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PERSPECTIVE

Predictability and Preparedness in Influenza Control

Derek J. Smith

The threat of pandemic human influenza looms as we survey the ongoing avian influenza pandemic and wonder if and when it will jump species. What are the risks and how can we plan? The nub of the problem lies in the inherent variability of the virus, which makes prediction difficult. However, it is not impossible; mathematical models can help determine and quantify critical parameters and thresholds in the relationships of those parameters, even if the relationships are nonlinear and obscure to simple reasoning. Mathematical models can derive estimates for the levels of drug stockpiles needed to buy time, how and when to modify vaccines, whom to target with vaccines and drugs, and when to enforce quarantine measures. Regardless, the models used for pandemic planning must be tested, and for this we must continue to gather data, not just for exceptional scenarios but also for seasonal influenza.

Few would be surprised if there were an influenza H5 (bird flu) pandemic in humans. The source and basic mechanisms of the threat are clear, yet there is much we cannot predict: how severe such a pandemic would be, how fast it would spread, where it would start, whether it would become resistant to existing drugs, what strain to use in a vaccine, or whether a vaccine would be available in time to protect a large proportion of the population. Most important, we do not know how close the virus is to sustained human-to-human transmission, and thus to initiating a pandemic.

How can there be this much uncertainty when many of the best virologists, molecular biologists, epidemiologists, and public health scientists work or have worked on the influenza virus, when so much is already known, and when the global surveillance system is better than the system for any other pathogen? The answer lies in the inherent variability of influenza viruses, in their seemingly endless capacity to continue to change, and, in the case of type A viruses, in their rich and diverse ecology in many species and their ability to cross species barriers and adapt to new hosts (1, 2).

An influenza H5 virus capable of causing a pandemic in humans is likely to differ from the avian H5 viruses that have caused a pandemic in birds and have occasionally caused highly pathogenic infections in humans. A human-adapted H5 virus, by definition, should be able to transmit effectively among humans; it might have antigenic differences compared with avian strains and would possibly be less pathogenic in humans. Adaptation to the human host may occur as a result of either mutation or a

combination of mutation and reassortment with an existing human virus. A key event would probably be a change in the binding specificity of the virus from a receptor in the lower respiratory tract to one in the upper respiratory tract. This may result in a decrease in at least the initial pathogenicity, as the infection would be more likely to start with a tracheal bronchitis rather than pneumonia (3, 4). In addition, if human adaptation resulted from reassortment with a human virus, pathogenicity factors on gene segments not in the resulting reassortment would be lost, and there may be a degree of prior immunity in the population to the human virus-derived gene segments, both further reducing pathogenicity in humans.

The large possible range for pathogenicity is also evident in the differences in mortality during the three influenza pandemics of the past century: The 1918 pandemic killed an estimated 40 to 50 million people, the 1957 pandemic killed an estimated 2 million people, and the 1968 pandemic killed an estimated 1 million people.

Despite these uncertainties, national and international public health bodies have to prepare for a potential influenza pandemic. Math-

ematical and computational methods can provide valuable quantitative information for influenza preparedness in the face of uncertainty. Here, I discuss how such methods are being used to improve preparedness.

The Dynamics of Spread and Effect of Interventions

Because of the delay before a pandemic vaccine will be available, the immediate defenses against pandemic influenza are the neuraminidase-inhibitor antiviral drugs, oseltamivir and zanamivir. The World Health Organization (WHO) has a stockpile of oseltamivir to use in early cases of human-to-human transmissions of a potential pandemic virus to attempt to slow the outbreak and create more time for vaccine production and other preparations. However, the unknowns regarding a potential pandemic virus, including how quickly the virus spreads, the efficacy of the drugs, and the rate of acquisition of drug resistance by the virus, make it difficult to predict how useful a drug stockpiling strategy would be.

