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Environmental transmission scrambles coexistence patterns of avian influenza viruses

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ABSTRACT

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 (R_0^{dir} and R_0^{env}) 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.

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., 2001; Rohani et al., 2003), as well as numerous empirical documentations of spillover of zoonotic infectious diseases to a diversity of host species (Taylor et al., 2001; Woolhouse and Gowtage-Sequeria, 2005).

Influenza A viruses are among the best-studied infectious diseases, especially with regards to their transmission dynamics among humans, with a significant body of interesting theoretical (Ferguson et al., 2003; Viboud et al., 2006; Koelle et al., 2006) and empirical (Holmes et al., 2005; Flahault et al., 2006) research. In contrast, the ecology and evolution of these viruses in their wild avian reservoirs remain relatively poorly understood (Webster et al., 1992; Olsen et al., 2006). This may be partly because of the impressive genetic and antigenic diversity of avian influenza viruses (AIVs) in their reservoir species. Influenza A viruses are classically divided into subtypes depending on two surface glycoproteins (Spackman, 2008; Cox and Subbarao, 2000), hemagglutinin (H) and neuraminidase (N). Thus far, 16 distinct H and 9 distinct N types have been isolated from avian species in the wild (Swayne, 2008). AIVs came to prominence after the identification of the highly pathogenic (HPAIV) H5N1 in Southeast Asia during the late 1990s (Subbarao et al., 1998). This virus is unusual among AIVs due to its abnormally high virulence in bird species. The subsequent high-profile transmission of HPAIV H5N1 to humans and its geographical spread has resulted in 262 deaths to date, with an alarming estimated case fatality probability of 60% (Li et al., 2008). 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; Gökaydin et al., 2007). Here, we examine how coexistence is affected by different components of transmission. The

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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 unconcentrated lake water (Vong et al., 2008) and the observation of long persistence times of AIVs in water (Webster et al., 1978; Stallknecht et al., 1990; Webster et al., 1992). 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 (λ_i; $i=1, 2$), which integrates both direct ($\beta_i I_i$) and environmental $\left(\delta\rho\frac{V_i}{V_i+\kappa}\right)$ transmission (model parameters are described in detail below). Upon infection, individuals move to the N_{SI} class or the N_{IS} class, depending on the infecting strain. We incorporate partial cross immunity, as determined by our parameter, $\epsilon(0\le\epsilon\le1)$, 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_{II}. 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 ω_i, with viral decay at a constant rate, given by ξ_i.

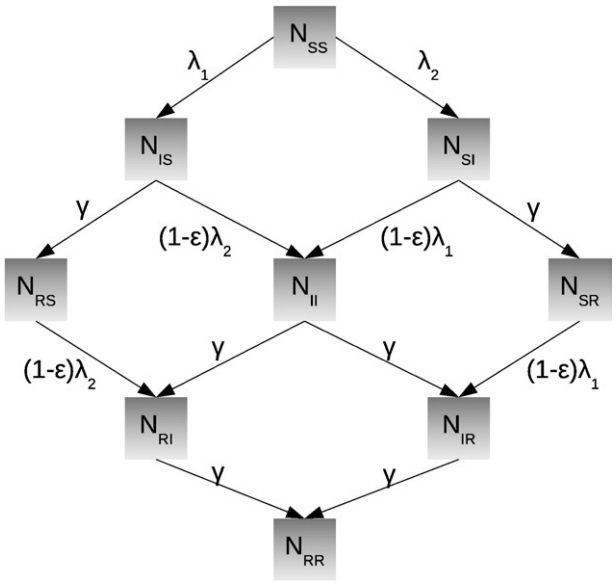

Fig. 1. Diagram of mathematical model. See equations in main text for further details.

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

$$\frac{dN_{SS}}{dt} = \mu N-\lambda_1 N_{SS}-\lambda_2 N_{SS}-\mu N_{SS} \quad (1)$$

$$\frac{dN_{IS}}{dt} = \lambda_1 N_{SS}-(1-\epsilon)\lambda_2 N_{IS}-\gamma N_{IS}-\mu N_{IS} \quad (2)$$

$$\frac{dN_{RS}}{dt} = \gamma N_{IS}-(1-\epsilon)\lambda_2 N_{RS}-\mu N_{RS} \quad (3)$$

$$\frac{dN_{SI}}{dt} = \lambda_2 N_{SS}-(1-\epsilon)\lambda_1 N_{SI}-\gamma N_{SI}-\mu N_{SI} \quad (4)$$

