytopathology (Proud, 2005), even in the foci of infection (van Kempen et al.,

1999). The virus can survive in the lower respiratory tract (Hayden, 2004) with potentially deadly effects in immunosuppressed lung transplant recipients (Kaiser et al., 2006).

Rhinoviruses belong to the family Picornaviridae, a diverse group of positive-sense single-stranded RNA viruses (Hughes, 2004), and to the enterovirus genus (Laine et al., 2005) which includes the potentially much more virulent polioviruses and coxsackieviruses. The rhinoviruses break into three species, HRV-A, HRV-B and the more recently identified HRV-C (Palmenberg et al., 2009). Over 100 serotypes have been distinguished, often showing relatively low levels of immunological cross-reactivity, particularly among more distantly related serotypes (Cooney et al., 1982).

In experimental infections, virus is detectable in nasal discharge after 10 h and rises rapidly thereafter, with nasal symptoms appearing in as little as 2 h (Harris and Gwaltney, 1996). Symptoms peak after 2–3 days (Barclay et al., 1989), and viral titers at around the same time (Douglas, 1970). Natural killer cells (cells of the innate immune system) and the associated cytokine IFN- γ are both at high levels during the first five days of infection

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(Hsia et al., 1990). Shedding of virus declines after about 14 days, not long after the appearance of neutralizing antibodies (Douglas, 1970).

Antibodies are protective against later infection but may not be produced by some infected individuals (Fox et al., 1975; Kirchberger et al., 2007), although data on this point remain incomplete and mixed (Couch, 1996). An early student found that 77% of symptomatic individuals developed antibodies, but only 15% of asymptomatic carriers (Gwaltney et al., 1967). In one study with volunteers, 15 out of 17 or 88% of infected individuals showed a strong response over a full year (Barclay et al., 1989). Infection studies in volunteers may have higher antibody response probabilities (Couch, 1996). In families, adults do have a lower proportion of symptomatic infections, presumably due to antibodies built up over years of experience (Peltola et al., 2008), but this does not mean that an immune response occurs with each infection. The presence of rhinovirus antibodies in 90% of two-year-olds (Kieninger et al., in press) could indicate a partial response because less than 10% of children would be expected to reach age 2 with no infection (Monto et al., 1987).

Rhinovirus antibodies do decay faster than those for influenza, over a period of 2–4 years, and reduce the reinfection rate by about 50% (Couch, 1996). Evidence that antibody responses are only temporary comes from the severe rhinovirus infections suffered by roughly half of otherwise healthy men returning from isolation in the Antarctic. As further evidence of antibody loss, children enrolled in large daycare facilities had more rhinovirus infections at age 2, fewer at age 6, but the same number as other children at age 13, indicating the only temporary response (Ball et al., 2002).

Because of the low level of cell damage, rhinovirus infections do not appear to be target-cell limited. They must therefore be regulated and eliminated by the immune system, but without necessarily generating effective immune memory. Influenza, in contrast, creates both high levels of cell damage and highly effective immunity. The goal of this paper is to gain some insight into this contrast by comparing rhinoviruses that use different receptors to enter cells.

Rhinoviruses in the HRV-A and HRV-B species break into major and minor groups based on receptor usage, with about 90 major and 12 minor group viruses (Palmenberg et al., 2009). All members of HRV-B fall into the major group, and all of the minor group viruses thus fall within HRV-A. The receptor (or receptors) used by HRV-C remains unknown.

Major group HRV bind ICAM-1, a cell adhesion molecule that is upregulated on both target cells (epithelial cells) and a variety of white blood cells in response to inflammatory cytokines released by infected cells (Norkin, 2010; Proud et al., 2008). Although generally not thought to infect white blood cells (but see Laza-Stanca et al., 2006), rhinovirus attachment alters the behavior of these cells with profound effects on the course of the immune response and the viral infection itself (Kirchberger et al., 2007).

When exposed to virus, dendritic cells (DCs), which serve as primary antigen-presenting cells that bring signals of infection to the adaptive immune system, migrate more slowly to the lymph nodes and provide less inflammatory signals. Infected epithelial cells continue to make pro-inflammatory cytokines, thus concentrating the immune response in the periphery, away from the lymph node (Kirchberger et al., 2007).

Multiple mechanisms generate these effects on antigen presenting cells. Viral binding of ICAM-1 blocks binding of the molecule LFA-1. LFA-1 binding creates costimulatory signals that activate T cells, and treatment of DCs with the major group rhinoviruses HRV-16 (HRV-A) or HRV-14 (HRV-B) reduces proliferation of T cells (Gern et al., 1996; Kirchberger et al., 2005).

This reduction is greater when more DCs have been exposed to major group rhinovirus (Kirchberger et al., 2005).

Binding of the major group rhinovirus HRV-14 to monocytes (the pre-cursors of DCs) induces production of the anti-inflammatory cytokine IL-10, and reduces production of pro-inflammatory signals. This cytokine profile, and an associated reduction in antigen presentation, may bias the T cells they activate in turn toward a more tolerant response (Kirchberger et al., 2007). Virally bound DCs also induce production of the inhibitory cytokine IL-35 by T cells (Seyerl et al., 2010). By a separate mechanism, DCs infected with ssRNA from HRV-14 show an interferon response, but do not fully mature, and thus fail to trigger further T cell activation (Schrauf et al., 2009).

The minor group rhinoviruses attach to members of the Low Density Lipoprotein receptor family (Hofer et al., 1994), which are not known to have these complex inhibitory effects on the immune system (Kirchberger et al., 2005). Dendritic cells exposed to the minor group rhinovirus HRV-2 do not slow T cell proliferation (Kirchberger et al., 2005).

From this distinction between major and minor group rhinoviruses, we have derived two key hypotheses.

- Minor group viruses will elicit more immunity
- Minor group viruses will evolve more quickly in antigenic sites

Consistent with the first prediction, major group viruses induce antibodies in a minority of infected individuals, while minor group viruses induce antibodies in a majority (Fox et al., 1985). However, another study observed no difference in the fraction of tonsillar-derived T cells from children that respond to selected major group (HRV-15) or minor group (HRV-1a or HRV-2) viruses (Wimalasundera et al., 1997). In line with the second prediction, positive selection has occurred most commonly among minor group serotypes, and often in sites close to antigenic and receptor-binding locations (Lewis-Rogers et al., 2009).

In this paper we develop a mathematical model of the interaction between rhinoviruses and the immune system to examine whether known mechanisms can explain the distinction between major group and minor group rhinoviruses. We focus on the effects of three key mechanisms on the level of cell damage and host immunity:

1. The rate at which rhinoviruses bind to DCs and thus sacrifice their own future replication,
2. The delay in DCs migration to the lymph node, and
3. The tolerogenic effects of rhinovirus-bound DCs when they do arrive in the lymph node.

We begin by deriving the model, exploring a range of parameter values to see which syndromes can result, and conclude by outlining model extensions and applications.

2. Methods

As in viral dynamics models, we use differential equations to track viruses, infected and susceptible cells (Nowak and May, 2000), and include sets of equations for DCs, and for the two types of effector cells, T cells and natural killer (NK) cells (Fig. 1, Table 1).