A better use of resources may be to pursue alternative routes to vaccine development, vaccine stockpiling, or prepandemic vaccination. Here, mathematical models can be valuable to help decide strategy, particularly for quantifying the variability of possible outcomes for a range of estimates of critical parameters, such as the transmission rate of the virus. Detailed epidemiological models have recently been developed to make quantitative predictions of the spread of an unchecked outbreak (Fig. 1), and how effective an antiviral stockpile could be in slowing or stopping an outbreak before it causes a pandemic (5, 6). Taking Thailand as the scenario, the models show what it would take to stop an outbreak in terms of speed and accuracy of detection, speed of delivery, delivery strategy (contact-based or geographic-based), and the total quantity of drugs required. Thus, if the

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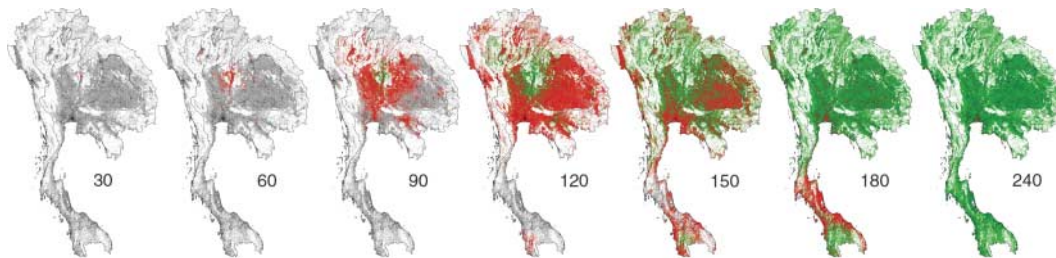


Fig. 1. Expected pattern of spread of an uncontrolled influenza epidemic in Thailand. Time sequence (in days) of an epidemic, showing spread in a single simulation of an epidemic parameterized such that, on average, in a fully susceptible population, each person infects 1.5 others (i.e., $R_0 = 1.5$). Red indicates presence of infected individuals, green the density of people who have recovered from infection or died. [Reprinted from (5).]

delivery of antivirals is rapid enough, and the transmission rate of the virus is approximately the same as that observed for previous pandemic viruses, then it should be possible to stop a

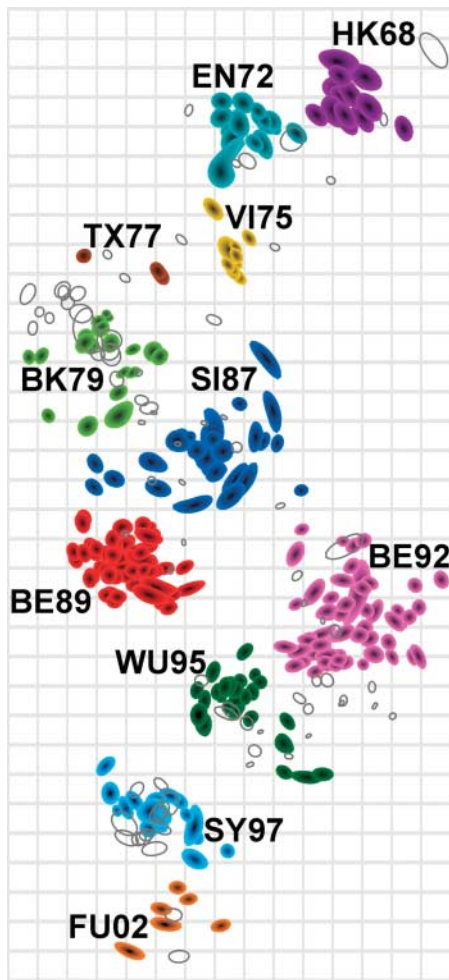


Fig. 2. Antigenic evolution of human influenza A (H3N2) virus from 1968 to 2003. The relative positions of strains (colored shapes) and antisera (open shapes) were adjusted such that the distances between strains and antisera in the map represent the corresponding hemagglutination inhibition (HI) measurements with the least error. The periphery of each shape denotes a 0.5 unit increase in the total error and is a measure of confidence in the placement of the strain or antiserum. Strain color represents the antigenic cluster to which the strain belongs; antisera are not colored. Clusters were identified by a *k*-means clustering algorithm and named after the first vaccine strain in the cluster. Two letters refer to the location of isolation: HK, Hong Kong, China; VI, Victoria, Australia; TX, Texas, United States; BK, Bangkok, Thailand; SI, Sichuan, China; BE, Beijing, China; WU, Wuhan, China; SY, Sydney, Australia; and FU, Fujian, China) and the two digits refer to year of isolation. The grid represents one unit of antigenic distance (i.e., a two-fold dilution in HI titer). [Reprinted from (10).]

