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Mechanisms of replacement of circulating viruses by seasonal and pandemic influenza A viruses

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SUMMARY

Background: Seasonal influenza causes annual epidemics by the accumulation of antigenic changes. Pandemic influenza occurs through a major antigenic change of the influenza A virus, which can originate from other hosts. Although new antigenic variants of the influenza A virus replace formerly circulating seasonal and pandemic viruses, replacement mechanisms remain poorly understood.
Methods: A stochastic individual-based SEIR (susceptible–exposed–infectious–recovered) model with two viral strains (formerly circulating old strain and newly emerged strain) was developed for simulations to elucidate the replacement mechanisms.
Results: Factors and conditions of virus and host populations affecting the replacement were identified. Replacement is more likely to occur in tropical regions than temperate regions. The magnitude of the ongoing epidemic by the old strain, herd immunity against the old strain, and timing of appearance of the new strain are not that important for replacement. It is probable that the frequency of replacement by a pandemic virus is higher than a seasonal virus because of the high initial susceptibility and high basic reproductive number of the pandemic virus.
Conclusions: The findings of this study on replacement mechanisms could lead to a better understanding of virus transmission dynamics and may possibly be helpful in establishing an effective strategy to mitigate the impact of seasonal and pandemic influenza.

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1. Introduction

Infectious diseases are still of great concern for public health, particularly emerging and re-emerging infectious diseases such as pandemic influenza. Globalization has also increased the risk of the worldwide spread of infectious diseases. For example, after the 2009 detection of human infections with the novel swine-origin influenza A (H1N1) virus in North America, the virus spread worldwide within a few weeks and resulted in a pandemic.[1–3]

Pandemic influenza occurs through a major antigenic change (antigenic shift) of the influenza A virus, which can originate from other hosts, such as birds and swine.[4] Historically, pandemic influenza has replaced the previously circulating seasonal influenza virus.[5,6] In 1918, a novel H1N1 virus emerged (Spanish flu) that expelled the H3N8 virus that had been circulating among humans since the late 19th century. Similarly, a novel H2N2 virus (Asian flu) expelled the H1N1 virus in 1957, and a novel H3N2 virus (Hong Kong flu) expelled the H2N2 virus in 1968. However, the H1N1 virus, which re-emerged in 1977 (Russian flu), did not expel the H3N2 virus, and both H1N1 and H3N2 have been co-circulating since 1977.[7,8] The swine-origin H1N1 virus emerged and led to a pandemic in 2009. This virus was closely related to the virus that caused Spanish flu in 1918,[9] and some people, particularly the elderly, had some immunity to it.[10,11] After the emergence of the A(H1N1)pdm09 virus, the H3N2 virus (progeny of Hong Kong flu) did not disappear, whereas the former H1N1 virus disappeared; since then, both H1N1 and H3N2 viruses have continued to co-circulate in the human population.[12,13] The next influenza pandemic is an imminent threat to human health. Sporadic human infections with avian influenza viruses, such as H5N1 and H7N9, continue to occur, and these avian influenza viruses have the potential to cause a pandemic once they acquire the ability to efficiently transmit between humans.[14,15]

Seasonal influenza causes annual epidemics by the accumulation of antigenic changes (antigenic drift), which allows viruses to evade herd immunity.[4,16] It has been proposed that a new

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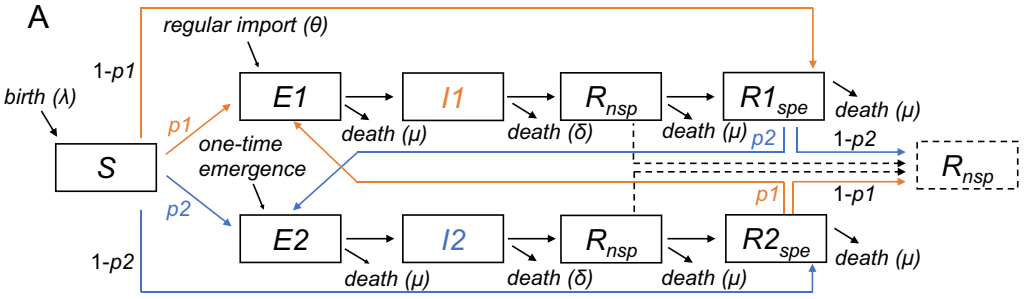
antigenic variant, generated by antigenic drift, first evolved in Southeast Asia and then spread to other parts of the world, replacing previously circulating viruses.[16–18] Therefore, genetically similar influenza viruses can cause global epidemics at almost the same time.[16,19] The influenza A virus epidemic shows a clear winter peak in temperate regions and year-round circulation with minor peaks in tropical regions.[20–22] Patterson Ross et al. showed that no strains persisted over the influenza season in temperate regions.[23] They suggested that an epidemic in temperate regions was caused by a strain imported from other areas, rather than strains lingering locally. Yet, little is known about the mechanisms through which a previously circulating strain is replaced by a new antigenic variant in temperate and tropical regions.