Viral dynamics:

$$\frac{dV}{dt} = n\delta_I I - \delta_V V - \beta_S VS - \beta_D V(D_M + D_V)$$

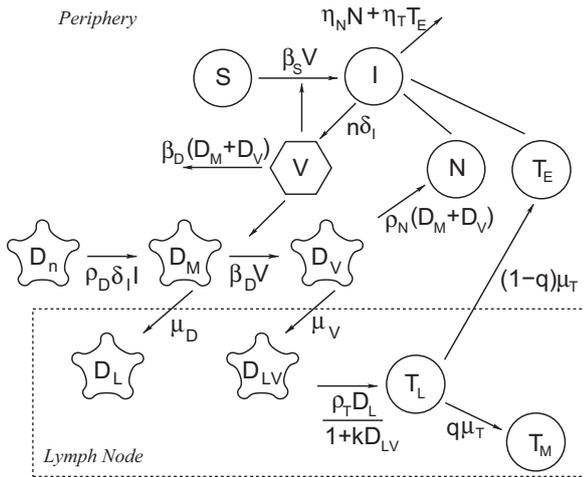


Fig. 1. Diagram illustrating the state variables and transitions in the model. Small arrowheads indicate transitions, solid triangular arrowheads indicate activation, and short bars indicate inhibition. Arrows denoting death are left out for readability. Variable names are given in Table 1.

Table 1
Variable definitions.

Symbol	Definition
Viral dynamics	
V	Free viable virus
S	Susceptible epithelial cells
I	Infected epithelial cells
Dendritic cells	
D_I	Immature DCs
D_M	Mature DCs
D_V	Virally bound DCs
D_L	Mature DCs in lymph node
D_{LV}	Virally bound DCs in lymph node
T cells and NK cells	
T_L	Activated T cells in the lymph node
T_E	Effector T cells
T_m	Memory T cells
N	Natural killer cells

$$\frac{dS}{dt} = \delta_S(S_0^* - S) - \beta_S V S$$

$$\frac{dI}{dt} = \beta_S V S - \delta_I I - \eta_N N I - \eta_T T_E I$$

Dendritic cells

$$\frac{dD_I}{dt} = \delta_D(D_0^* - D_I) - \rho_D \delta_I I D_I$$

$$\frac{dD_M}{dt} = \rho_D \delta_I I D_I - \beta_D V D_M - \mu_D D_M - \delta_D D_M$$

$$\frac{dD_V}{dt} = \beta_D V D_M - \mu_V D_V - \delta_D D_V$$

$$\frac{dD_L}{dt} = \mu_D D_M - \delta_{DL} D_L$$

$$\frac{dD_{LV}}{dt} = \mu_V D_V - \delta_{DL} D_{LV}$$

T and NK cells

$$\frac{dT_L}{dt} = \rho_T \frac{D_L}{1 + k D_{LV}} - \mu_T T_L - \delta_T T_L$$

$$\frac{dT_E}{dt} = (1 - q) \mu_T T_L - \delta_T T_E$$

Table 2
Parameter definitions and estimates.

Symbol	Definition	Estimate
Initial conditions		
S_0^*	Equilibrium number of epithelial cells	1.0×10^9
D_0^*	Equilibrium number of DCs	1.0×10^6
V_0	Initial virus load	10
Death		
δ_V	Death rate of free virus	10.0/day
δ_I	Death rate of infected cells	1.0/day
δ_S	Death rate of epithelial cells	0.01/day
δ_D	Death rate of DCs in the periphery	0.04/day
δ_{DL}	Death rate of DCs in the lymph node	0.25/day
δ_N	Death rate of NK cells	0.5/day
δ_T	Death rate of T cells	0.1/day
Viral infection and spread		
β_S	Infection rate of epithelial cells	1.0×10^{-9} /virus/day
β_D	Rate of binding to DCs	1.0×10^{-8} /virus/day
n	Burst size	100
Cell movement and activation		
μ_D	Movement of mature DCs to lymph node	1.0/day
μ_V	Movement of virally bound DCs to lymph node	1.0/day
ρ_N	Recruitment of NK cells by mature DCs	10.0/day
ρ_D	Maturation rate of DCs	1.0×10^{-6} /infected cell/day
η_N	Kill rate by NK cells	1.0×10^{-6} /infected cell/day
ρ_T	Activation rate of T cells by DCs	1.0/DC/day
μ_T	Migration rate of T cells to periphery	1.0/day
q	Fraction T cells that become memory	0.05
η_T	Kill rate by T cells in periphery	1.0×10^{-5} /T cell/day
k	Interference of virally bound DCs	1.0/DC

$$\frac{dT_m}{dt} = q \mu_T T_L$$

$$\frac{dN}{dt} = \rho_N (D_M + D_V) - \delta_N N.$$

The viral dynamics module: Susceptible cells S , in the absence of infection, remain at the equilibrium S_0^* with turnover rate δ_S . They are infected by free virus at rate $\beta_S V$ and converted to infected cells I . Infected cells are removed by NK cells at rate $\eta_N N$ or effector T cells at rate $\eta_T T_E$. Those that die by lysis, at rate δ_I release a burst of n viruses (although viruses might escape by other mechanisms while the cell is alive Buenz and Howe, 2006). These can infect susceptible cells, stick to mature peripheral DCs at rate $\beta_D (D_M + D_V)$, or die at rate δ_V .

The DC module: In the absence of infection, immature DCs D_I remain at the equilibrium D_0^* with turnover rate δ_D . Immature DCs mature in response to by infected cells at rate $\rho_D \delta_I I$. These mature cells can be bound by viruses, move to the lymph node at rate μ_D to become D_L , or die. Dendritic cells bound by viruses, D_V , move to the lymph node at the rate μ_V .

The T cell and NK cell module: Rhinovirus specific T cells T_L , counted after they have proliferated in response to the appropriate signal, are recruited into the population at rate $\rho_T D_L$ by DCs in the lymph node, but this rate is reduced by a factor of $1 + k D_{LV}$ by virally bound DCs. These T cells take on a new fate at rate μ_T , with a fraction $1 - q$ becoming effector cells, T_E , that return to the periphery and attack infected cells with the rest becoming memory cells, T_m . An alternative model where an equivalent fraction of effector T cells later become memory produces nearly identical results (results not shown). Natural killer cells are recruited at rate $\rho_N (D_M + D_V)$ through encounter with mature peripheral DCs.

Parameter estimates: We can use basic properties of the virus and the immune system to develop order of magnitude estimates of the many parameters (Table 2). The initial conditions for S , D and V come from general estimates of the size of the host tissue and a rough estimate of one DC per thousand epithelial cells. The initial virus number of 10 derives from the 1–30 viruses needed to infect a new host (Douglas, 1970).

We assume a death rate parameter δ_V for the virus of 10.0/day to be approximately equal to the value for HIV (Rong and Perelson, 2009). The death rate of infected cells of $\delta_I = 1.0$ /day derives from the life cycle of rhinovirus within a cell (Heikkinen and Jarvinen, 2003). Uninfected cells die at rate $\delta_S = 0.01$ /day, giving a lifespan of 100 days. We set the death rates of DCs and T cells, δ_D and δ_T , equal to 0.1/day, basing values of turnover rates for other immune cells (De Boer et al., 2003). We set the death rate of NK cells to $\delta_N = 0.5$ because these activated cells survive only a short amount of time.