$$\frac{dN_{SR}}{dt} = \gamma N_{SI}-(1-\epsilon)\lambda_1 N_{SR}-\mu N_{SR} \quad (5)$$

$$\frac{dN_{II}}{dt} = (1-\epsilon)\lambda_1 N_{SI} + (1-\epsilon)\lambda_2 N_{IS}-2\gamma N_{II}-\mu N_{II} \quad (6)$$

$$\frac{dN_{RI}}{dt} = (1-\epsilon)\lambda_2 N_{RS} + \gamma N_{II}-\gamma N_{RI}-\mu N_{RI} \quad (7)$$

$$\frac{dN_{IR}}{dt} = (1-\epsilon)\lambda_1 N_{SR} + \gamma N_{II}-\gamma N_{IR}-\mu N_{IR} \quad (8)$$

$$\frac{dN_{RR}}{dt} = \gamma N_{IR} + \gamma N_{RI}-\mu N_{RR} \quad (9)$$

$$\frac{dV_1}{dt} = (1-\phi_1)\omega_1 I_1-\xi_1 V_1 \quad (10)$$

$$\frac{dV_2}{dt} = (1-\phi_2)\omega_2 I_2-\xi_2 V_2 \quad (11)$$

$$\frac{d\lambda_2}{dt} = \phi_1\beta_1 I_1 + \delta\rho\frac{V_1}{\kappa_1+V_1}-(\mu+\gamma)\lambda_1 \quad (12)$$

$$\frac{d\lambda_2}{dt} = \phi_2\beta_2 I_2 + (1-\delta)\rho\frac{V_2}{\kappa_2+V_2}-(\mu+\gamma)\lambda_2 \quad (13)$$

Here, μ is the host *per capita* birth and death rate, $1/\gamma$ determines the mean duration of the infectious period, ρ is the uptake rate of environmental virions, κ_i denotes the strain-specific dose that yields a 50% probability of infection (ID_{50}), and $I_1=N_{IS}+N_{IR}+N_{II}$ and $I_2=N_{SI}+N_{RI}+N_{II}$. The host population size is denoted by N and is assumed to be constant. Note that in models where coinfection is assumed possible, care needs to be taken to ensure the infectious period for each strain is, on average, the same as in the single infection models. A discrepancy may arise if, for example, an individual who has spent several days in the I_i class becomes coinfected with strain j ($i\neq j$), with time spent in the dually infected class leading to an overall infectious period for strain i that exceeds $1/\gamma_i$. Following the lead of Vasco et al. (2007), we overcome this systematic bias by tracking, in addition to the infectious population size, the "force of infection" λ_i ($i=1, 2$), as shown by Eqs. (12) and (13) (see also Rohani et al., 2008).

The environmental transmission terms $\frac{V_i}{V_i + \kappa_i}$ $(i=1,\ 2)$ 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 δ, which establishes the probability that infection is due to strain 1. δ is proportional to the number of infectious doses of strain 1 that susceptible individuals encounter. Note that the parameter δ 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 δ is defined by:

$$\delta = \frac{V_1/\kappa_1}{(V_1/\kappa_1) + (V_2/\kappa_2)} \tag{14}$$

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 ϕ_i, which simply quantifies the relative contribution of direct transmission to the basic reproductive ratio for strain i (i.e., $R_0^i = \phi_i\ R_0^{[i]\text{dir}} + (1-\phi_i)\ R_0^{[i]\text{env}}$ where $0 \le \phi_i \le 1$). We modulate the contribution of density-dependent transmission by scaling the transmission rate β_i by ϕ_i. For environmental transmission, modulation may be implemented by either reducing the shedding rate (ω_i) by $(1-\phi_i)$ or the uptake rate ρ. 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 ϕ may result in a different overall R_0 when $R_0^{\text{env}} \neq R_0^{\text{dir}}$, but it allows us to explore the strategy for each strain in a given situation characterized by R_0^{env} and R_0^{dir}. Hence, the formula describing R_0 for a single strain is:

$$R_0^{[i]} = \phi_i R_0^{[i]\text{dir}} + (1-\phi_i) R_0^{[i]\text{env}} = \frac{\phi_i \beta_i N}{\mu + \gamma_i} + \frac{\rho(1-\phi_i)\omega_i/\kappa_i N}{\kappa_i \xi_i (\gamma_i + \mu)} \tag{15}$$

