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Does homologous reinfection drive multiple-wave influenza outbreaks? Accounting for immunodynamics in epidemiological models

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ABSTRACT

Epidemiological models of influenza transmission usually assume that recovered individuals instantly develop a fully protective immunity against the infecting strain. However, recent studies have highlighted host heterogeneity in the development of this immune response, characterized by delay and even absence of protection, that could lead to homologous reinfection (HR). Here, we investigate how these immunological mechanisms at the individual level shape the epidemiological dynamics at the population level. In particular, because HR was observed during the successive waves of past pandemics, we assess its role in driving multiple-wave influenza outbreaks. We develop a novel mechanistic model accounting for host heterogeneity in the immune response. Immunological parameters are inferred by fitting our dynamical model to a two-wave influenza epidemic that occurred on the remote island of Tristan da Cunha (TdC) in 1971, and during which HR occurred in 92 of 284 islanders. We then explore the dynamics predicted by our model for various population settings. We find that our model can explain HR over both short (e.g. week) and long (e.g. month) time-scales, as reported during past pandemics. In particular, our results reveal that the HR wave on TdC was a natural consequence of the exceptional contact configuration and high susceptibility of this small and isolated community. By contrast, in larger, less mixed and partially protected populations, HR alone cannot generate multiple-wave outbreaks. However, in the latter case, we find that a significant proportion of infected hosts would remain unprotected at the end of the pandemic season and should therefore benefit from vaccination. Crucially, we show that failing to account for these unprotected individuals can lead to large underestimation of the magnitude of the first post-pandemic season. These results are relevant in the context of the 2009 A/H1N1 influenza post-pandemic era.

Introduction

Mathematical models of infectious diseases often rely on a compartmental description in order to reduce the population diversity to a few key characteristics which are relevant to the infection under consideration. An extensively used model for influenza infection is of susceptible-exposed-infectious-removed (SEIR) form: after exposure to the virus, susceptible hosts (S) pass through an exposed state (E) of latent infection, become infectious (I) and are finally removed (R) from the infectious pool as they simultaneously recover (or die) and acquire permanent protection against the infecting strain. The SEIR model was particularly successful during the 2009 pandemic in estimating the key transmission parameters of the novel H1N1 virus (nH1N1) (Fraser et al., 2009) and assessing the effectiveness of alternative vaccination strategies (Baguelin et al., 2010).

Nevertheless, proper consideration of the primary immune response, which occurs on the first exposure to a novel influenza virus, motivates a more accurate description of the different stages from recovery to development of long-term protective immunity. Indeed, the primary immune response to influenza in humans operates on two different time scales. Usually, the viral load is cleared by the innate and cellular immune responses within a few days following infection (Woodland, 2003), thus leading to recovery of infected hosts. By contrast, the humoral (antibody-mediated)

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immune response, which provides long-term protection against the infecting strain as well as closely related strains (Fairlie-Clarke et al., 2008), takes several weeks to become efficient (Cox et al., 2004; Miller et al., 2010; Baguelin et al., 2011). Finally, at the population level, there is host heterogeneity in the development of this long-term protective immunity as some individuals show high antibody titres shortly after recovery whereas some other fail to reach a protective level (Cox et al., 2004; Miller et al., 2010; Chen et al., 2010; Hung et al., 2010; Chan et al., 2011).

In a recent study, Camacho et al. (2011) showed that a precise account of these host heterogenities was necessary to explain the reinfection episodes reported during the "natural experiment" of Tristan da Cunha (TdC), a remote island that underwent a two-wave A/H3N2 influenza epidemic in 1971 (Mantle and Tyrrell, 1973). More precisely, in the next few days that followed its introduction, the virus spread rapidly throughout the whole island population and after three weeks of propagation, 273 (96%) of 284 islanders had been infected. However, while the epidemic was nearing its end, several recovered islanders developed a second illness, thus initiating the second epidemic wave during which at least 92 (32%) islanders were reinfected (see section "Data" for more details). The main finding of Camacho et al. (2011) is that, among six biologically realistic reinfection mechanisms, only two could be retained: some hosts with either a delayed or deficient humoral immune response to the primary influenza infection were reinfected following rapid re-exposure to the same strain. This historical event illustrates that host heterogeneity at the individual level can not only lead to HR but also shape the epidemiological dynamics by triggering a second epidemic wave.