We base our estimate of the maximum value of rhinovirus binding to DCs, $\beta_D = 1.0 \times 10^{-8}$ /virus/day, on rates of HIV attachment to T cells (Rong et al., 2009), and experiment with smaller values. Because major group viruses are more likely to bind DCs, we fix β_S to the smaller value 1.0×10^{-9} /virus/day. The burst size of rhinovirus is thought to be smaller than that of HIV or influenza, and we set that to 100. This value also gives a reasonable time course of the initial infection.

For DCs, we set death rate δ_D of peripheral DCs to 0.04 to match their roughly one month lifespan, and δ_{DL} for DCs in the lymph node to 0.25 to match their 3–5 day lifespan (Lutz and Schuler, 2002).

It takes approximately 18 h for a mature DC to reach the lymph node from the periphery (Catron et al., 2004), which we simplify to $\mu_D = 1.0$ /day. We experiment with values of μ_V less than this baseline. We set ρ_N , the recruitment of rate of NK cells

by mature DCs, to 10.0/day based on the assumption that NK cells arrive in hours rather than days like T cells.

The kill rate by NK cells is estimated to be in the range of 10^{-5} – 10^{-6} per infected cell per day (de Pillis et al., 2005), so we set our NK kill rate η_N to the low end of this range. On the other hand, we assume that antigen-specific T cells kill more effectively, and set η_T to the high end. We assume DC maturation ρ_D occurs at a similar rate due to encounter with infected cells. Because rhinovirus tends not to elicit a strong DC response, we use the lower end of the range, or $\rho_D = 1.0 \times 10^{-6}$ /infected cell/day. Interactions between T cells and DCs take roughly 24 h to result in sustained T cell activation and proliferation (Bousso, 2008), so we estimate a T cell activation rate of $\rho_T = 1.0$ /day. Using data on the effects of rhinovirus treatment of DCs (Kirchberger et al., 2005), we estimate $\rho_T = 6.5$ and $k = 0.001$ for major group rhinoviruses, but use simplified values in the model because the units and concentrations in the body differ from those in cell culture.

We assume the migration rate of T cells to the periphery is similar to the activation time, or $\mu_T = 1.0$ /day. The fraction of T cells that become memory cells is typically 5–10% (Lefrancois and Masopust, 2009), and we use the value $q = 0.05$.

Three key parameters determine the severity of the infection and extent of immune memory and differentiate the behavior of major and minor group infections.

β_D is the rate of binding to DCs, assumed to be relatively large for major group viruses that bind to ICAM-1, which is upregulated on DCs by inflammation, and small for minor group viruses.

μ_V is the rate at which virally bound DCs migrate to the lymph node, assumed to be reduced from the baseline rate by major group viruses.

k is the reduction of T cell activation in the lymph node by virally bound DCs in the lymph node.

We conducted sensitivity analysis of the other 20 parameters by testing values both double and half of the baselines shown in Table 2.

3. Results

Using standard values of the parameters and varying the three key parameters β_D , μ_V , and k , the model produces roughly a triangle of possible outcomes (Fig. 2). Although all outcomes are plausible consequences of the model, we highlight the parameters that determine the outcome by examining regions near the three corners, defined by the distance to the most extreme outcome chosen to include roughly 10% of the points, in more detail. In the upper left corner (highlighted as green stars), almost all target cells survive with little memory generated, as in infections by the major group. These viruses attach at high rates to DCs (β_D), slow those DCs down (low μ_V) and slow activation of T cells (positive value of k) (green stars in Fig. 3). On the far right (highlighted as blue squares), infections produce substantial memory and lower target cell survival level due to very low rates of attachment of viruses to DCs (low β_D) and low interference with DC function when DCs do reach the lymph node (low or zero value of k when μ_V is large). Finally, the lower left (red triangles) illustrates a virus that effectively shuts off the immune system through sufficient movement of DCs (not overly low μ_V) and interference with T cell activation (relatively large k), and which can create both high damage and low memory. The black dots lie between these extremes, and should correspond to other less extreme viral strategies. Our model does not imply higher or lower viral fitness in any part of the region.

In the high memory case that resembles the minor group rhinoviruses, the infection is cleared after about a week by a mix

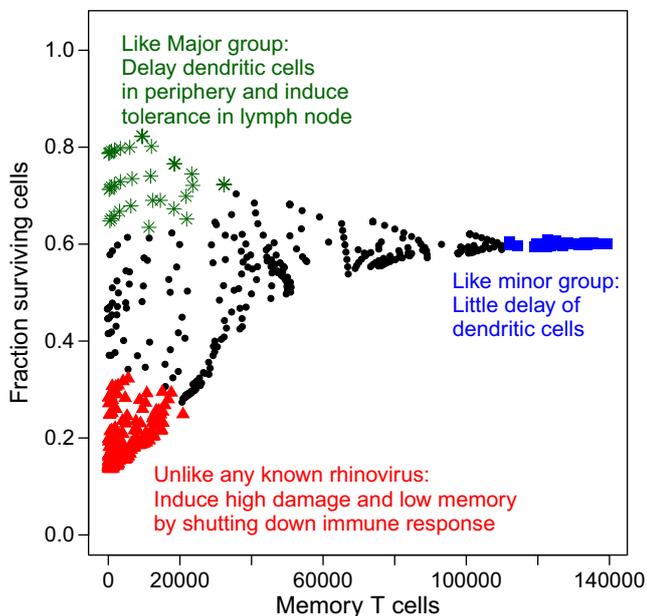


Fig. 2. The number of remaining susceptible cells plotted against the number of memory cells at the time of viral clearance (set to the time when $V < 0.01$). All parameter values as in Table 2, except for β_D , μ_V and k . Simulations are run for all combinations with β_D from 1.0×10^{-10} to 1.0×10^{-6} , μ_V from 0.0 to 1.0 in steps of 0.1, and $k = 0.0$ and from 1.0×10^{-5} to 1.0×10^{-2} . The fraction of surviving cells is the minimum number of susceptible cells S over the course of infection divided by the equilibrium value S_0^* . The corners highlight the different groups, all with scaled Euclidean distance less than 0.2 from the point with the highest fraction of surviving cells (dark green stars), the highest memory (blue squares), or the lowest fraction of surviving cells (red triangles). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

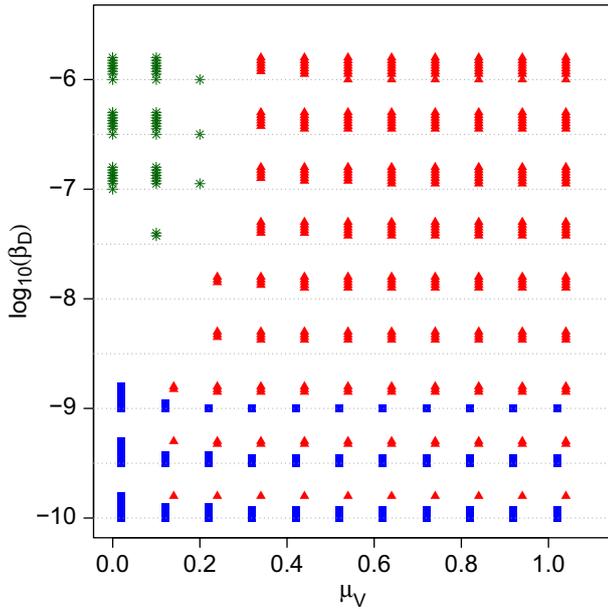


Fig. 3. The parameter values that characterize the corners in Fig. 2. The value of k is encoded by the vertical shift, with $k=0$ showing no shift and successively larger values of k being higher. Dotted horizontal lines show where $k=0$. Dark green stars indicate parameter combinations with a high fraction of surviving cells, blue squares combinations with high memory, and red triangles combination with a low fraction of surviving cells. All missing parameter combinations correspond to outcomes that lie within the triangle (the black dots in Fig. 2).

of cells with a large contribution by effector T cells (Fig. 4). Mature DCs peak on day 4, and soon thereafter arrive at the lymph node to initiate a T cell response that supplements the NK response. The viral infection is predicted to be cleared in about 10 days.

