COMPETITIVE INTERFERENCE BETWEEN INFLUENZA VIRAL STRAINS

SEYED M. MOGHADAS, CHRISTOPHER S. BOWMAN
AND JULIEN ARINO

ABSTRACT. We propose a modelling framework for investigating the dynamics of competition between immunologically-related influenza viral strains in the absence of pre-existing immunity. Assuming that the host immune system will mount partial protection (cross-immunity) against one strain by virtue of having interacted with the other through exposure, we discuss the conditions for the occurrence of two distinct waves of infection during a single epidemic episode. Numerical simulations are presented to illustrate the possibility of infection waves with respect to the protection level induced by the first strain, and the time-lag for evolving the second strain. We propose directions for future work that involves extension of the model to include vaccination.

1 Introduction An important feature of influenza virus replication is the high mutation rates exhibited over short time scales [**7, 11**]. Influenza epidemics are usually triggered by viruses in the same subtype which may confer protection against re-infection by successor mutants with similar characteristics [**14**]. The level of this protection, however, depends on several factors, and in particular, the antigenic properties of such mutants [**10, 14, 16**]. If mutations with sufficiently distinct antigenicity arise (usually referred to as "drift" during seasonal influenza epidemics), then pre-existing strain-specific immune responses of the host may not provide adequate protection to inhibit virus replication. As the level of protection (cross-immunity) due to prior exposure increases, the disease is more likely to be asymptomatic if infection occurs [**8**].

While the dynamics of influenza virus drift during seasonal epidemics

have been discussed in previous work [**1, 3, 9, 12, 13, 15, 17**], the literature on competitive interference between immunologically-related viral strains during the course of a single epidemic is rather scant. Here we propose a mathematical model including two strains of influenza, and investigate the effects of two important factors in the population dynamics of infection: (i) cross-immunity, considered as the reduction in the individual risk of infection by one strain after recovery from infection by the other strain; and (ii) the time-lags for the emergence of the second strain after the onset of epidemic with the first strain. While co-circulation of different subtypes of influenza viruses have been documented during influenza seasons [**22**], we consider the model for two strains of a single subtype of influenza viruses (e.g., several known strains of influenza A/H1N1 virus that have been used for vaccine composition in the past 10 years include A/Solomon Islands/3/2006; A/Brisbane/59/2007; A/New Caledonia/20/99; A/Beijing/262/95; [**21**]). The model is simulated to illustrate two subsequent infection waves, a phenomenon that has been observed in previous influenza outbreaks, most notably in the 1918 pandemic [**19**].

2 The model   We develop a homogeneous compartmental model that includes two influenza strains competing for a given susceptible population (Figure 1). For the course of a single epidemic event, we ignore recruitment, natural death, and other demographic variables. Infection with either strain may lead to asymptomatic or symptomatic infection. We assume that recovery from infection by one strain confers partial protection (cross-immunity) against the other strain, which reduces the transmissibility of the secondary exposure, and increases the probability of being asymptomatic if a second infection occurs. The model does not include simultaneous co-infection by different strains, but assumes that subsequent infections with both strains will prevent re-infection. With these assumptions, the model can be expressed by the following systems of differential equations:

(1a) $S' = -(f + g)S,$

(1b) $A_1' = (1 - p)Sf - \mu_A A_1,$ $A_2' = (1 - p)Sg - \mu_A A_2,$

(1c) $I_1' = pSf - \mu I_1$ $I_2' = pSg - \mu I_2,$

(1d) $P_1' = \mu_A A_1 + \mu I_1 - \delta_{12} g P_1,$ $P_2' = \mu_A A_2 + \mu I_2 - \delta_{21} f P_2,$

(1e) $A_{21}' = (1 - p_{21})\delta_{21} f P_2$ $A_{12}' = (1 - p_{12})\delta_{12} g P_1$