The usual approach to understanding the coexistence dynamics in multistrain 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 ($\epsilon = 1$). 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 $R_0^{1[\text{dir}]} = R_0^{2[\text{dir}]}$ and $R_0^{1[\text{env}]} = R_0^{2[\text{env}]}$. In Fig. 2, we present the outcome of competition experiments as the relative contributions of direct (ϕ_i) and environmental $(1-\phi_i)$ transmission are altered for each strain. These patterns are systematically studied assuming a range of values of R_0^{dir} and R_0^{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 ϕ_i) that is competitively dominant, except when $R_0^{\text{dir}} < 1$. This preference for direct instead of environmental transmission is due to competition between viral particles in the environmental reservoir, captured via our δ 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 ϕ_1 tends to 1 and $\phi_2 < \phi_1$, δ will tend to 1 (Fig. 3), resulting in extinction of strain 2.

Different coexistence patterns (white areas in Fig. 2) are observed as R_0^{dir} and R_0^{env} are varied. When $R_0^{\text{dir}} > R_0^{\text{env}}$, 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 $R_0^{\text{env}} \ge R_0^{\text{dir}}$. In this case, a strain i 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 ρ is not affected by ϕ_j) and its direct transmission component (which allows rapid growth). When strain j does not benefit of density-dependent transmission ($\phi_j \to 0$) or if R_0^{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., ϕ_i close to 0 when $R_0^{\text{env}} < 1$ or ϕ_i close to 1 when $R_0^{\text{dir}} < 1$).

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 δ (Fig. 3). In the limit of no cross-immunity ($\epsilon \to 0$), 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 ϕ_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 δ (Fig. 3). Finally, the increase of R_0^{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.

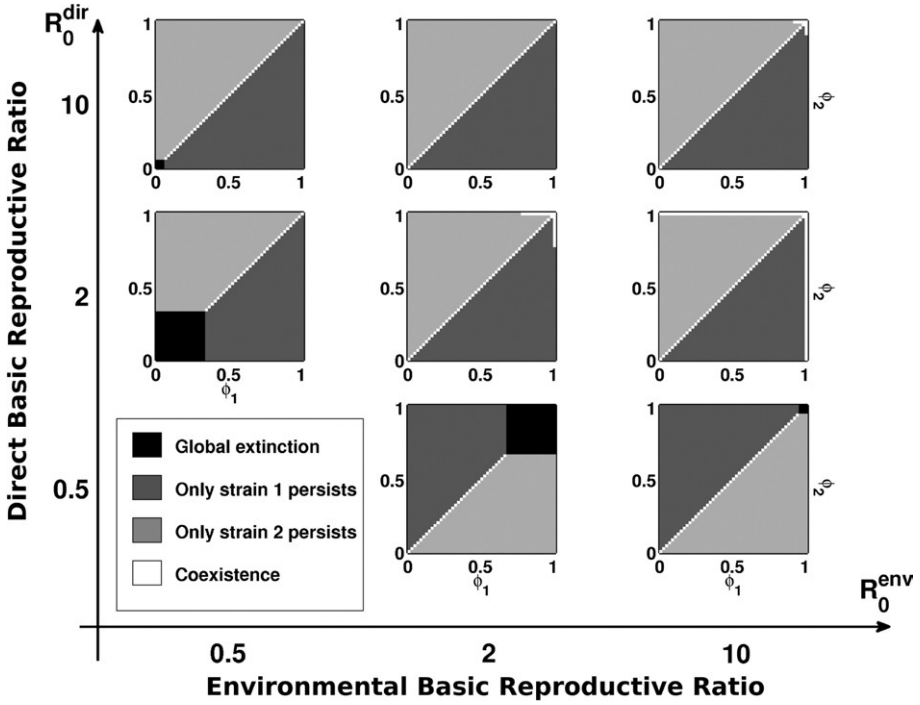

Fig. 2. Competition patterns between two strains with full cross-immunity. The epidemiological traits of the two strains are assumed identical, except the ϕ_i parameter. The light grey area shows area where strain 2 dominates and dark grey indicates area where strain 1 dominates. The white area shows coexistence area and black area indicates global extinction. ϕ_i is the preference for direct transmission for strain i (0: only environmental transmission, 1: only direct transmission). Parameters: $\mu = 0.5$, $N = 10000$, $\rho = 0.000004$, $\kappa_i = 10$, $1/\gamma_i = 7$ days and $1/\xi_i = 74$ days. β_i and ω_i are modified to have different values of R_0^{dir} and R_0^{env}, respectively. Simulations started with 1 infectious individual and 100 viral particles for each strain. The equilibrium dynamics are presented after discarding 150 years of transient dynamics. A strain is considered persistent if the number of infectious individuals with the strain exceeds 10^{-10} and its force of infection is greater than 10^{-12}. In the Supplementary Information, we explore the sensitivity of our findings to assumptions regarding the initial conditions.