In the low memory case that resembles major group rhinoviruses, the infection is also cleared in about 10 days but largely by the NK cells that are activated in the periphery by the virally bound DCs that linger there (Fig. 5). A virus that suppresses the adaptive whole immune system creates high damage, lack of viral clearance without the help of effector T cells, and a lack of memory (Fig. 6).

These time courses match the empirical observations. Most people clear the virus by about day 10 (Barclay et al., 1989), although another study found clearance closer to day 16 (Winther et al., 1986). Symptoms peak on days 2–3 (Barclay et al., 1989), matching the time of peak cell death. NK cells rise quickly to a peak after about 5 days, while the cytokine IL-2 that is associated with T cell proliferation increases from days 1 through 5 (Hsia et al., 1990).

We found high sensitivity to some parameters, which we illustrate in Fig. 7 by showing the positions of the corners of the triangle from Fig. 2 when parameter values are doubled (the results with halved parameter values are nearly mirror images of these). Parameters that produce only small changes are not shown. We focus the discussion on the low memory (Fig. 7a, like major group) and high memory (Fig. 7b, like minor group) corners. Highly damaging viruses that shut down the adaptive immune response (red triangles in Fig. 2) remain highly damaging and produce little memory for all parameters (Fig. 7c). Complete results of the sensitivity analysis are shown in the supplementary figure.

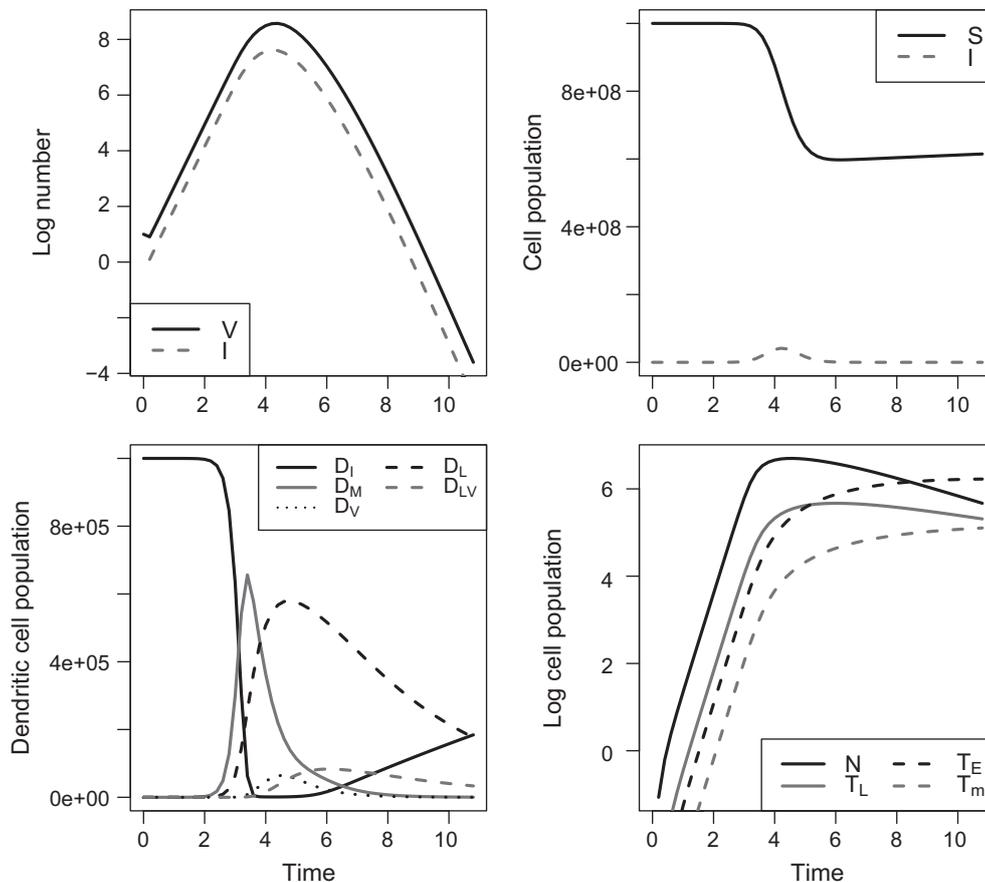


Fig. 4. Dynamics of the model in a case that produces high memory. Parameters as in Fig. 2 with $\beta_D = 1.0 \times 10^{-9}$, $\mu_V = 1.0$ and $k=0$, meaning that viruses bind inefficiently to DCs, do not slow down DC movement to the lymph node or make them tolerogenic when they get there. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

Increasing the ratio of DCs to susceptible cells (increasing D_0 or decreasing S_0) leads to increased target cell survival and memory, while changing the initial virus number V_0 has essentially no effect.

The results are sensitive to all aspects of viral fitness, including the viral death rate δ_V , infected cell death rate δ_I , burst size n and binding rate to target cells β_S . More fit viruses consistently produce more damage.

Increasing the clearance rate δ_{DL} of DCs in the lymph node decreases memory without altering damage. Speeding the movement rate μ_D of DCs to the lymph node leads to higher memory and similar target cell survival in the low memory corner that resembles the major group, but low cell survival and similar memory in the high memory corner that resembles the minor group. More rapid DC maturation ρ_D improves the overall immune response in terms of both memory and target cell survival.

Changing the properties of NK cells also has significant effects on the position of the triangle. The effects of the kill rate η_N and the recruitment rate ρ_N are identical (with only one shown in Fig. 7), with increases leading to greater target cell survival in both the major and minor group cases. Increasing the NK cell death rate has the opposite effect.

Changing the parameters associated with T cells has more mixed effects. Increasing their rate of activation (ρ_T), migration (μ_T) or killing (η_T) reduces cell damage, but relatively slightly, in the minor group case. However, increased activation generates much more memory while increasing killing generates much less. Increasing the fraction q of T cells that become memory cells increases memory without altering damage.

4. Discussion

Our models show that known mechanisms by which rhinovirus interferes with the immune system can explain the differences between major and minor group rhinovirus. In particular, the combination of low damage and low memory generated by major group rhinovirus depends on slowing dendritic cells (DCs) in the periphery and making them somewhat, but not overly, tolerogenic. The low level of immune manipulation by minor group rhinovirus creates a course of infection with higher damage to target cells and a larger role for T cells in viral clearance, leading to more immunological memory.

The models make several novel predictions about the course and effects of rhinovirus infections. First, minor group rhinovirus infections are predicted to create more damage and thus potentially more symptoms. To our knowledge, no study has quantified symptoms by serotype (Monto et al., 1987; Fox et al., 1975). Second, we predict that viral clearance is due primarily to natural killer (NK) cells in major group infections and to a mix of NK and T cells in minor group infections (Figs. 4 and 5). More detailed examination of individual serotypes, or even specific accessions, could reveal substantial variation in rhinovirus effects, clearance and memory. The model predicts the possibility of much more damaging rhinoviruses (Fig. 6), and perhaps describe HRV-C for which the cell receptor remains unknown and which may be associated with more severe infections (Arden and Mackay, 2010).