$\qquad\qquad\qquad - \mu_A A_{21},$ $- \mu_A A_{12},$

(1f) $I'_{21} = p_{21}\delta_{21}P_2 f - \mu I_{21}, \qquad I'_{12} = p_{12}\delta_{12}P_1 g - \mu I_{12},$

where

$$f = \beta(\delta_A(A_1 + A_{21}) + I_1 + I_{21}),$$
$$g = \beta(\delta_A(A_2 + A_{12}) + I_2 + I_{12}),$$

and β is the baseline transmission rate; p, p_{12} and p_{21} are the probabilities of developing symptomatic infection with no prior exposure, with prior exposure to strain 1, and with prior exposure to strain 2, respectively; δ_A is the reduction in infectiousness of asymptomatic infection; μ and μ_A are the recovery rates from symptomatic and asymptomatic infections, respectively; and δ_{12} and δ_{21} represent the reduction in transmissibility as a result of cross-immunity induced by previous exposure to strain 1 and strain 2, respectively. Applying a previously established technique [20], the basic reproduction number (defined as the number of secondary infections generated by a single infected individual in an entirely susceptible population [7]) can be expressed as

(2) $R_0 = \beta S_0 \left(\dfrac{(1-p)\delta_A}{\mu_A} + \dfrac{p}{\mu} \right),$

where S_0 is the initial size of the susceptible population. By simulating the model, we illustrate that the epidemic dynamics can be affected by the lag-time between emergence of different strains and the level of cross-immunity conferred through exposure to one strain.

3 Numerical simulations   Using parameter values given in Table 1, we simulated the model to illustrate the possibility of two infection waves during a single epidemic episode. For a given value of the basic reproduction number, the transmission rate β can be obtained by substituting parameter values into the expression (2). It is assumed that strain 2 emerges at time $T^* \geq 0$ after the onset of an epidemic involving strain 1. For simplicity, we assumed that exposure to different strains results in the same level of cross-immunity with $\delta_{12} = \delta_{21}$.

We seeded the epidemic with an individual infectious with strain 1 in a susceptible population of 100,000 individuals, and assumed $R_0 = 1.6$. Given 40% cross-immunity between the two strain ($\delta_{12} = \delta_{21} = 0.6$), Figure 2(a) illustrates the time-courses of disease (all infections) when the second strain arises on day 10 (solid curves, $T^* = 10$) and day 60 (dashed curve, $T^* = 60$) after the onset of an epidemic with the first
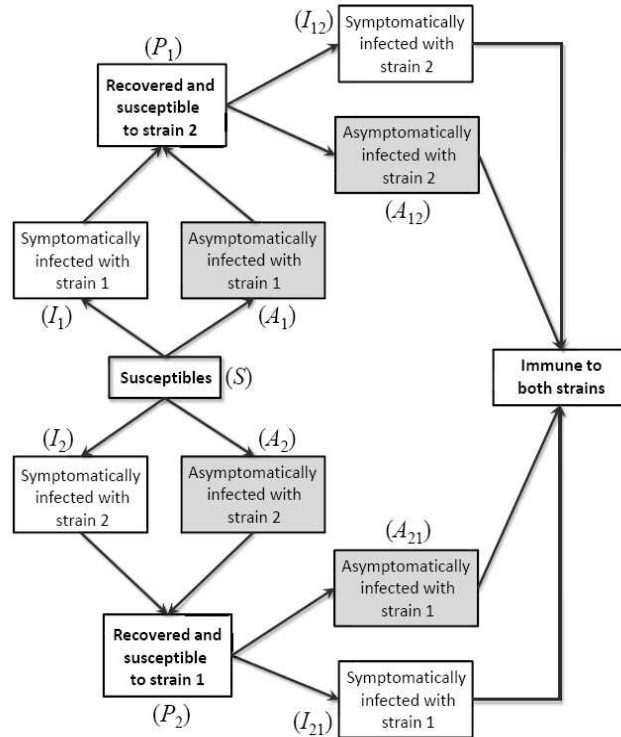
FIGURE 1: Model diagram for the movements of individuals between population compartments.

strain. We observed that two infection waves can occur if the time-lag for the emergence of the second strain during the epidemic is sufficiently large. A similar scenario can be observed for different levels of cross-immunity as shown in Figure 2(b). For a given time $T^* = 60$ days for the emergence of the second strain, a single peak of infection occurs for 60% cross-immunity (solid curve, $\delta_{12} = \delta_{21} = 0.6$), whereas two infection peaks take place as the level of cross-immunity reduces to 10% (dashed curve, $\delta_{12} = \delta_{21} = 0.9$). We also observed qualitatively similar behaviour by simulating the stochastic version of the model proposed here, where "random effects" are taken into account.