Historically, multiple-wave outbreaks and rapid reinfections have commonly been observed during influenza pandemics. The most striking example remains the "Spanish" influenza pandemic of 1918–1919 that occurred in three waves (Taubenberger and Morens, 2006) and during which several reinfection episodes were reported, sometimes in proportions similar to that of the 1971 TdC epidemic (Medical Department of the Local Government Board, 1919; Ministry Of Health, 1920; Barry et al., 2008). However, the three epidemic waves in 1918–1919 were spread out over 9 months (Taubenberger and Morens, 2006) whereas the two-wave epidemic on TdC lasted only 59 days (Mantle and Tyrrell, 1973). Accordingly, the time-scale between successive infections in the same individual was of the order of months during the pandemic whereas it was of the order of a few weeks for the TdC islanders, thus questioning their common underlying biological mechanisms. More recently, many populations experienced a spring and a fall waves during the 2009 pandemic and several cases of HR were virologically confirmed (Perez et al., 2010; Kim et al., 2010). Most of these HR episodes occurred within 2–3 weeks following recovery, a time-scale similar to that observed among the TdC islanders. However, both infection and HR occurred over the same epidemic wave in 2009 whereas they were separated across both waves in TdC, thus questioning the role of HR in driving multiple-wave outbreaks.

Overall, these observations call for clarification of the significance of HR and its role in driving multiple-wave outbreaks during pandemics. In particular, to what extent a better consideration of the immunological dynamics may be important in epidemiological models of influenza pandemics? In order to investigate these issues, we propose to explore and characterize the interplay between the immunological and epidemiological dynamics of a novel influenza virus. We start by defining an extended SEIR model accounting for the primary immune response to influenza and its inherent host heterogeneity. Using a maximum-likelihood (ML) approach, we confront our mechanistic model with the time-series of the daily incidence counts of the 1971 TdC epidemic and obtain ML estimates for the key immunological parameters. This analysis also reveals the exceptional setting of the TdC population and lead us to explore the impact of HR on the epidemiological dynamics for various population settings. We conclude with a discussion on the role of HR in the current post-pandemic era.

Materials and methods

The primary immune response to influenza infection in humans

A multi-pronged innate (McGill et al., 2009) and adaptive (Brown et al., 2004) immune response has been described for clearing influenza infection. The innate response is the first to be activated and plays a key role through its ability to control early viral replication and to promote and regulate the virus-specific adaptive immune response (McGill et al., 2009). The adaptive response itself may be broken into two critical sub-components: (i) the cellular immune response by which antigen-specific cytotoxic T lymphocytes (CTLs) eliminate infected cells and thus prevent viral release; and (ii) the humoral immune response by which serum and mucosal antibodies efficiently neutralize the virus (as explained in Text S1 the separation between serum and mucosal antibodies is not necessary for our study). Antibodies can remain detectable for years after infection and prevent reinfection by the same strain as well as by sufficiently cross-reactive variants (Fairlie-Clarke et al., 2008). Genetic variation in any of these immune components might determine whether or how rapidly an individual develops protective immunity following influenza infection.

As schematized in Fig. 1A, it is important to note that, during a primary influenza infection, the innate and cellular responses (blue curve) play the key role in viral clearance whereas neutralizing antibodies (green curve) are generated later and do not play a significant role unless the viral load is high and sustained (Woodland, 2003). The primary CTL response is detectable in blood after 6–14 days whereas the neutralizing antibody response peaks at 4–6 weeks (Cox et al., 2004). Critically, the CTL response is down-regulated after viral clearance (Woodland, 2003), disappears by day 21 post-infection (Cox et al., 2004) and is followed by a state of immunological "memory" with antigen-specific T cells. The memory cells cannot prevent HR as well as specific antibodies could, but they can reduce the severity of the disease (Woodland, 2003). Finally, it has been reported that a serum or mucosal antibody response cannot be detected in approximately 10 to 20% of subjects after natural influenza infection (Cox et al., 2004; Tamura and Kurata, 2004; Miller et al., 2010; Chen et al., 2010; Hung et al., 2010; Chan et al., 2011).

Mechanistic modelling

Fig. 1B shows the SEICWH model which extends the classical SEIR model to account for the dynamics and host heterogeneity of the primary immune response to influenza in humans. Following recovery, hosts remain temporarily protected against HR thanks to the cellular response. Accordingly, they enter the C stage (cellular protection). Then, following down-regulation of the CTL response, the humoral response has a probability α to reach a level sufficient to protect against HR. In this case, recovered hosts enter the H stage (humoral protection) but otherwise they remain unprotected and re-enter the susceptible pool (S). Finally, in order to account for potential delay between completion of CTL contraction and full development of the neutralizing antibody response, recovered hosts pass through a time window of susceptibility (W) before entering the *H* stage. Crucially, while in the W stage, individuals can be reinfected following re-exposure to the same strain

In order to account for host heterogeneity in the development of the immune response, we use a stochastic framework to simulate the durations of the successive immunological stages. Defining τ_E,