single outbreak with a realistically sized stockpile of antiviral drugs. The models also predict that for effective control, antiviral prophylaxis would have to be started within about 3 weeks of the first human-to-human transmissions and within 2 days of the onset of a new case after an outbreak is underway; in practice, this would be extremely difficult to achieve in rural Southeast Asia. These examples show how models can reveal weaknesses, inform plans for training, indicate ways of deploying an antiviral stockpile, and estimate its necessary size (7). However, it is important to recognize that even if drug intervention were successful, it may only temporarily stall a potential pandemic (8).

The Thailand scenario was also used to predict the effect of control measures such as quarantine, restriction of movement, the closing of schools and workplaces, vaccination, and their effects on slowing an outbreak. Likewise, such models can be adjusted for geographic, demographic, and movement patterns in other countries, and be used to update national pandemic preparedness plans before and even during the course of a pandemic.

Antigenic Evolution and Vaccine Strain Selection

The mainstay of seasonal influenza control is vaccination. The primary target for the human immune response is the viral hemagglutinin protein. Consequently, the hemagglutinin of the strain of influenza virus used to produce the vaccine needs to be a good antigenic match to that of the wild-type strains. The hemagglutinin of human influenza viruses evolves sufficiently rapidly that an extensive global surveillance network is necessary to track the evolution of the virus, and the strains used in the seasonal influenza virus vaccine have to be updated, often annually, to maintain antigenic similarity between wild-type and vaccine strains (9).

Antigenic differences among viral isolates are measured by the hemagglutination inhibition assay, but these data are sometimes difficult to interpret. Antigenic cartography resolves many of these difficulties, increases the resolution at which antigenic data can be interpreted, makes the interpretation more quantitative, and provides a visualization of antigenic differences among strains (10) (Fig. 2). These methods are now integrated into the biannual WHO seasonal vaccine strain-selection process. They are also being used to map the antigenic evolution of H5 viruses and will be used to evaluate the breadth of immunity offered by pandemic vaccines.

Although the hemagglutinin of avian influenza viruses is usually antigenically stable compared with that of human influenza viruses, the antigenic properties of the hemagglutinin of avian H5 viruses have changed substantially since 1997; the magnitude of the change is

similar to that seen in human H3 over the same period. Thus, as with seasonal vaccine strain selection, the choice of strains for a pandemic vaccine will be critical.

The somewhat regular patterns seen in the human H3 antigenic map (Fig. 2) suggest that some aspects of its antigenic evolution are predictable. Less is known about the predictability of the antigenic evolution of avian H5 viruses. It is not clear whether the mutations in the hemagglutinin that have caused the antigenic changes in avian H5 since 1997 are directly selected for escape from prior immunity (i.e., allowing re-infection) or if the mutations accompany other changes in the virus and are selectively neutral for the hemagglutinin; if the latter, they would be difficult to predict.

Improving Predictions

Models are approximations of the systems they represent; by necessity, they are built with incomplete knowledge and need to be tested against either experimental or observational data. Thus, it is important to be aware of potential inaccuracies and parameter sensitivities when interpreting their results and to assess the accuracy of the models. Hence, to test the robustness of antigenic cartography (11), the human H3 antigenic map was repeatedly constructed from a random subset of the data and the constructs used to predict the omitted data. Predicted measurements for specific antigen-antiserum combinations not present in the original data were also checked by subsequent laboratory measurements. Testing models by prediction has not yet become standard practice in epidemiological modeling.

The pandemic influenza models discussed here are tours de force of painstaking gathering and synthesis of relevant details, but their predictions have not yet been tested by comparison with real outbreak data. This does not mean that the models are not useful in their current form; similar models were instrumental in shaping successful control policies during the Foot and Mouth Disease virus outbreak in the United Kingdom in 2001 (12, 13) and were valuable in supplying rapid estimates of key epidemiological parameters including the mortality rate and transmissibility during the severe acute respiratory syndrome outbreak in 2003 (14, 15). Nevertheless, we need data sets, such as those of seasonal influenza in regions with good surveillance data, that can be used to test the model predictions.

