Environmental transmission scrambles coexistence patterns of avian influenza viruses

Benjamin Roche a,⁎, Pejman Rohani a,b,c

⁎ Corresponding author. Department of Ecology and Evolutionary Biology, 2014 Kraus Natural Science Building 830, North University, Ann Arbor, MI, 48109, USA. Tel.: +1 706 248 9035. E-mail address: benroche@umich.edu (B. Roche).

Contents lists available at ScienceDirect
Epidemics

Article history:
Received 22 January 2010
Revised 16 March 2010
Accepted 16 March 2010

Keywords:
Avian influenza
Strain competition
Mathematical modeling

A B S T R A C T

Despite the recent accumulation of theoretical and empirical studies on avian influenza viruses (AIVs), the interactions among the diverse pool of strains remain poorly understood. One potential reason is multiple transmission routes. In this paper, we explore the behavior of a two-strain mathematical model of AIV dynamics with lifelong immunity to understand how the combination of direct and environmental transmission (via a persistent viral reservoir) determines strains coexistence and dominance. We find that coexistence requires the magnitude of basic reproductive ratios of the strains to be identical for each transmission route (R0dir and R0env) when cross-immunity is assumed to be perfect. Coexistence may be also possible when one strain is only directly transmitted and the contribution by environmental transmission is high. When we relax this assumption, the level of cross-protection does not modify coexistence criteria when strains are mainly environmentally transmitted, in contrast to the case where direct transmission dominates. Finally, when competitive exclusion is observed, the strain with the largest contribution from direct transmission outcompetes the other through competition for viral particle acquisition. Overall, we conclude that environmental transmission can affect the patterns of coexistence predicted by direct transmission models in complex ways.

© 2010 Elsevier B.V. All rights reserved.

Introduction

Over the past three decades, the application of ecological perspectives to the study of infectious diseases has provided critical insights in our understanding of pathogens that are of major public health concern (Grenfell and Dobson, 1995; Guernier et al., 2004; Collinge and Ray, 2006; Anderson and May, 1979), especially emerging and re-emerging infectious diseases (Daszak et al., 2001; Morens et al., 2004). This success is, in part, due to the introduction of ecological methods and concepts to the study of infectious diseases dynamics (Grenfell et al., 2002; Boni et al., 2006; Gökaydin et al., 2007). Here, we examine the infection of these viruses has assumed an increased urgency.

Consequently, understanding the dynamics, persistence, and evolution of these viruses has assumed an increased urgency.

One of the open questions in the biology of AIVs remains the ecological and immunological interactions among strains that give rise to and maintain this impressive diversity of viral subtypes. In particular, strain coexistence and sequential strain dominance patterns observed in the field are not consistent with simple density-dependent transmission, which predicts limited strain diversity for influenza viruses (Gog and Grenfell, 2002; Boni et al., 2006; Gökkaydin et al., 2007). Here, we examine how coexistence is affected by different components of transmission.
process of AIV transmission is thought to be predominantly fecal–oral, which has been interpreted as essentially direct because of (i) the necessary proximity between susceptible and infected birds for infection and (ii) the fact that transmission scales with the duration of the infectious period. There is also recent evidence that, in some bird species, direct transmission may also be occurring as via the respiratory route (Kleijn et al., 2010). In addition, however, there is an accumulation of evidence suggesting that transmission via long-lived viruses in environmental reservoirs may be an important, although overlooked component (Hinshaw et al., 1979; Markwell and Shortridge, 1982; Laudert et al., 1993; Roche et al., 2009). This evidence is based in part on the routine isolation of AIVs from mud samples, soil swabs (Hinshaw et al., 1979), and un-concentrated lake water (Vong et al., 2008) and the observation of long persistence times of AIVs in water (Webster et al., 1978; Stallknecht, 1993; Roche et al., 2009). This evidence is based in part on the routine isolation of AIVs from mud samples, soil swabs (Hinshaw et al., 1979), and un-concentrated lake water (Vong et al., 2008) and the observation of long persistence times of AIVs in water (Webster et al., 1978; Stallknecht, 1993; Roche et al., 2009). The environmental transmission mechanism is indirect and acts on a distinctly longer time scale than direct transmission. Recently, studies by Rohani et al. (2009) and Breban et al. (2009) have examined the epidemiology of such mixed transmission systems and the impact of environmental transmission. These authors report that environmental transmission increases the invasion likelihood of AIVs and facilitates the long-term inter-annual persistence of these viruses. In this paper, we propose a mathematical model for the dynamics of two AIV subtypes with both direct and environmental transmission, subject to partial cross-protection. We study this model to examine the consequences of multiple transmission modes for the patterns of coexistence and subtype dominance of AIVs.

