Electronic Supplementary Material

for

Ecological factors driving the long-term evolution

of influenza’s host range

Sarah Cobey, Mercedes Pascual, and Ulf Dieckmann

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I. Equations for intermediate and target hosts for model with frequency-dependent transmission

SIRS equations for the population of intermediate hosts are given in the main text (eqs. 2a-c). The corresponding SIRS equations for the population of reservoir hosts are

\[
\frac{dS_r}{dt} = \gamma_r R_r - P(\alpha 2, 3) \left( \frac{\beta_{rI} I_r + \beta_{mI} I_m}{N_r + cN_m} \right) S_r,
\]  
(S1a)

\[
\frac{dI_r}{dt} = P(\alpha 2, 3) \left( \frac{\beta_{rI} I_r + \beta_{mI} I_m}{N_r + cN_m} \right) S_r - \nu_r I_r,
\]  
(S1b)

\[
\frac{dR_r}{dt} = \nu_r I_r - \gamma_r R_r.
\]  
(S1c)

Analogously, SIRS equations for the population of target hosts are

\[
\frac{dS_t}{dt} = \gamma_t R_t - P(\alpha 2, 6) \left( \frac{\beta_{rI} I_t + \beta_{mI} I_m}{N_t + cN_m} \right) S_t,
\]  
(S2a)

\[
\frac{dI_t}{dt} = P(\alpha 2, 6) \left( \frac{\beta_{rI} I_t + \beta_{mI} I_m}{N_t + cN_m} \right) S_t - \nu_t I_t,
\]  
(S2b)

\[
\frac{dR_t}{dt} = \nu_t I_t - \gamma_t R_t.
\]  
(S2c)
II. The Jacobian of the model with frequency-dependent transmission

The Jacobian matrix of a rare mutant’s epidemiological dynamics is given by

\[
J = \begin{bmatrix}
\frac{\beta_m S^*}{N_i + cN_a} - v_i & P_1(\alpha_2,3)\frac{\beta_m cS^*}{cN_i + N_a + cN_i} & 0 \\
\max[P_1(\alpha_2,3),P_1(\alpha_2,6)]\frac{\beta_m cS^*}{cN_i + N_a + cN_i} - v_a & \max[P_1(\alpha_2,3),P_1(\alpha_2,6)]\frac{\beta_m cS^*}{cN_a + N_i} & P_1(\alpha_2,6)\frac{\beta_m S^*}{cN_a + N_i} \\
0 & P_1(\alpha_2,6)\frac{\beta_m S^*}{cN_a + N_i} & -v_i
\end{bmatrix}
\]

\(P_1\) refers to the phenotype of the rare mutant virus. The elements \(J_{ij}\) are the instantaneous per capita rates of mutant infections spreading from infected hosts in population \(j\) to susceptible hosts in population \(i\). Host abundances at the endemic equilibrium of the resident virus are denoted by an asterisk.

III. Default parameters

We choose parameters in keeping with general observations on the relative growth rates of different influenza subtypes in different hosts (Webster et al. 1992) (table S1):

- The rates of loss of immunity, \(\gamma_i\), are qualitative estimates based on several observations. Rates are highest in waterfowl, since they appear to have little long-term immunity to influenza. The intermediate hosts, as domesticated animals, also have relatively high turnover. Turnover rates in the target population are low due to longer host lifespans and long-lasting immunity (the loss of immunity in hosts is here a proxy for antigenic evolution). However, we assume that these factors are offset by relatively high host mobility (migration).
• The assumption of frequent, regular contact (suitable for transmission) between intermediate hosts and target hosts such as humans, in both rural and more industrial settings, is supported by serological surveys of pigs (Brown et al. 1995; Olsen et al. 2000; Yu et al. 2007), as well as by observations on asymptomatic pig-farm workers (Campitelli et al. 1997; Halvorson et al. 1983; Karunakaran et al. 1983; Myers et al. 2006; Olsen et al. 2002; Sivanandan et al. 1991) and poultry workers (Koopmans et al. 2004).