Experimental epidemiological studies, such as the vaccination of school children (16), or those that follow family units (17), provide core information for model design and parameterization, and (especially if there are multiple independent studies) for model testing. The large-scale study proposed to test the herd

immunity effect of vaccinating school children against influenza (18) would be extremely valuable in this context. Not only would the study test an important prediction for seasonal influenza, but it would also provide information about whom to prioritize for vaccination when vaccine is scarce, as it could be during a pandemic, and it also could provide repeated data sets for model testing.

A Final Caveat

We do not know that a human-adapted H5 will have similar epidemiology to human H3. We do know that when in humans, avian H5 infections currently have a substantially different clinical picture than that of human-adapted H3 infections. Hence, even a perfect epidemiological model for human H3 might be a poor model for human H5. Nevertheless, a well-understood and accurate human H3 model would be extremely valuable in its own right and would be a good starting point for any reparameterization necessary for a human H5 epidemiological model once the characteristics of the virus are known.

As we focus attention and funds on preparedness for a pandemic, we must not lose sight of the necessity for medium-term and longer term investments to expand basic understanding of influenza viruses at the molecular, immunological, evolutionary, epidemiological, and ecological levels. Such increases in our basic understanding, some already within reach, will increase our options both to control seasonal influenza and our ability to predict and thus increase preparedness for the next influenza pandemic—regardless of whether it is imminent or many years away.

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PERSPECTIVE

Host Species Barriers to Influenza Virus Infections

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Most emerging infectious diseases in humans originate from animal reservoirs; to contain and eradicate these diseases we need to understand how and why some pathogens become capable of crossing host species barriers. Influenza virus illustrates the interaction of factors that limit the transmission and subsequent establishment of an infection in a novel host species. Influenza species barriers can be categorized into virus-host interactions occurring within individuals and host-host interactions, either within or between species, that affect transmission between individuals. Viral evolution can help surmount species barriers, principally by affecting virus-host interactions; however, evolving the capability for sustained transmission in a new host species represents a major adaptive challenge because the number of mutations required is often large.

The highly pathogenic avian influenza H5N1 virus is just one example of a zoonotic pathogen capable of transmission from animal reservoir species to humans (1). If we are to contain and eradicate such emerging infectious diseases (EIDs), we need to understand how and why some pathogens

become capable of infecting and being maintained in novel host species. Here, we review the interaction of factors that collectively limit the transmission of an infection from a donor host species to a recipient species and that constitute the host species barrier. We discuss these factors specifically as they apply to influenza, but the underlying principles apply to any EID.

The host species barrier is not a simple concept; the likelihood of a virus becoming endemic in a new host species depends on the interaction of three sets of processes (Fig. 1): interspecific interactions between hosts of the donor and recipient species, host-virus interactions within individual hosts of the recipient

species, and host-host interactions within the recipient species. For any type of species transfer, there must be sufficient contact between donor and recipient species and enough compatibility between the virus and the new host to allow replication and the possibility of transmission to other members of the recipient species. If this transmission can occur, the contact network structure of the recipient species, together with variations in transmission through this network, are critical in determining whether the virus will persist or die out. As the history of influenza pandemics and epidemics illustrates, viral evolution can help considerably in lowering the species barrier. However, we argue below that the relative rarity of successful species jumps testifies to the complex adaptations often required to achieve sustained transmission in a new species. We also review the components and evolutionary dynamics of the species barrier as they apply to influenza and then suggest areas for future work.

The Virus-Host Interaction: Within-Host Barriers

Cell entry-exit and receptor biology. For a virus shed by one host to infect another, it must breach entry barriers (e.g., mucus, alveolar macrophages, and epithelium) and find its way to tissues in which it can replicate. For example, chimpanzees are relatively resistant to experimental respiratory exposure to human influenza viruses, possibly because their respiratory tract secretions contain mucins that can specifically bind viruses before they reach airway epithelial cells (2). Once in appropriate

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Special Section on Influenza: Perspectives: "Predictability and preparedness in influenza control" by D. J. Smith (21 Apr. 2006, p. 392). In reference (8), the journal is incorrect. The reference should read "C. E. Mills, J. M. Robins, C. T. Bergstrom, M. Lipsitch, *PLoS Med.* **3**, e135 (2006)."