Mathematical model

To explore the behavior of competition between two AIV strains with mixed transmission, we develop a deterministic model based on the familiar SIR framework (Anderson and May, 1991; Keeling and Rohani, 2008). Our two-strain model (Fig. 1 and Eqs. (1)–(13)) assumes that individuals are born susceptible to both strains (\(N_{SS}\)) and are subject to strain-specific force of infection (\(\lambda_i; i = 1, 2\)), which integrates both direct (\(\beta d_i\)) and environmental (\(\kappa \rho_i \Phi N_i \frac{C_1}{C_2} \)) transmission (model parameters are described in detail below). Upon infection, individuals move to the \(N_R\) class or the \(N_I\) class, depending on the infecting strain. We incorporate partial cross immunity, as determined by our parameter, \(\epsilon (0 \leq \epsilon \leq 1)\), which measures the level of protection against infection with a strain as a result of current or previous infection with a different strain. Individuals infectious with strain \(i\) may become coinfected with strain \(j (i \neq j)\), leading to class \(N_{IR}\). Partial cross-immunity further determines whether those who have recovered from a previous infection become infected with the other strain (thus entering classes \(N_{RI} \) or \(N_{IR}\)). Finally, after infection with both strains, we assume individuals are immune to both strains (\(N_{RR}\)). In addition, to keep track of infection status within the host population, we also need to determine the kinetics of virus in the environment for each strain. Infectious hosts are assumed to shed virus into the environment at rate \(\omega_i\), with viral decay at a constant rate, given by \(\xi_i\).

The complete set of equations describing our system is given by:

\[
\frac{dN_{SS}}{dt} = \mu N_0 - \lambda_1 N_{SS} - \lambda_2 N_{SS} - \mu N_{SS} \tag{1}
\]

\[
\frac{dN_S}{dt} = \lambda_1 N_{SS} - (1-\epsilon)\lambda_2 N_{IS} - \gamma N_{IS} - \mu N_{S} \tag{2}
\]

\[
\frac{dN_{RS}}{dt} = \gamma N_{IS} - (1-\epsilon)\lambda_2 N_{RS} - \mu N_{RS} \tag{3}
\]

\[
\frac{dN_{IS}}{dt} = \lambda_2 N_{SS} - (1-\epsilon)\lambda_1 N_{SI} - \gamma N_{SI} - \mu N_{IS} \tag{4}
\]

\[
\frac{dN_{SR}}{dt} = \gamma N_{SI} - (1-\epsilon)\lambda_1 N_{SR} - \mu N_{SR} \tag{5}
\]

\[
\frac{dN_{II}}{dt} = (1-\epsilon)\lambda_1 N_{II} + (1-\epsilon)\lambda_2 N_{IR} - 2\gamma N_{II} - \mu N_{II} \tag{6}
\]

\[
\frac{dN_{RI}}{dt} = (1-\epsilon)\lambda_2 N_{RS} + \gamma N_{II} - \gamma N_{IR} - \mu N_{RI} \tag{7}
\]

\[
\frac{dN_{IR}}{dt} = (1-\epsilon)\lambda_1 N_{IR} + \gamma N_{IS} - \gamma N_{IR} - \mu N_{IR} \tag{8}
\]

\[
\frac{dN_{RR}}{dt} = \gamma N_{IR} + \gamma N_{RI} - \mu N_{RR} \tag{9}
\]

\[
\frac{dv_1}{dt} = (1-\phi_1)\omega_1 N_I - \xi_1 V_1 \tag{10}
\]