The results also raise new questions. If minor group viruses do indeed produce more immunological memory, why do they persist? The frequency of infections by minor group viruses

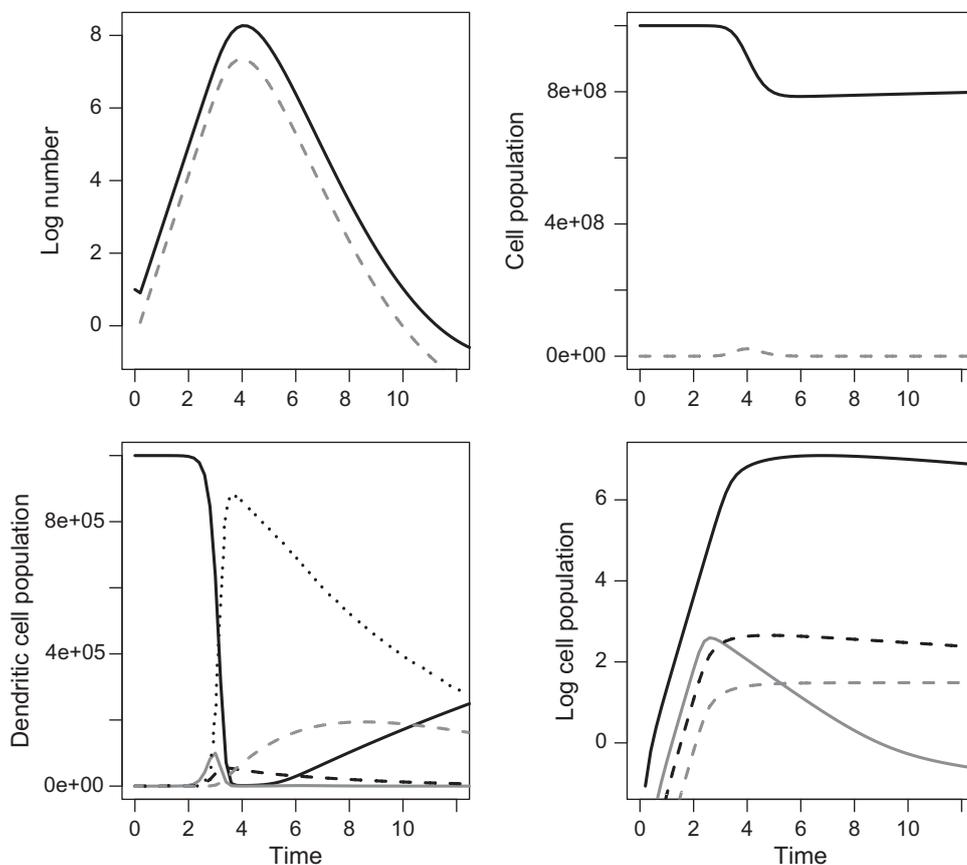


Fig. 5. Dynamics of the model in a case that produces low memory. Parameters as in Fig. 2 with $\beta_D = 1.0 \times 10^{-6}$, $\mu_V = 0.1$ and $k=0.2$, meaning that viruses bind efficiently to DCs, greatly slow DC movement to the lymph node and make them tolerogenic when they get there. Curves labeled as in Fig. 4.

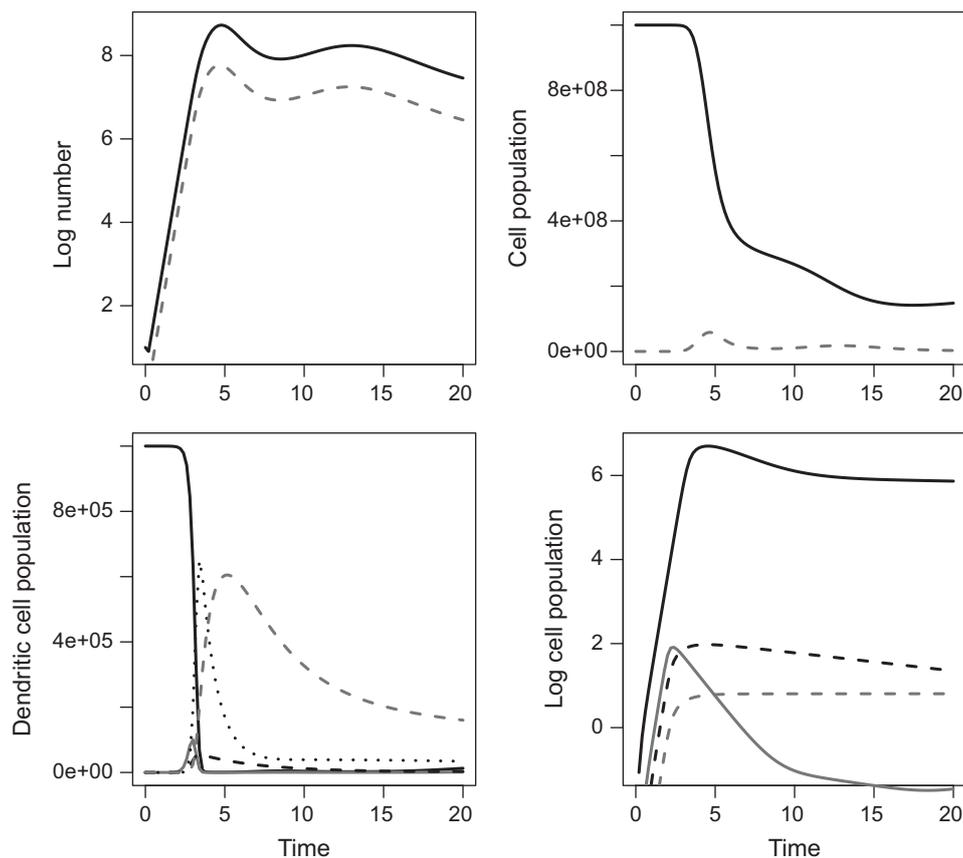


Fig. 6. Dynamics of the model in a case that produces low memory and low cell survival. Parameters as in Fig. 2 with $\beta_D = 1.0 \times 10^{-6}$, $\mu_V = 1.0$ and $k=0.5$, meaning that viruses bind efficiently to DCs, do not slow DC movement to the lymph node but do make them highly tolerogenic when they get there, thus effectively shutting down the adaptive immune response. Curves labeled as in Fig. 4.

remains in the fairly constant range of 10–30% in studies over recent decades. The minor group has also arisen independently within HRV-A at least three times (Palmenberg et al., 2009). Although a mutation that emerged in one virus spread to other parts of the phylogeny through recombination (Lewis-Rogers et al., 2009), that these three groups have persisted and diversified indicates some selective advantage. Possible advantages include

- Immunological escape may counterbalance increased immunity (Lewis-Rogers et al., 2009),
- Higher damage might lead to more effective transmission (Bull, 1994),
- If multiple infections are sufficiently common, minor group viruses might use the ability of major group viruses to suppress the immune response.

Many aspects of the immune system are not included in our model.

1. Neutrophils, like NK cells, represent the innate immune system. Studies have shown that high neutrophil numbers are associated with more severe symptoms (Turner et al., 1998). Our models effectively treat the innate system in the NK cell term, but neglect the different dynamics of neutrophils generated, for example, by their recruitment by the cytokine IL-8 (Grünberg et al., 1997).