parameter	baseline value
R_0	1.6
δ_{12}, δ_{21}	variable
p	0.67
p_{12}	$p\delta_{12}$
p_{21}	$p\delta_{21}$
δ_A	0.142
μ_A	$1/4.1$ day^{-1}
μ	$1/4.1$ day^{-1}
T^*	variables

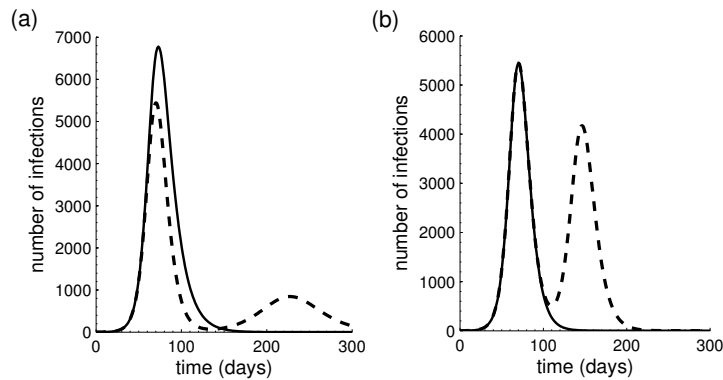TABLE 1: Model parameters with their values [**2, 5**].

FIGURE 2: Time courses of epidemics with two-strains: single wave (solid curve) and two waves (dashed curve). (a) $\delta_{12} = \delta_{21} = 0.6$, solid curve: $T^* = 10$ and dashed curve: $T^* = 60$; (b) $T^* = 60$, solid curve: $\delta_{12} = \delta_{21} = 0.4$, and dashed curve: $\delta_{12} = \delta_{21} = 0.9$.

4 Concluding remarks   We developed a simple homogeneous model with two influenza strains and demonstrated that subsequent infection peaks can occur in a single epidemic season for different combination of two key parameters: the timing for the emergence of the second strain, and the level of cross-immunity between the two strains. Our simulations indicate that if the second strain emerges with a sufficiently small delay, or the level of cross-immunity is sufficiently high, the epidemic

unfolds with only a single illness peak. For the early evolution of the second strain, infections with different strains merge into a single epidemic wave. When the degree of cross-immunity is sufficiently high, the time at which the second strain emerges during the epidemic of the first strain is crucial. If a significant number of susceptible hosts have already been infected with the first strain, cross-immunity will prevent the occurrence of a subsequent peak of illness.

In the context of cross-immunity, vaccination is an important factor [18] which has not been included in our model. Vaccination can impact the antigenic drift of influenza viruses and therefore the competitive interference between influenza strains in several ways [4, 18]. First of all, a vaccine could provide some level of cross-immunity between successor strains related to its composition, and therefore reduce the population incidence of a second emerging strain. Secondly, vaccination (with reasonable individual's protection and population's coverage) can suppress the epidemic of the first strain and decelerate its progression, resulting in a sufficiently large pool of susceptibles for the second strain (if it emerges) to cause a subsequent outbreak. Furthermore, vaccination against the first strain may start during the outbreak and provide insufficient level of protection (i.e., poor-match vaccine) or inadequate level of cross-immunity between strains (due to antigenic drift of the virus), which can influence disease dynamics in a complex manner. The impact of these factors on epidemic dynamics is currently under investigation.

REFERENCES

1. V. Andreasen, J. Lin and S. A. Levin, *The dynamics of cocirculating influenza strains conferring partial cross-immunity*, J. Math. Biol. **35** (1997), 825–842.
2. J. Arino, C. S. Bowman and S. M. Moghadas, *Antiviral resistance during pandemic influenza: implications for stockpiling and drug use*, BMC Infect Dis 2009; DOI:10.1186/1471-2334-9-8.
3. M. F. Boni, J. R. Gog, V. Andreasen and M. W. Feldman, *Epidemic dynamics and antigenic evolution in a single season of influenza A*, Proc. R. Soc. B **273** (2006), 1307–1316.
4. M. F. Boni, *Vaccination and antigenic drift in influenza*, Vaccine **26**(3) (2008), C814.