\[
\frac{dv_2}{dt} = (1-\phi_2)\omega_2 N_I - \xi_2 V_2 \tag{11}
\]

\[
\frac{dn_1}{dt} = \phi_1 \beta_1 N_I + \phi_0 \frac{V_1}{K_1} + \frac{V_1}{K_1} - (\mu + \gamma)N_1 \tag{12}
\]

\[
\frac{dn_2}{dt} = \phi_2 \beta_2 N_I + (1-\delta)\rho \frac{V_2}{K_2} + \frac{V_2}{K_2} - (\mu + \gamma)N_2 \tag{13}
\]

Fig. 1. Diagram of mathematical model. See equations in main text for further details.
The environmental transmission term $\frac{V_i}{V_i + \kappa_i} (i = 1, 2)$ in Eqs. (12) and (13), describe the strain-specific probability of infection, given uptake of $V_i$ virus. In the presence of two competing strains, however, we need to determine the infecting strain given the volume of ingested virus. This is achieved using the parameter $\delta$, which establishes the probability that infection is due to strain 1. $\delta$ is proportional to the number of infectious doses of strain 1 that susceptible individuals encounter. Note that the parameter $\delta$ also guarantees the “ecological neutrality” (sensu Lipsitch et al., 2009) of our two-strain model. This means that if the two strains are deemed functionally equivalent, the environmental transmission rate for the sum of the strains, $f(V_1 + V_2)$, is identical to $f(V_1) + f(V_2)$. The term $\delta$ is defined by:

$$\delta = \frac{V_1 / \kappa_1}{(V_1 / \kappa_1) + (V_2 / \kappa_2)}$$

In previous studies (Rohani et al., 2009), it has been demonstrated that when only one strain is involved, the basic reproductive ratio, $R_0$, is simply the sum of the direct and environmental transmission components (i.e., $R_0 = R_0^{\text{dir}} + R_0^{\text{env}}$). To explore the coexistence mechanisms of competing AIV strains and the role played by environmental transmission, we introduce a new strain-specific parameter $\phi_i$, which simply quantifies the relative contribution of direct transmission to the basic reproductive ratio for strain $i$ (i.e., $R_0 = \phi_i R_i^{\text{dir}} + (1 - \phi_i) R_i^{\text{env}}$, where $0 \leq \phi_i \leq 1$). We modulate the contribution of density-dependent transmission by scaling the transmission rate $\beta_i$ by $\phi_i$. For environmental transmission, modulation may be implemented by either reducing the shedding rate ($\omega_i$) by $(1 - \phi_i)$ or the uptake rate $\rho$. We present our findings assuming that reduced environmental transmission is achieved via a reduction in the shedding rate, although we have verified that our conclusions remain qualitatively unaffected by the specific implementation of this effect.

It is important to point out that changing $\phi_i$ may result in a different overall $R_0$ when $R_i^{\text{env}} \neq R_i^{\text{dir}}$, but it allows us to explore the strategy for each strain in a given situation characterized by $R_i^{\text{env}}$ and $R_i^{\text{dir}}$. Hence, the formula describing $R_0$ for a single strain is:

$$R_0^{i} = \phi_i R_i^{\text{dir}} + (1 - \phi_i) R_i^{\text{env}} = \frac{\phi_i \beta_i N}{\mu + \gamma_i} + \frac{\rho(1 - \phi_i) \omega_i / \kappa_i N}{\kappa_i (\gamma_i + \mu)}$$

The usual approach to understanding the coexistence dynamics in multispecies pathogen interactions has been to derive the criterion by which the invasion of a second strain into a single-strain system is guaranteed. This analytical technique has been used in simpler systems, namely those with partial cross-immunity and only direct transmission (Castillo-Chavez et al., 1989; Bremermann and Thieme, 1989; Gupta et al., 1994; Vasco et al., 2007) or systems with both direct and environmental transmission modes and perfect cross-immunity (Breban et al., 2010). In our system, consisting of two transmission modes and partial protection between strains, the analytical derivation of an invasion or coexistence criterion has not been feasible. Hence, we adopt a numerical approach to understand core epidemiological outcomes of this complex but realistic system. We integrate the system to understand equilibrium dynamics.