A mathematical model, specifically the compartment SIR (susceptible–infectious–recovered) model, is used widely to investigate the transmission dynamics of the influenza A virus. A simple compartment model has been used successfully to predict the behaviour of epidemics, which is consistent with that observed in 'real' epidemics.[24] In the compartment model, individuals in the population are assigned to different subgroups or compartments, each representing a specific stage of infection. The advancement of the compartment model can tell us the future of an ongoing pandemic,[1] effective control measures against a potential pandemic,[25] and the global dynamics of the virus.[26]

Although studies have shown that the host's immunity plays an important role in virus replacement by antigenic shift or drift,[27,28] we still have a limited understanding of the mechanisms of the replacement. Such information would lead to a better understanding of virus transmission dynamics. It could also possibly be helpful for establishing an effective avoidance strategy, such as vaccination and social distancing measures, to mitigate the impacts of seasonal and pandemic influenza. In this study, the compartment model was used to elucidate how a newly emerged influenza A virus (antigenic variant of seasonal influenza virus or pandemic influenza virus) is capable of replacing the currently circulating influenza A virus.

2. Methods

A stochastic individual-based SEIR (susceptible–exposed–infectious–recovered) model was developed for simulations (Figure 1A). In a population of N, say that S are susceptible, E are exposed, I are infectious, and R are recovered. I makes effective contact to transmit the infection during an infectious period randomly in the homogeneous mixing population. When effective contact occurs between I and S or R, one (S or R) has a probability, p, of becoming either $E\,(p)$ or $R\,(1-p)$. An effective contact number (c) is generated for each I by Poisson distribution (R_0); R_0 is a basic reproductive number. In addition, R_0 at time t (day) can oscillate as seasonality. R_0



	p1	p2
S	1 or p_{pst} or $p1_{vac}$	1 or p_{pst} or 'cross immunity from $p1_{vac}$'
R_{nsp}	0	0
$R1_{spe}$	0	'cross immunity from $p1$'
$R2_{spe}$	'cross immunity from $p2$'	0

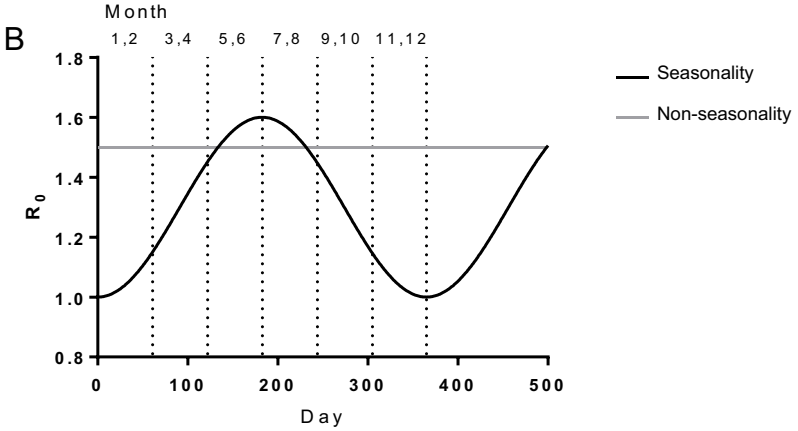


Figure 1. Simulation model. (A) Schematic diagram of the compartment model used in the present study (S, susceptible; E, exposed; I, infectious; R, recovered). Transitions made by effective contact with infectious individuals for strains 1 and 2 ($I1$ and $I2$) are coloured in orange and blue, respectively. When effective contact occurs between I and S or R, one (S or R) has a probability, p, of becoming either $E\,(p)$ or $R\,(1-p)$. p at each stage is listed in a table in the figure. The R state can have strain-specific immunity (R_{spe}) or non-strain-specific immunity (R_{nsp}). Details of the model are described in the Methods. (B) Time courses of R_0 (basic reproductive number) for simulations in the 'seasonality model' and 'non-seasonality model' are shown; months are grouped as depicted.