Motivation for density-dependent transmission between the reservoir and intermediate host populations comes from Brown et al. (2000), Ly et al. (2007), and Alexander (2000).
Table S1. Default parameter values used in models with non-neutral host ecology. Note that “individuals” in the denominator of $\beta_{rr}$ and $\beta_{mm}$ for the model with density-dependent transmission is a pseudo-unit.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nu_t$</td>
<td>Rate of recovery in reservoir hosts</td>
<td>$1/(12 \text{ days})$</td>
<td>Hulse-Post et al. (2005)</td>
</tr>
<tr>
<td>$\nu_m$</td>
<td>Rate of recovery in intermediate hosts</td>
<td>$1/(7 \text{ days})$</td>
<td>Hinshaw et al. (1981), Brown (2000); Van der Goot et al. (2003)</td>
</tr>
<tr>
<td>$\nu_t$</td>
<td>Rate of recovery in target hosts</td>
<td>$1/(6 \text{ days})$</td>
<td>Leekha et al. (2007); Carrat et al. (2008)</td>
</tr>
<tr>
<td>$\gamma_t$</td>
<td>Rate of susceptible replenishment in reservoir hosts</td>
<td>$1/(90 \text{ days})$</td>
<td>Kida et al. (1980); Hulse-Post et al. (2005)</td>
</tr>
<tr>
<td>$\gamma_m$</td>
<td>Rate of susceptible replenishment in intermediate hosts</td>
<td>$1/(180 \text{ days})$</td>
<td></td>
</tr>
<tr>
<td>$\gamma_t$</td>
<td>Rate of susceptible replenishment in target hosts</td>
<td>$1/(730 \text{ days})$</td>
<td></td>
</tr>
<tr>
<td>$c (c_1, c_2)$</td>
<td>Ratio of probabilities of interpopulation and intrapopulation contact (for reservoir and intermediate hosts, for intermediate and target hosts)</td>
<td>1.0 (except where explicitly varied)</td>
<td></td>
</tr>
<tr>
<td>$\beta_{tt}$</td>
<td>Transmission rate among target hosts</td>
<td>$1/(4 \text{ days})$</td>
<td>Saenz et al. (2006)</td>
</tr>
<tr>
<td>$\beta_{rr}$</td>
<td>Transmission rate among reservoir hosts</td>
<td>$1/(3 \text{ days})$</td>
<td></td>
</tr>
<tr>
<td>$\beta_{mm}$</td>
<td>Transmission rate among intermediate hosts</td>
<td>$1/(4 \text{ days})$</td>
<td>Saenz et al. (2006)</td>
</tr>
</tbody>
</table>

**Model with frequency-dependent transmission**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_{rr}$</td>
<td>Transmission rate among reservoir hosts</td>
<td>$1/(300 \text{ days} \cdot \text{individuals})$</td>
<td></td>
</tr>
<tr>
<td>$\beta_{mm}$</td>
<td>Transmission rate among intermediate hosts</td>
<td>$1/(400 \text{ days} \cdot \text{individuals})$</td>
<td>Saenz et al. (2006)</td>
</tr>
</tbody>
</table>
IV. Equations for model with density-dependent transmission

All parameters and variables are as defined in the main text.

**Reservoir hosts, r**

\[
\frac{dS_r}{dt} = \gamma_r R_r - P(\alpha 2, 3) S_r \left( \beta_{rr} I_r + \beta_{rm} c_1 I_m \right) \tag{S3a}
\]

\[
\frac{dI_r}{dt} = P(\alpha 2, 3) S_r \left( \beta_{rr} I_r + \beta_{rm} c_1 I_m \right) - \nu_r I_r \tag{S3b}
\]

\[
\frac{dR_r}{dt} = \nu_r I_r - \gamma_r R_r \tag{S3c}
\]