5. S. Cauchemez, F. Carrat, C. Viboud, A. J. Valleron and P. Y. Boelle, *A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data*, Stat. Med. **23** (2004), 3469–3487.

6. O. Diekmann and J. A. P. Heesterbeek, *Mathematical Epidemiology of Infectious Diseases*, Wiley, Chichester, 2000.

7. E. Domingo and J. J. Holland, *RNA virus mutations and fitness for survival*, Ann. Rev. Microb. **51** (1997), 151–178.

8. C. Fraser, S. Riley, R. M. Anderson and N. M. Ferguson, *Factors that make an infectious disease outbreak controllable*, Proc. Natl. Acad. Sci. USA **101** (2004), 6146–6151.

9. J. R. Gog and B. T. Grenfell, *Dynamics and selection of many-strain pathogens*, Proc. Natl. Acad. Sci. USA **99**(26) (2002), 17209–17214.

10. R. A. Lamb, *Genes and proteins of the influenza virus*, in: R. M. Krug, H. Fraenkel-Conrat, R. R. Wagner (eds.), The Influenza Viruses, Plenum, New York, 1989, 1.

11. S. A. Levin, J. Dushoff and J. B. Plotkin, *Evolution and persistence of influenza A and other diseases,* Math. Biosci. **188** (2004), 17–28.

12. J. Lin, V. Andreasen, R. Casagrandi and S. A. Levin, *Traveling waves in a model of influenza A drift*, J. Theor. Biol. **222**(4) (2003), 437–445.

13. J. Lin, V. Andreasen and S. A. Levin, *Dynamics of influenza A drift: the linear three-strain model*, Math. Biosci. **162**(1,2) (1999), 33–51.

14. B. R. Murphy and R. G. Webster, *Orthomyxoviruses*, in: B. N.Fields, D. M. Knipe, P. M. Howley *et al.*, (eds.) Fields Virology, 3rd ed., Philadelphia, PA: Lippincott-Raven Publishers, 1996, 1397–1445.

15. Nũno, Z. Feng, M. Martcheva and Castillo-Chavez, *Dynamics of two-strain influenza with isolation and partial cross-immunity*, SIAM J. Appl. Math. **65**(3) (2005), 964–982.

16. J. B. Plotkin, J. Dushoff and S. A. Levin, *Hemagglutinin sequence clusters and the antigenic evolution of influenza A virus*, Proc. Natl. Acad. Sci. USA **99**(9) (2002), 6263–6268.

17. M. Recker, O. G. Pybus, S. Nee and S. Gupta, *The generation of influenza outbreaks by a network of host immune responses against a limited set of antigenic types*, Proc. Natl. Acad. Sci. USA **104**(18) (2007), 7711–7716.

18. S. Tamura, T. Tanimoto and T. Kurata, *Mechanisms of broad cross-protection provided by influenza virus infection and their application to vaccines*, Jpn J. Infect. Dis. **58**(4) (2005), 195–207.

19. J. K. Taubenberger and D. M. Morens, *1918 influenza: the mother of all pandemics*, Emerg. Infect. Dis. **12** (2006), 15–22.

20. P. van den Driessche and J. Watmough, *Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission*, Math. Biosc. **180** (2000), 29–48.

21. Recommendations for Influenza Vaccine Composition, http://www.who.int/csr/disease/influenza/vaccinerecommendations1/en/index.html.

22. Weekly FluWatch Reports Archive, http://www.phac-aspc.gc.ca/fluwatch/archive-eng.php.

Institute for Biodiagnostics, National Research Council Canada

435 Ellice Avenue, Winnipeg, MB, Canada R3B 1Y6

Department of Mathematics and Statistics, University of Winnipeg,

Winnipeg, MB, Canada R3B 2E9

E-mail address: seyed.moghadas@nrc-cnrc.gc.ca

Institute for Biodiagnostics, National Research Council Canada
435 Ellice Avenue, Winnipeg, MB, Canada R3B 1Y6
E-mail address: christopher.bowman@nrc-cnrc.gc.ca

Department of Mathematics, University of Manitoba,
Winnipeg, Manitoba, Canada R3T 2N2
Institute for Biodiagnostics, National Research Council Canada
435 Ellice Avenue, Winnipeg, MB, Canada R3B 1Y6
E-mail address: arinoj@cc.umanitoba.ca