**Results**

**Exclusion and coexistence patterns with full cross-immunity**

To explore patterns of strains exclusion and coexistence systematically, we start with the assumption of perfect cross-immunity ($\phi = 1$). If perfect cross-immunity and only direct transmission are considered, theory suggests that coexistence is possible only when both strains are identical. Otherwise, the strain with the biggest $R_0$ should competitively exclude the other strain (Castillo-Chavez et al., 1989). We analyze how these outcomes are scrambled with environmental transmission by assuming $R_0^{\text{dir}} = R_i^{\text{dir}}$ and $R_0^{\text{env}} = R_i^{\text{env}}$.

In Fig. 2, we present the outcome of competition experiments as the relative contributions of direct ($\phi_i$) and environmental ($1 - \phi_i$) transmission are altered for each strain. These patterns are systematically studied assuming a range of values of $R_i^{\text{dir}}$ and $R_i^{\text{env}}$.

Within the large regions of parameter space in which competitive exclusion is observed (dark and light gray areas in Fig. 2), it is the strain with the greater contribution from direct transmission (bigger $\phi_i$) that is competitively dominant, except when $R_i^{\text{dir}} < 1$. This preference for direct instead of environmental transmission is due to competition between viral particles in the environmental reservoir, captured via our $\delta$ parameter (Eq. (14)). As shown by Rohani et al. (2009), environmental transmission leads to a slower epidemic growth than direct transmission for a given $R_0$; therefore, the strain with a larger direct transmission component will numerically dominate, both in terms of the number of infectious individuals and the environmental virus reservoir. In mathematical terms, if $\phi_1$ tends to 1 and $\phi_2 < \phi_1$, $\delta$ will tend to 1 (Fig. 3), resulting in extinction of strain 2.

Different coexistence patterns (white areas in Fig. 2) are observed as $R_i^{\text{dir}}$ and $R_i^{\text{env}}$ are varied. When $R_i^{\text{dir}} > R_i^{\text{env}}$, coexistence requires that the two strains have the same $R_0 (> 1)$, as might be expected from theory (Anderson and May, 1982). What is unexpected, however, is our finding that strain coexistence is possible only when competing subtypes have identical ratios of direct and environmental transmission ($\phi_1 = \phi_2$). This is despite the fact that when restrictive coexistence is due to the competition process for viral particles acquisition in the environment, as explained above.

This pattern is slightly modified when $R_0^{\text{env}} > R_0^{\text{dir}}$. In this case, that is only directly transmitted can coexist with a partly environmentally transmitted strain $j$ ($i \neq j$). Since strain $i$ does not shed any viral particle ($1 - \phi_i = 0$), this strain cannot outcompete strain $j$ through environmentally mediated competition. Strain $j$ will be competitively excluded through a lack of susceptible individuals, but it can persist via environmental transmission chains (since uptake rate $\rho$ is not affected by $\phi_j$) and its direct transmission component (which allows rapid growth). When strain $j$ does not benefit of density-dependent transmission ($\phi_j \rightarrow 0$) or if $R_0^{\text{env}}$ is too low, coexistence becomes impossible once again.

Finally, when $R_0^{\text{dir}} < 1$ or $R_0^{\text{env}} < 1$, both strains go extinct if their $R_0$ values below 1 (i.e., $\phi_1$ close to 0 when $R_0^{\text{dir}} < 1$ or $\phi_2$ close to 1 when $R_0^{\text{env}} < 1$).