**Intermediate hosts, m**

\[
\frac{dS_m}{dt} = \gamma_m R_m - \max[P(\alpha 2, 3), P(\alpha 2, 6)] S_m \left( \beta_{mr} c_1 I_r + \beta_{mm} I_m + \frac{\beta_{mi} c_2 I_t}{c_2 N_m + N_t} \right) \tag{S4a}
\]

\[
\frac{dI_m}{dt} = \max[P(\alpha 2, 3), P(\alpha 2, 6)] S_m \left( \beta_{mr} c_1 I_r + \beta_{mm} I_m + \frac{\beta_{mi} c_2 I_t}{c_2 N_m + N_t} \right) - \nu_m I_m \tag{S4b}
\]

\[
\frac{dR_m}{dt} = \nu_m I_m - \gamma_m R_m \tag{S4c}
\]

**Target hosts, t**

\[
\frac{dS_t}{dt} = \gamma_t R_t - P(\alpha 2, 6) S_t \left( \frac{\beta_{mt} c_2 I_m}{c_2 N_t + N_m} + \frac{\beta_{tt} I_t}{N_t + c_2 N_m} \right) \tag{S5a}
\]

\[
\frac{dI_t}{dt} = P(\alpha 2, 6) S_t \left[ \frac{\beta_{mt} c_2 I_m}{c_2 N_t + N_m} + \frac{\beta_{tt} I_t}{N_t + c_2 N_m} \right] - \nu_t I_t \tag{S5b}
\]

\[
\frac{dR_t}{dt} = \nu_t I_t - \gamma_t R_t \tag{S5c}
\]
V. Figures

Figure S1. Pairwise invasibility (a) and trait evolution (b) plots for hosts that are identical except for their receptor preferences. Parameters are identical to those in figure 2, except for $\nu_r = \nu_m = \nu_t = 1/4.5 \text{ day}^{-1}$ (so that $R_0$ for the appropriate specialist in each host population is 1.5). Gray areas in (a) indicate regions where the resident is inviable, whereas in (b) they indicate regions of coexistence. In the trait evolution plots, black lines are evolutionary isoclines and black circles correspond to evolutionary attractors if filled and repellors if open. Arrows show the direction, at the quadrant level, of selection pressure. For clarity, they are sometimes shown extending outside the plot, even though phenotypes are bounded by the axes.

Figure S2. Pairwise invasibility (a) and trait evolution (b) plots for hosts that are identical except for their receptor preferences. Parameters are identical to those in figure 2, except for $\nu_r = \nu_m = \nu_t = 1/12 \text{ day}^{-1}$ (so that $R_0$ for the appropriate specialist in each host population is 4). Gray areas in (b) indicate regions of coexistence. In the trait evolution plots, black lines are evolutionary isoclines and black circles correspond to evolutionary attractors if filled and repellors if open. Arrows show the direction, at the quadrant level, of selection pressure. For clarity, they are sometimes shown extending outside the plot, even though phenotypes are bounded by the axes.

Figure S3. Pairwise invasibility (a, c) and trait evolution (b, d) plots for host populations differing in their rates of susceptible replenishment, $\gamma$, but not in $R_0$. In all plots, $\gamma_r = 1/90$
day$^{-1}$ and $\gamma_m = 1/180$ day$^{-1}$. The intraspecific $R_0$ for all hosts is $2$ ($\beta_{rr} = \beta_{mm} = \beta_{tt} = 1/3$ day$^{-1}$, $\nu_r = \nu_m = \nu_t = 1/6$ day$^{-1}$). Hosts have equal population sizes, populations mix freely ($c = 1$), and transmission rates are frequency-dependent. In ($a$) and ($b$), $\gamma_t = 1/730$ day$^{-1}$.

In ($c$) and ($d$), $\gamma_t = 1/7300$ day$^{-1}$. Gray areas in ($a$) indicate regions where the resident is inviable, whereas in ($b$) they indicate regions of coexistence. In the trait evolution plots, black lines are evolutionary isoclines and black circles correspond to evolutionary attractors if filled and repellors if open. Arrows show the direction, at the quadrant level, of selection pressure. For clarity, they are sometimes shown extending outside the plot, even though phenotypes are bounded by the axes.