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 ($\epsilon = 1$) where $R_0^{env} = R_0^{dir}$ for the sake of simplicity. We ensure the components of the basic reproductive ratio for competing strains are identical, i.e., $R_0^{[1]env} = R_0^{[2]env}$ and $R_0^{[1]dir} = R_0^{[2]dir}$. Now, in turn, we modify the main epidemiological parameters for each transmission mode (β_i and γ for direct transmission and ω_i and ξ_i for environmental transmission) and explore its consequences for strains domination. This is achieved via transmission mode-specific parameters η_i^d and η_i^e. For instance, if we fix the components of environmental transmission for both strains and modify the components of direct transmission by setting $\eta_1^d = 2$ and $\eta_2^d = 0.5$, 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 (β_1) and rapid host clearance (γ_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 η_i^d and η_i^e 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 η_i^e is small, the shedding rate (ω_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 η_i^e is large, viral shedding rate increases, reversing

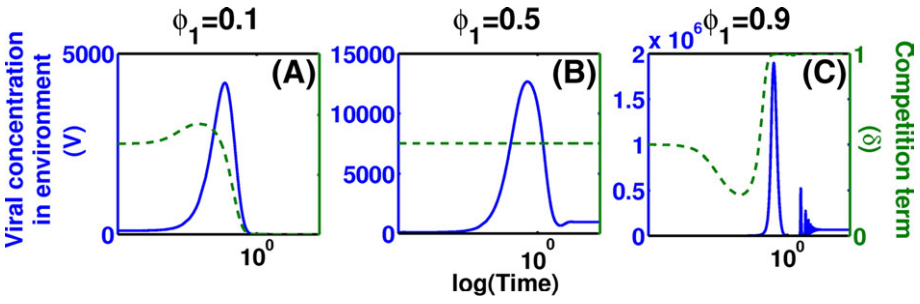

Fig. 3. Illustration of competition for viral particles in environment. Left Y-axis (solid line) is the load of viral particles into environment. δ parameter (right Y-axis, dashed line) represents proportion of viral particles from strain 1 into environment. (A) $\phi_1 = 0.1$, (B) $\phi_1 = 0.5$, and (C) $\phi_1 = 0.9$. Parameters: $\phi_2 = 0.5$, $\mu = 0.5$, $N = 10000$, $\rho = 0.000004$, $\kappa_i = 10$, $1/\gamma_i = 7$ days, $\omega_i = 2.10^5$, $\beta_i = 0.18$, $1/\xi_i = 74$ days, $\varepsilon = 1$.