2. The antiviral type I interferons can be expressed by both epithelial cells and monocytes and play a role in modulating the course of infection (Korpi-Steiner et al., 2006).
3. The IgA antibodies that appear about 11–14 days into the infection play a role in clearance (Barclay et al., 1989).
4. An alternative hypothesis for the failure to mount an effective immune response is misdirection against peptides that are not exposed on the capsid (Niespodziana et al., 2012).
5. We do not explicitly follow the dynamics of ICAM-1, which includes a soluble form (sICAM-1) which interferes with the course of infection by acting as a decoy. The major group rhinovirus HRV14 induces a reduction in sICAM-1, thus reducing this protecting effect, while still provoking an increase in the membrane bound ICAM-1 it requires to proliferate (Whiteman et al., 2003).
6. The mechanism of immune interference might differ sufficiently in HRV-B to require modification of the model structure (Kirchberger et al., 2007; Stockl et al., 1999).

Our model follows only fully susceptible individuals. People with pre-existing immunity, even if to a different rhinovirus serotype, might have a later and lower viral peak with fewer symptoms (Douglas, 1970), and might contribute to the relatively large number of asymptomatic infections (Peltola et al., 2008). Patterns of cross-immunity in rhinovirus are complex, with even major and minor group viruses affecting each other (Cooney et al., 1982). T cells derived from a major group (HRV16) and a minor group (HRV49) infection also show significant if complex patterns of cross-reactivity (Gern et al., 1997).

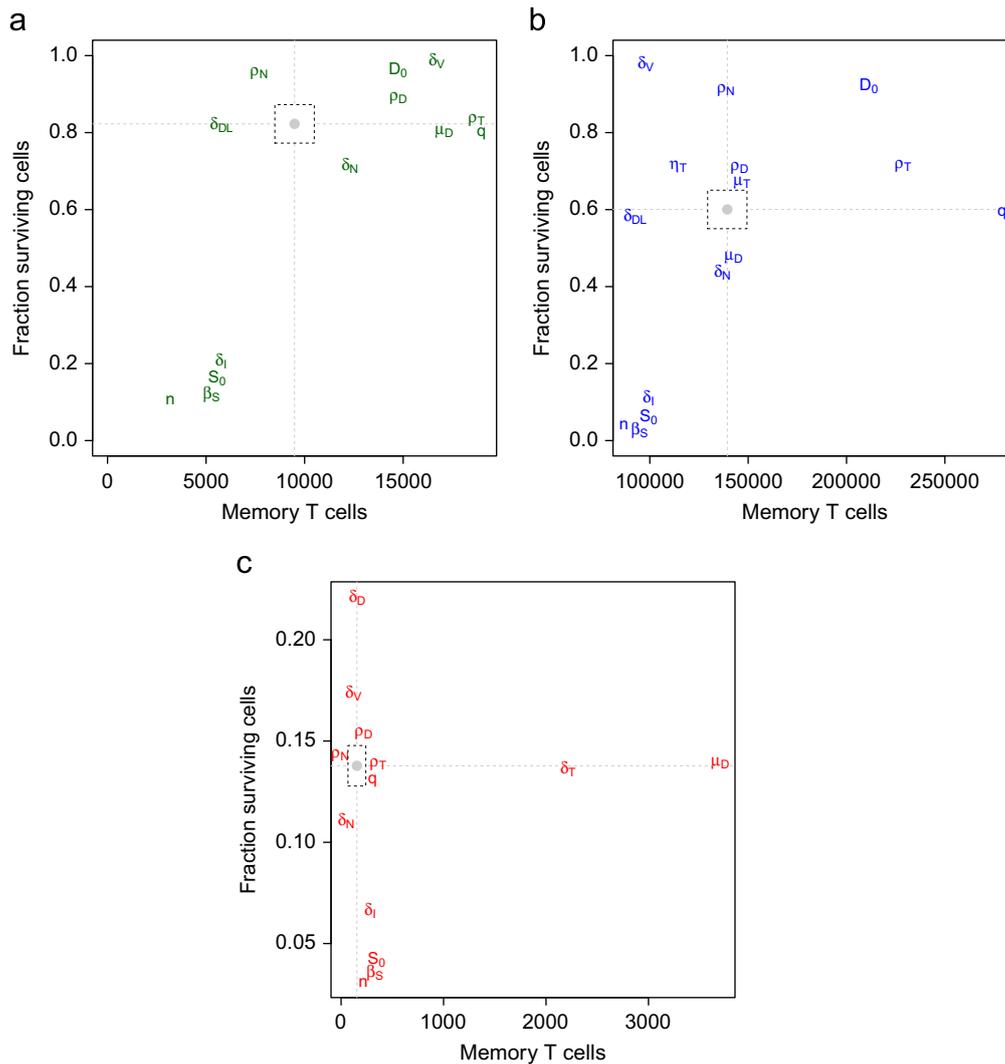


Fig. 7. Summary of the results of the sensitivity analysis with doubled values of the baseline parameters in Table 2: (a) Position of the corner with low memory (the green stars in Fig. 2), (b) Position of the corner with high memory (the blue squares in Fig. 2), (c) Position of the corner with high damage (the red triangles in Fig. 2). The gray circle indicates the position of the corner in the basic case, and only changes that lie outside the rectangle are shown. The effects of η_N are not shown because they are identical to those of ρ_N . The positions of a few symbols were adjusted slightly for readability: q down in **a**; n left, δ_I up, and β_S up in **b**; q down, ρ_T right, and ρ_N left in **c**. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

Our model does not address the spatial pattern of infection within the body (Winther et al., 1986). The observed concentration of virus in foci of infection could alter the spread of infection and create localized immune responses. Infection of other cells types, such as fibroblasts could generate a different set of signals and course of infection (Ghildyal et al., 2005).

Medically, rhinovirus might be most important in triggering asthma (Mallia and Johnston, 2006; Proud and Chow, 2006). Although RSV infections show some association, severe rhinovirus infections with wheezing in early life provides the strongest predictor of asthma at age 6 (Jackson et al., 2008). In symptomatic cases, HRV is the only virus strongly associated with concurrent asthma exacerbations (Khetsuriani et al., 2007). Because asthma results from poor regulation of the immune system, the details of how rhinovirus manipulates the immune response could be key in establishing the mechanism.

Our model could provide a starting point to include mechanisms underlying dysregulation. Children with wheezing have lower interferon gamma response in response to rhinovirus (Gern et al., 2006), and this cytokine is associated with both the NK and T cell responses. Upregulation of ICAM-1 on epithelial cells in the lower respiratory tract could lead to recruitment of

eosinophils that are associated with asthma (Papi and Johnston, 1999).

Although rhinovirus is a highly adapted human specialist with low virulence, factors that favor its success do not necessarily parallel those that promote human health. The breakdown of the uneasy truce between humans and these viruses could provide valuable insights into both constraints on viral evolution and the functioning or malfunctioning of the human immune system.

5. Conclusions

A simple model of rhinovirus infection and resulting immunity predicts that possible results fall within a triangular region of the plane describing damage and memory. Major group rhinoviruses, by delaying and inhibiting the adaptive immune system, focus the innate response at the site of infection and create little damage and low memory. Minor group rhinoviruses attach to a different receptor that does not inhibit adaptive immunity and create more damage and more memory. The model predicts the possibility of highly damaging viruses, which could describe the newly

discovered HRV-C species, and provides a useful starting point in modeling more severe rhinovirus-associated pathologies.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jtbi.2013.02.010>.