**Figure S4.** Pairwise invasibility ($a$) and trait evolution ($b$) plots for host populations differing in their $R_0$ but not their rate of susceptible replenishment. Here, $R_0$ is $4$ in reservoir hosts ($\beta_{rr} = 1/3$ day$^{-1}$, $\nu_r = 1/12$ day$^{-1}$), $1.75$ in the intermediate host ($\beta_{mm} = 1/4$ day$^{-1}$, $\nu_m = 1/7$ day$^{-1}$), and $1.5$ in target hosts ($\beta_{tt} = 1/4$ day$^{-1}$, $\nu_t = 1/6$ day$^{-1}$), as in table S1. Hosts have identical population sizes and rates of susceptible replenishment ($\gamma_r = \gamma_m = \gamma_t = 1/180$ day$^{-1}$), populations mix freely ($c = 1$), and transmission rates are frequency-dependent. Gray areas in ($a$) indicate regions where the resident is inviable, whereas in ($b$) they indicate regions of coexistence. In the trait evolution plots, black lines are evolutionary isoclines and black circles correspond to evolutionary attractors if filled and repellors if open. Arrows show the direction, at the quadrant level, of selection pressure.

**Figure S5.** Pairwise invasibility ($a$, $c$) and trait evolution ($b$, $d$) plots allowing both the $R_0$ within host populations and the rates of susceptible replenishment to vary among hosts.
Parameters are the same as those in figure S4, except where noted, and rates of susceptible replenishment are the same as those in figure S3 and listed in table S1. For (c) and (d), the $R_0$ in reservoir hosts ($R_0 = 2; \nu_r = 1/6$ day$^{-1}$) is lower than in (a) and (b), even though in both cases it is still higher than in the intermediate ($R_0 = 1.75$) and target hosts ($R_0 = 1.5$). Gray areas in (a) indicate regions where the resident is inviable, whereas in (b) they indicate regions of coexistence. In the trait evolution plots, black lines are evolutionary isoclines and black circles correspond to evolutionary attractors if filled and repellors if open. Arrows show the direction, at the quadrant level, of selection pressure.

**Figure S6.** Coexistence plots showing the effects of changing intermediate host abundance in a neutral host ecology, assuming (a) frequency-dependent and (b) density-dependent transmission. Ecological parameters are the same as those in figure 2 (for all hosts, $R_0 = 2$ and $\gamma = 1/180$ day$^{-1}$). Pairwise invasibility and trait evolution plots for $N_m = N_i = N_t$ and frequency-dependent transmission are shown in figure 2. Plus signs indicate areas of coexistence, which correspond to the gray regions of trait evolution plots.

**Figure S7.** Coexistence plots showing the effects of changing intermediate host abundance in a non-neutral host ecology, assuming (a) frequency-dependent and (b) density-dependent transmission. Ecological parameters are the same as those in table S1. Pairwise invasibility and trait evolution plots for $N_m = N_i = N_t$ and frequency-dependent transmission are shown in figure S5(a,b). Plus signs indicate areas of coexistence, which correspond to the gray regions of trait evolution plots.
**Figure S8.** Coexistence plots showing the effects of changing target host abundance in a neutral host ecology, assuming frequency-dependent transmission. Ecological parameters are the same as those in figure 2 (for all hosts, $R_0 = 2$ and $\gamma = 1/180$ day$^{-1}$). Pairwise invasibility and trait evolution plots for $N_t = N_m = N_r$ and frequency-dependent transmission are shown in figure 2. Plus signs indicate areas of coexistence, which correspond to the gray regions of trait evolution plots.