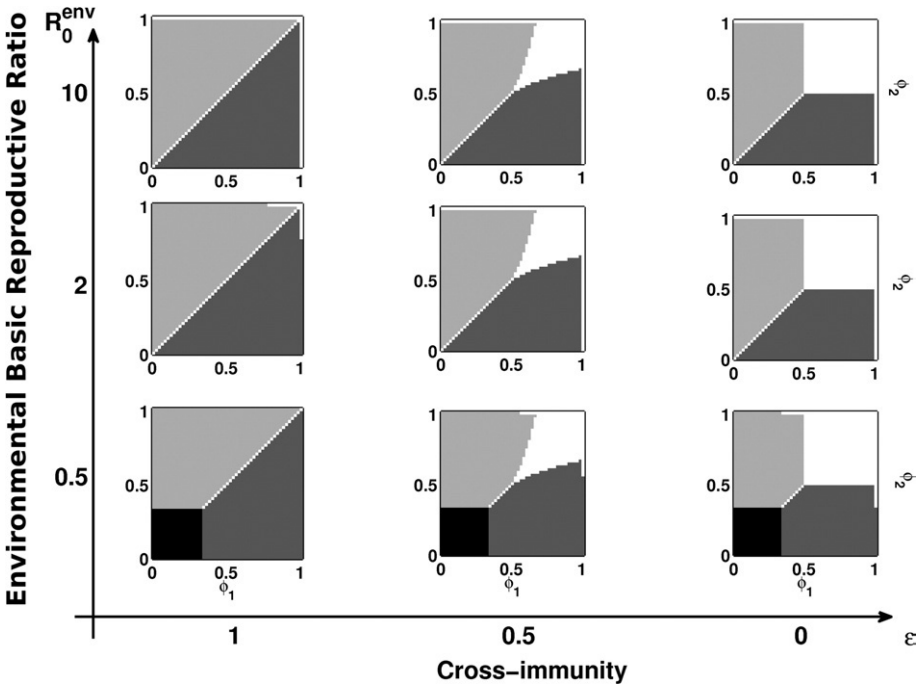

Fig. 4. Influence of partial cross-immunity. Colors codification are the same than in previous figure. Parameters: $\mu = 0.5$, $N = 10000$, $\rho = 0.000004$, $\kappa_i = 10$, $1/\gamma_i = 7$ days, $1/\xi_i = 74$ days. R_0^{dir} is equal to 2 and ω_i is modified to have different values of R_0^{env}. Initial conditions are the same as in previous figure.

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^{dir} 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^{dir} 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 $R_0^{[1]env} = R_0^{[2]env}$. 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 $R_0^{[1]} \neq R_0^{[2]}$. 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

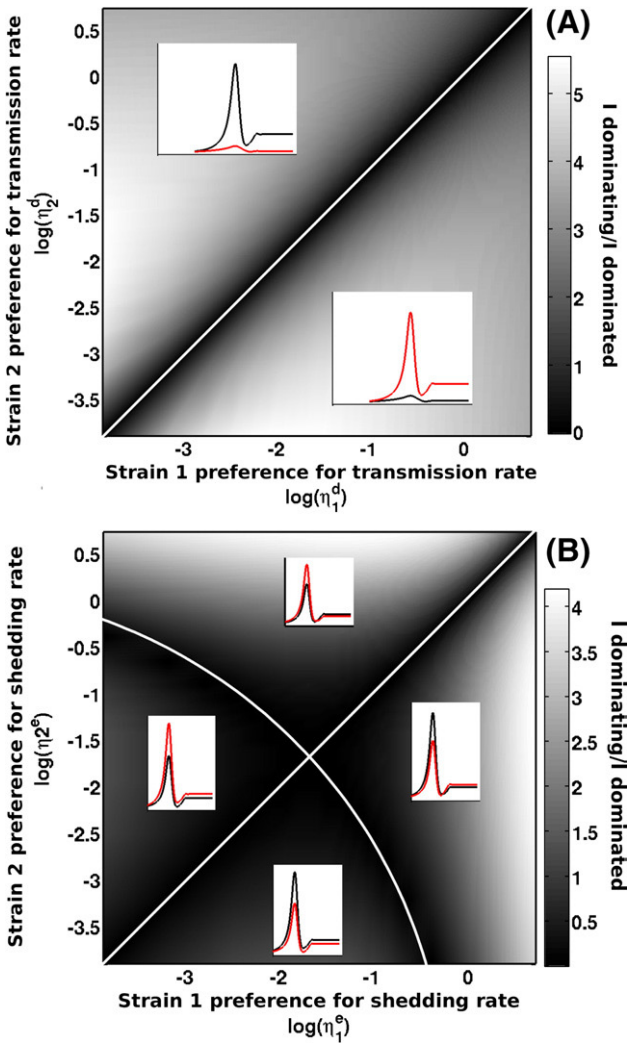

Fig. 5. Dominating strain in case of coexistence (when $R_0^{[1]dir} = R_0^{[2]dir}$ and $R_0^{[1]env} = R_0^{[2]env}$). Colors of contours represent ratio between infectious population size of dominating strain and infectious population size of dominated strain. Brightest areas represent a high ratio of dominating over dominated strain and darkest area shows a low ratio. White lines represents shift for dominating strain at equilibrium. The four insets plot the time course of dynamics with grey and black lines representing prevalence of strains 1 and 2, respectively. Parameters: $\phi_i = 0.5$, $\mu = 0.5$, $N = 10000$, $\rho = 0.000004$, $\kappa_i = 10$ (A) $1/\xi = 74$ days, $\beta_0 = 0.18$, (B) $\beta_i = 0.18$, $1/\gamma_i = 7$ days.

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 sequential dominance is a research priority.

Acknowledgments

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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.

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