**Influence of partial cross-immunity**

We now relax the assumption of perfect cross-immunity and explore its consequences on patterns of strain coexistence. Fig. 4 shows that viral coexistence is enhanced by partial cross-immunity, but only when both strains are predominantly directly transmitted. This is because when transmission is direct, strains compete for susceptible individuals. Partial cross-immunity reduces the strength of this competitive effect by introducing the possibility for (i) coinfection and (ii) subsequent infection. In contrast, the strength of competition mediated via environmental transmission remains unaffected by reduced cross-immunity, with coexistence still determined by $\delta$ (Fig. 3). In the limit of no cross-immunity ($\delta \rightarrow 0$), we observe a threshold in the coexistence condition as strains become increasingly environmentally transmitted (Fig. 4). This is again a manifestation of the process discussed above. As $\phi_i$ values approach zero, competition among strains is environmentally mediated and strong and, as a result, the coexistence likelihood is unaffected by factors that affect host immunity, but by the competition term $\delta$ (Fig. 3). Finally, the increase of $R_0^{\text{env}}$ alters only the specific case where an exclusively directly transmitted strain $i$ and a strain $j$ which is partly environmentally transmitted can coexist, as it was shown with the assumption of full cross-immunity.
Strain dominance

We now turn our attention to the question of avian influenza virus subtype diversity. In particular, we wish to explore the epidemiological trade-offs that determine strain dominance and persistence. We examine the case of permanent full cross-immunity (\(c = 1\)) where \(R_0^{\text{env}} = R_0^{\text{dir}}\) for the sake of simplicity. We ensure the components of the basic reproductive ratio for competing strains are identical, i.e., \(R_0^{1\text{env}} = R_0^{2\text{env}} \) and \(R_0^{1\text{dir}} = R_0^{2\text{dir}}\). Now, in turn, we modify the main epidemiological parameters for each transmission mode (\(\beta_i\) and \(\gamma_i\) for direct transmission and \(\omega_i\) and \(\xi_i\) for environmental transmission) and explore its consequences for strains dominance. This is achieved via transmission mode-specific parameters \(\eta_i^{\text{dir}}\) and \(\eta_i^{\text{env}}\). For instance, if we fix the components of environmental transmission for both strains and modify the components of direct transmission by setting \(\eta_i^{\text{dir}} = 2\) and \(\eta_i^{\text{env}} = 0.5\), we study the outcome of competition among two strains with identical \(R_0\) values but very contrasting life history strategies. Strain 1 represents a ‘live fast, die young’ strategy, with a high transmission rate (\(\beta_1\)) and rapid host clearance (\(\gamma_1\)). Strain 2, on the other hand, while having the same overall reproductive fitness (measured in terms of \(R_0\)), adopts a ‘slow but steady’ strategy with a moderate transmission rate but a longer infectious period (see Supplementary materials for \(\eta_i^{\text{dir}}\) and \(\eta_i^{\text{env}}\) calculations).

In Fig. 5A, we study the aspects of direct transmission. We find that competition clearly favors the strain with the higher transmission rate, despite the shorter infectious period of such strains. This finding is intuitive since higher transmission rate leads to more transmission in the early stages, and this numerical advantage drives the eventual outcome of competition.

In contrast, when we fix the components of direct transmission and study the environmental transmission strategies, the outcome is more complex (Fig. 5B). We find four different scenarios with strain dominance determined by the interplay between viral shedding rate of infectious individuals and direct transmission.

When \(\eta_i^{\text{env}}\) is small, the shedding rate (\(\omega_i\)) is low and environmental persistence (\(1/\xi_i\)) is high. In this case, direct transmission plays the most important role in determining strain dominance: the dominant strain at equilibrium is also the dominant strain at the peak of the epidemic. When \(\eta_i^{\text{env}}\) is large, viral shedding rate increases, reversing
the pattern (the most abundant strain at the epidemic peak is not the most prevalent strain at equilibrium). This result suggests the existence of a threshold when shedding rate becomes sufficiently large to guarantee a higher level of persistence at equilibrium than direct transmission.