**Figure S9.** Effects of changing target host abundance in a non-neutral host ecology, assuming frequency-dependent transmission. Ecological parameters are the same as those in table S1. Pairwise invasibility and trait evolution plots for $N_t = N_m = N_r$ and frequency-dependent transmission are shown in figure S5(a,b). Plus signs indicate areas of coexistence, which correspond to the gray regions of trait evolution plots.

**Figure S10.** Coexistence plots showing effects of changing the degree of mixing between populations ($c = c_1 = c_2$) when all transmission rates are frequency-dependent. Coexistence plots are shown for (a) neutral and (b) non-neutral host ecologies. Pairwise invasibility and trait evolution plots for $c = 1$ are shown in figure 2 and figure S5(a,b), respectively, assuming frequency-dependent transmission. Plus signs indicate areas of coexistence, which correspond to the gray regions of trait evolution plots.

**Figure S11.** Coexistence plots showing effects of changing only the scaling on rates of interspecific transmission between reservoir and intermediate hosts ($c_1$) in (a) neutral and (b) non-neutral host ecologies, assuming density-dependent transmission between
reservoir and intermediate hosts. Plus signs indicate areas of coexistence, which correspond to the gray regions of trait evolution plots.

**Figure S12.** Coexistence plots showing effects of changing only the degree of mixing between intermediate and target hosts ($c_2$) in (a) neutral and (b) non-neutral host ecologies, assuming density-dependent transmission between reservoir and intermediate hosts. Plus signs indicate areas of coexistence, which correspond to the gray regions of trait evolution plots.
Figure S1

(a) $s = 0.05$

$\begin{array}{c}
\text{mutant phenotype} \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

$\begin{array}{c}
s = 0.25 \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

$\begin{array}{c}
s = 0.5 \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

$\begin{array}{c}
s = 0.75 \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

$\begin{array}{c}
s = 1 \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

$\begin{array}{c}
s = 1.5 \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

(b) $s = 0.05$

$\begin{array}{c}
\text{resident phenotype} \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

$\begin{array}{c}
s = 0.25 \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

$\begin{array}{c}
s = 0.5 \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

$\begin{array}{c}
s = 0.75 \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

$\begin{array}{c}
s = 1 \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$

$\begin{array}{c}
s = 1.5 \\
\hline
0 & 0.5 & 1 \\
0 & 0.5 & 1 \\
0.5 & 1 \\
\end{array}$
Figure S2

(a) $s = 0.05$  
(b) $s = 0.25$  
(c) $s = 0.5$  
(d) $s = 0.75$  
(e) $s = 1$  
(f) $s = 1.5$
Figure S3 (continued)

(c) \[ s = 0.05, s = 0.25, s = 0.5 \]

(d) \[ s = 0.05, s = 0.25, s = 0.5 \]
Figure S5

(a)

$(s = 0.05)$

$(s = 0.25)$

$(s = 0.5)$

$(s = 0.75)$

$(s = 1)$

$(s = 1.5)$

(mutant phenotype vs. resident phenotype)

(b)

$(s = 0.05)$

$(s = 0.25)$

$(s = 0.5)$

$(s = 0.75)$

$(s = 1)$

$(s = 1.5)$

(resident 2 phenotype vs. resident 1 phenotype)
Figure S5 (continued)

(c) $s = 0.05$, $s = 0.25$, $s = 0.5$, $s = 0.75$, $s = 1$, $s = 1.5$

(d) $s = 0.05$, $s = 0.25$, $s = 0.5$, $s = 0.75$, $s = 1$, $s = 1.5$
Figure S6

(a) 

(b)
Figure S7

(a) region of inviability

(b) relative intermediate host abundance
Figure S8
Figure S9
Figure S10

(a) 

(b)
Figure S11
Figure S12
VI. Additional references


Myers, K. P., Olsen, C. W., Setterqust, S. F., Capuano, A. W., Donham, K. J., Thacker, E. L., Merchant, J. A. & Gray, G. C. 2006 Are swine workers in the United States...
at increased risk of infection with zoonotic influenza virus? *Clinical Infectious Diseases* **42**, 14-20.