References

- Arden, K.E., Mackay, I.M., 2010. Newly identified human rhinoviruses: molecular methods heat up the cold viruses. *Rev. Med. Virol.* 20, 156–176.
- Ball, T.M., Holberg, C.J., Aldous, M.B., Martinez, F.D., Wright, A.L., 2002. Influence of attendance at day care on the common cold from birth through 13 years of age. *Arch. Pediatr. Adolesc. Med.* 156, 121–126.
- Barclay, W.S., al Nakib, W., Higgins, P.G., Tyrrell, D.A., 1989. The time course of the humoral immune response to rhinovirus infection. *Epidemiol. Infect.* 103, 659–669.
- Bousoo, P., 2008. T-cell activation by dendritic cells in the lymph node: lessons from the movies. *Nat. Rev. Immunol.* 8, 675–684.
- Buenz, E.J., Howe, C.L., 2006. Picornaviruses and cell death. *Trends Microbiol.* 14, 28–36.
- Bull, J.J., 1994. Virulence. *Evolution* 48, 1423–1437.
- Catron, D.M., Itano, A.A., Pape, K.A., Mueller, D.L., Jenkins, M.K., 2004. Visualizing the first 50 h of the primary immune response to a soluble antigen. *Immunity* 21, 341–347.
- Cooney, M.K., Fox, J.P., Kenny, G.E., 1982. Antigenic groupings of 90 rhinovirus serotypes. *Inf. Immun.* 37, 642–647.
- Couch, R.B., 1996. Rhinoviruses. In: Fields, B.N., Knipe, D.M., Howley, P.M. (Eds.), *Fields Virology*, 3rd ed. Lippincott-Raven Publishers, Philadelphia, pp. 713–734.
- De Boer, R.J., Homann, D., Perelson, A.S., 2003. Different dynamics of CD4+ and CD8+ T cell responses during and after acute lymphocytic choriomeningitis virus infection. *J. Immunol.* 171, 3928–3935.
- de Pillis, L.G., Radunskaya, A.E., Wiseman, C.L., 2005. A validated mathematical model of cell-mediated immune response to tumor growth. *Cancer Res.* 65, 7950–7958.
- Douglas Jr., R.G., 1970. Pathogenesis of rhinovirus common colds in human volunteers. *Ann. Otol. Rhinol. Laryngol.* 79, 563–571.
- Fox, J.P., Cooney, M.K., Hall, C.E., 1975. The Seattle virus watch. V. Epidemiologic observations of rhinovirus infections, 1965–1969, in families with young children. *Am. J. Epidemiol.* 101, 122–143.
- Fox, J.P., Cooney, M.K., Hall, C.E., Foy, H.M., 1985. Rhinoviruses in Seattle families, 1975–1979. *Am. J. Epidemiol.* 122, 830–846.
- Gern, J.E., Joseph, B., Galagan, D.M., Borcherding, W.R., Dick, E.C., 1996. Rhinovirus inhibits antigen-specific T cell proliferation through an intercellular adhesion molecule-1-dependent mechanism. *J. Infect. Dis.* 174, 1143–1150.
- Gern, J.E., Dick, E.C., Kelly, E.A.B., Vrtis, R., Klein, B., 1997. Rhinovirus-specific T cells recognize both shared and serotype-restricted viral epitopes. *J. Infect. Dis.* 175, 1108–1114.
- Gern, J.E., Brooks, G.D., Meyer, P., Chang, A., Shen, K., Evans, M.D., Tisler, C., Dasilva, D., Roberg, K.A., Mikus, L.D., Rosenthal, L.A., Kirk, C.J., Shult, P.A., Bhattacharya, A., Li, Z., Gangnon, R., Lemanske, R.F.J., 2006. Bidirectional interactions between viral respiratory illnesses and cytokine responses in the first year of life. *J. Allergy Clin. Immunol.* 117, 72–78.
- Ghildyal, R., Dagher, H., Donninger, H., de Silva, D., Li, X., Freezer, N.J., Wilson, J.W., Bardin, P.G., 2005. Rhinovirus infects primary human airway fibroblasts and induces a neutrophil chemokine and a permeability factor. *J. Med. Virol.* 75, 608–615.
- Grünberg, K., Smits, H.H., Timmers, M.C., De Klerk, E.P.A., Dolhain, R.J.E.M., Dick, E.C., Hiemstra, P.S., Sterk, P.J., 1997. Experimental rhinovirus 16 infection. *Am. J. Crit. Care Resp. Med.* 156, 609–616.
- Gwaltney Jr., J.M., Hendley, J.O., Simon, G., Jordan Jr., W.S., 1967. Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. *J. Am. Med. Assoc.* 202, 494–500.
- Harris, J.M., Gwaltney, J.M., 1996. Incubation periods of experimental rhinovirus infection and illness. *Clin. Infect. Dis.* 23, 1287.
- Hayden, F.G., 2004. Rhinovirus and the lower respiratory tract. *Rev. Med. Virol.* 14, 17–31.
- Heikkinen, T., Jarvinen, A., 2003. The common cold. *Lancet* 361, 51–59.
- Hofer, F., Gruenberger, H., Kowalski, H., Machat, H., Huettinger, M., Kuechler, E., Blaas, D., 1994. Members of the low density lipoprotein receptor family mediate cell entry of a minor-group common cold virus. *Proc. Nat. Acad. Sci.* 91, 1839–1892.
- Hsia, J., Goldstein, A.L., Simon, G.L., Szein, M., Hayden, F.G., 1990. Peripheral blood mononuclear cell interleukin-2 and interferon- γ production cytotoxicity and antigen-stimulated blastogenesis during experimental rhinovirus infection. *J. Infect. Dis.* 162, 591–597.
- Hughes, A.L., 2004. Phylogeny of the Picornaviridae and differential evolutionary divergence of picornavirus proteins. *Infect. Gen. Evol.* 4, 143–152.
- Jackson, D.J., Evans, M.D., Anderson, E.L., Salazar, L., DaSilva, D.F., Pappas, T.E., Roberg, K.A., Tisler, C.J., Gangnon, R., Gern, J.E., Lemanske Jr., R.F., 2008. Wheezing rhinovirus illnesses during early childhood and the subsequent development of asthma. *J. Allergy Clin. Immunol.* 121, 667–672.
- Kaiser, L., Aubert, J.-D., Pache, J.-C., Deffernez, C., Rochat, T., Garbino, J., Wunderli, W., Meylan, P., Yerly, S., Perrin, L., Letovanec, I., Nicod, L., Tapparel, C., Soccia, P.M., 2006. Chronic rhinoviral infection in lung transplant recipients. *Am. J. Crit. Care Resp. Med.* 174, 1392–1399.
- Khetsuriani, N., Kazerouni, N.N., Erdman, D.D., Lu, X.Y., Redd, S.C., Anderson, L.J., Teague, W.G., 2007. Prevalence of viral respiratory tract infections in children with asthma. *J. Allergy Clin. Immunol.* 119, 314–321.
- Kieninger, E., Fuchs, O., Latzin, P., Frey, U., Regamey, N. Rhinovirus infections in infancy and early childhood. *European Respiratory Journal*, <http://dx.doi.org/http://dx.doi.org/10.1183/09031936.00203511>, in press.
- Kirchberger, S., Majdic, O., Steinberger, P., Bluml, S., Pfistershammer, K., Zlabinger, G., Deszcz, L., Kuechler, E., Knapp, W., Stockl, J., 2005. Human rhinoviruses inhibit the accessory function of dendritic cells by inducing sialoadhesin and B7-H1 expression. *J. Immunol.* 175, 1145–1152.
- Kirchberger, S., Majdic, O., Stockl, J., 2007. Modulation of the immune system by human rhinoviruses. *Int. Arch. Allergy Immunol.* 142, 1–10.
- Korpi-Steiner, N.L., Bates, M.E., Lee, W.M., Hall, D.J., Bertics, P.J., 2006. Human rhinovirus induces robust IP-10 release by monocytic cells, which is independent of viral replication but linked to type I interferon receptor ligation and STAT1 activation. *J. Leukoc. Biol.* 80, 1364–1374.
- Laine, P., Savolainen, C., Blomquist, S., Hovi, T., 2005. Phylogenetic analysis of human rhinovirus capsid protein VP1 and 2A protease coding sequences confirms shared genus-like relationships with human enteroviruses. *J. Gen. Virol.* 86, 697–706.
- Laza-Stanca, V., Stanciu, L.A., Message, S.D., Edwards, M.R., Gern, J.E., Johnston, S.L., 2006. Rhinovirus replication in human macrophages induces NF-kappa B-dependent tumor necrosis factor alpha production. *J. Virol.* 80, 8248–8258.
- Lefrançois, L., Masopust, D., 2009. The road not taken: memory T cell fate 'decisions'. *Nat. Immunol.* 10, 369–370.
- Lewis-Rogers, N., Bendall, M.L., Crandall, K.A., 2009. Phylogenetic relationships and molecular adaptation dynamics of human rhinoviruses. *Mol. Biol. Evol.* 26, 969–981.
- Lutz, M.B., Schuler, G., 2002. Immature, semi-mature and fully mature dendritic cells: which signals induce tolerance or immunity? *Trends Immunol.* 23, 445–449.
- Mallia, P., Johnston, S.L., 2006. How viral infections cause exacerbation of airway diseases. *Chest* 130, 1203–1210.
- Monto, A.S., Bryan, E.R., Ohmit, S., 1987. Rhinovirus infections in Tecumseh, Michigan: frequency of illness and number of serotypes. *J. Infect. Dis.* 156, 43–49.
- Niespodziana, K., Napora, K., Cabauatan, C., Focke-Tejkl, M., Keller, W., Niederberger, V., Tsoia, M., Christodoulou, I., Papadopoulos, N.G., Valenta, R., 2012. Misdirected antibody responses against an N-terminal epitope on human rhinovirus VP1 as explanation for recurrent RV infections. *The FASEB J.* 26, 1001–1008.
- Norkin, L.C., 2010. *Virology: Molecular Biology and Pathogenesis*. ASM Press.
- Nowak, M.A., May, R.M., 2000. *Virus Dynamics: Mathematical Principles of Immunology and Virology*. Oxford University Press.
- Palmenberg, A.C., Spiro, D., Kuzmickas, R., Wang, S., Djikeng, A., Rathe, J.A., Fraser-Liggett, C.M., Liggett, S.B., 2009. Sequencing and analyses of all known human rhinovirus genomes reveal structure and evolution. *Science* 324, 55–59.
- Papi, A., Johnston, S.L., 1999. Rhinovirus infection induces expression of its own receptor intercellular adhesion molecule 1 (ICAM-1) via increased NF- κ B-mediated transcription. *J. Biol. Chem.* 274, 9707–9720.
- Peltola, V., Waris, M., Österback, R., Susi, P., Ruuskanen, O., Hyypiä, T., 2008. Rhinovirus transmission within families with children: incidence of symptomatic and asymptomatic infections. *J. Infect. Dis.* 197, 382–389.
- Proud, D., 2005. Nitric oxide and the common cold. *Curr. Opin. Allergy Clin. Immunol.* 5, 37–42.
- Proud, D., Chow, C.W., 2006. Role of viral infections in asthma and chronic obstructive pulmonary disease. *Am. J. Resp. Cell Mol. Biol.* 35, 513–518.
- Proud, D., Turner, R.B., Winther, B., Wiehler, S., Tiesman, J.P., Reichling, T.D., Juhlin, K.D., Fulmer, A.W., Ho, B.Y., Walanski, A.A., Poore, C.L., Mizoguchi, H., Jump, L., Moore, M.L., Zukowski, C.K., Clymer, J.W., 2008. Gene expression profiles during in vivo human rhinovirus infection. *Am. J. Crit. Care Resp. Med.* 178, 962–968.
- Rong, L., Perelson, A.S., 2009. Modeling HIV persistence, the latent reservoir and viral blips. *J. Theor. Biol.* 260, 308–331.