Discussion and Conclusion

The importance of avian influenza viruses from both a public health perspective and the economics of poultry systems points to the need for a deep understanding of their ecology and evolution. One of the significant open questions concerning AIVs remains the mechanisms that determine the coexistence of a very large diversity of viral subtypes (Webster et al., 1992; Swayne, 2008). To address this, we have formulated a novel two-strain model with mixed transmission dynamics, incorporating both direct and environmentally mediated transmission mechanisms. Our ultimate aim has been to explore and understand the factors that shape coexistence of competing AIV strains. The finding that—with perfect cross-immunity—competing viruses need to have the same $R_0$ for coexistence is not surprising. However, our conclusion that strain coexistence is possible only when both strains have identical $R_0^{env}$ and $R_0^{env}$ is interesting and perhaps unexpected. This pattern is slightly modified when $R_0^{env} \geq R_0^{dir}$. Indeed, coexistence is possible when at least one strain is only directly transmitted (i.e., it does not shed any viral particles within environment), and the other is partly environmentally transmitted. In this case, competitive exclusion is mediated through susceptible individuals.

When transmission strategies include differential direct and environmental components, we find that the directly transmitted strain enjoys a substantial competitive advantage, unless $R_0^{env}$ is below one. When infection confers imperfect immunity to competing AIV strains, coexistence is most likely when strains are predominantly directly transmitted, modulated via reduced susceptible depletion. In contrast, partial cross-immunity does not affect coexistence of environmentally transmitted strains since they still compete in the environmental reservoir. This difference in competition processes leads to a threshold for the coexistence region where cross-immunity becomes small. In this case, competition for susceptible individuals is removed and competition for virions dominates. Finally, we have explored the epidemiological characteristics of coexisting AIVs, with a view to understanding the determinants of strain dominance. A complex pattern is documented when the components of environmental transmission are varied while keeping $R_0^{env1} = R_0^{env2}$. We find that strain dominance is not accurately predicted by conditions at the epidemic peak. Ultimately, while the strain with the higher viral shedding rate enjoys a numerical advantage at the peak of the outbreak, dominance, in the long run, is favored by long-term environmental persistence.

One of the strongest qualitative results from this work is that coexistence is more likely under predominantly direct transmission rather than environmental transmission. As we show in the Supplementary Information (specifically Figs. S4 and S5), this result holds even when $R_0^{env1} \neq R_0^{env2}$. This may be somewhat surprising since elsewhere it has been argued that environmental transmission may play a key role in the interannual persistence of AIVs (Breban et al., 2009; Rohani et al., 2009). By extension, one might expect the environmental reservoir to serve as a mixing vessel, permitting the coexistence of diverse virus strains.

Ultimately, the resolution of these issues may depend on aspects of our modeling framework. First, the issue of immunity, both homologous and heterologous, is central. We have assumed immunity to be lifelong, although this is the subject of contention in the literature. Several studies have shown that the period of immunity could be shorter than host life span (Kida et al., 1980; Hinshaw et al., 1981), while others have questioned this conclusion (Olsen et al., 2006). The inclusion of temporary immunity would probably lead to greater coexistence, despite it is questionable whether our qualitative conclusions would be affected. Second, there are alternative ways in which environmental transmission can be modelled (Dennis, 1989; Breban et al., 2009). In this paper, we have used a rectangular hyperbolic function, while others have proposed the negative exponential function (Breban et al., 2009). Our choice of this function has been biologically motivated and has been previously successfully applied to empirical AIV prevalence data (Roche et al., 2009). Third, and perhaps most importantly, we believe our conclusions would be significantly affected by the inclusion of seasonality, intended to
capture the breeding biology of hosts, their patterns of seasonal migration and differential environmental persistence driven by changes in temperature (Breban et al., 2009). Disentangling the effects of these forces on AIV strain proliferation and patterns of environmental persistence driven by migration and differential environmental persistence driven by changes in temperature (Breban et al., 2009). Disentangling the effects of these forces on AIV strain proliferation and patterns of seasonal migration and differential environmental persistence driven by changes in temperature (Breban et al., 2009). Disentangling the effects of these forces on AIV strain proliferation and patterns of seasonal migration and differential environmental persistence driven by changes in temperature (Breban et al., 2009).

Acknowledgments

This work is supported by the Centers for Disease Control and Prevention (SU19CI000401), the James S. McDonnell Foundation, and the National Science Foundation (DEB-0917853). P.R. was also supported by the RAPIDD program of the Science & Technology Directorate, Department of Homeland Security, and the Fogarty International Center, National Institutes of Health.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.epidem.2010.03.002.

References