- Rong, L., Perelson, A., Antia, R., 2009. Modeling latently infected cell activation: viral and latent reservoir persistence, and viral blips in HIV-infected patients on potent therapy. *PLoS Comput. Biol.* 5, e1000533.
- Schrauf, C., Kirchberger, S., Majdic, O., Seyerl, M., Zlabinger, G.J., Stuhlmeier, K.M., Sachet, M., Seipelt, J., Stockl, J., 2009. The ssRNA genome of human rhinovirus induces a type I IFN Response but fails to induce maturation in human monocyte-derived dendritic cells. *J. Immunol.* 183, 4440.
- Seyerl, M., Kirchberger, S., Majdic, O., Seipelt, J., Jindra, C., Schrauf, C., Stöckl, J., 2010. Human rhinoviruses induce IL-35-producing Treg via induction of B7-H1 (CD274) and sialoadhesin (CD169) on DCEur. *J. Immunol.* 40, 321–329.
- Stockl, J., Vetr, H., Majdic, O., Zlabinger, G., Kuechler, E., Knapp, W., 1999. Human major group rhinoviruses downmodulate the accessory function of monocytes by inducing IL-10. *J. Clin. Invest.* 104, 957–965.
- Turner, R.B., Weingand, K.W., Yeh, C.-H., Leedy, D.W., 1998. Association between interleukin-8 concentration in nasal secretions and severity of symptoms of experimental rhinovirus colds. *Clin. Infect. Dis.* 26, 840–846.
- van Kempen, M., Bachert, C., Van Cauwenberge, P., 1999. An update on the pathophysiology of rhinovirus upper respiratory tract infections. *Rhinology* 37, 97–103.
- Whiteman, S.C., Bianco, A., Knight, R.A., Spiteri, M.A., 2003. Human rhinovirus selectively modulates membranous and soluble forms of its intercellular adhesion molecule-1 (ICAM-1) receptor to promote epithelial cell infectivity. *J. Biol. Chem.* 278, 11954.
- Wimalasundera, S.S., Katz, D.R., Chain, B.H., 1997. Characterization of the T cell response to human rhinovirus in children: implications for understanding the immunopathology of the common cold. *J. Infect. Dis.* 176, 755–759.
- Winther, B., Gwaltney Jr, J.M., Mygind, N., Turner, R.B., Hendley, J.O., 1986. Sites of rhinovirus recovery after point inoculation of the upper airway. *J. Am. Med. Assoc.* 256, 1763–1767.