Model answers or trivial pursuits? The role of mathematical models in influenza pandemic preparedness planning

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The panzootic of H5N1 influenza in birds has raised concerns that the virus will mutate to spread more readily in people, leading to a human pandemic. Mathematical models have been used to interpret past pandemics and outbreaks, and to thus model possible future pandemic scenarios and interventions. We review historical influenza outbreak and transmission data, and discuss the way in which modellers have used such sources to inform model structure and assumptions. We suggest that urban attack rates in the 1918–1919 pandemic were constrained by prior immunity, that R_0 for influenza is higher than often assumed, and that control of any future pandemic could be difficult in the absence of significant prior immunity. In future, modelling assumptions, parameter estimates and conclusions should be tested against as many relevant data sets as possible. To this end, we encourage researchers to access FluWeb, an on-line influenza database of historical pandemics and outbreaks.

Keywords Communicable disease control, disease outbreaks, disease transmission, influenza A virus, H5N1 subtype, historical cohort studies, mathematical model.

Introduction

Recent outbreaks of H5N1 influenza among domesticated poultry in South-East Asia have had unprecedented economic impacts.[1,2] Seasonal migration of infected wild birds and trade in live poultry[3] have spread H5N1 viruses throughout Asia, Europe and Africa. Direct transmission of this avian virus to humans through contact with infected live birds, poultry products or excreta had caused 154 confirmed human deaths by November 2006,[4] with updates posted on the World Health Organization (WHO) website since that time (http://www.who.int/csr/disease/avian_influenza/updates/en/index.html). Earlier reports of suspected secondary infection in family members[1,5] have been supported by recent evidence of human-to-human transmission of an H5N1 mutant within a household.[6] In the absence of prior immunity, the emergence of novel virus that is more readily transmissible could cause a human pandemic to rival or surpass the pandemics of 1889–1891,[7] 1918–1919 (H1N1), 1957 (H2N2) and 1968 (H3N2).[1] Public health bodies and governments have sought urgent advice in planning how to respond to this new threat.[8]

Why bother with mathematical models?

The pandemic of 1918–1919 was characterized by high attack rates, several waves of infection and high mortality in young adults. Such observations can be better understood by fitting explanatory models to the data to estimate R_0 and other parameters governing influenza spread.[9,10] These parameter estimates can then be used to simulate model scenarios to examine the possible consequences of proposed outbreak control strategies.[11]

In an outbreak in a fully susceptible population, the average number of secondary cases infected by a primary case is denoted by the reproduction number, R_0, which depends on the duration of the infectious period ($1/\gamma$), and a transmission parameter (β), influenced by viral and host factors and contact opportunities. In its simplest form:

$$R_0 = \frac{\beta}{\gamma}$$

R_0 can be estimated from the final attack rate if the population was fully susceptible at the outset. However, in many situations, populations have pre-existing immunity, and a proportion of exposures leads to subclinical infections,

reducing the apparent attack rate. The proportion immune (ω) within a particular population determines the effective reproductive number (R) by the relationship:

$$R = (1 - \omega)R_0$$

R_0 provides a worst-case scenario for the attack rate. Furthermore, in combination with the mean generation time (serial interval between cases) and the proportion susceptible, R_0 determines the rate of spread of an outbreak. In favourable circumstances, R_0 can be estimated from outbreak data, with parallel inferences about levels of subclinical infection and prior immunity.

This article reviews aspects of influenza biology and epidemiological findings from past influenza epidemics. It provides insight into the nature of influenza infection in individuals, and the dissemination of virus in households, schools and populations. We highlight the importance of susceptibility, pre-existing immunity and subclinical infection in modifying the apparent attack rate and spread of influenza, and suggest that mathematical models of influenza transmission would be improved if they could account more adequately for such factors. Finally, we review the potential utility of interventions such as social distancing, antivirals and immunization to prevent or limit outbreaks.

Biology and epidemiology of influenza infections

Influenza viruses probably evolved in wild waterfowl, and then spread to other animals, including humans.[12] In order to successfully cross the species barrier, mutant strains had to acquire the capability to bind the dominant receptor in the human respiratory epithelium, which differs from that in birds.[12–14] Mutation of the virus sufficient to allow such binding could produce an H5N1 strain able to spread more effectively from person to person, potentially triggering a new pandemic.[15]

Inter-pandemic influenza affects 5–30% of the population each winter in temperate climes. Attack rates fall with age, presumably because of incremental immunity following repeated exposures, but rise again in the elderly. Mortality rates are generally low, but higher at extremes of age. As inter-pandemic viruses circulate in partially immune populations, haemagluttinin (HA) antigens mutate quickly to escape antibody directed against earlier viruses, a phenomenon known as 'antigenic drift'.[12]

T-cell immunity is also important; cytotoxic T-cells kill virus-infected epithelial cells to clear existing infections. If protective antibody is minimal, as with a new pandemic strain, many epithelial cells may become infected, and a hyperactive cytotoxic response against these cells can cause lung destruction and death. This scenario could explain the higher mortality for young adults during the 1918–1919 pandemic.[12,16]

Immunity and susceptibility to infection

Some hosts are more susceptible to influenza because they have little or no acquired immunity or because of intrinsic factors affecting innate immunity.[12,17] Isolated populations with no recent influenza exposure are particularly vulnerable, as with Native Americans and Pacific Islanders during the 1918–1919 pandemic.[18,19] Likewise, on Tristan da Cunha, where influenza had been absent for many years, the first arrival of H3N2 virus by ship from Cape Town in 1970 led to 96% of persons falling ill, with repeat attacks in a significant minority.[20]

Consistent with the premise of short-lived protection through past exposures to inter-pandemic influenza, much lower attack rates were reported in urbanized populations during the 1918–1919, 1957 and 1968 influenza pandemics. In Cleveland in 1957, 47% of household members had serologically confirmed influenza during a 10-week period. Disease incidence in children aged 10–14 years was three times that in adults, in keeping with their relative naivety to influenza.[21,22] In contrast, more uniform attack rates were observed up to 50 years of age in the 1968 H3N2 pandemic, with relative sparing of people born before 1918 suggesting that exposure to related viral antigens more than 50 years earlier had conferred lasting protection.[23–26]

In the Houston family study of 1976, high titres of sub-type-specific haemagglutination-inhibiting (HI) antibody titres protected against H3N2 influenza. Breakthrough infections did occur in those with high titres, but were usually milder.[27] In the Seattle cohort study from 1975 to 1979, HI antibody thresholds conferring protection differed for the three strains circulating over the period: A/H3N2, A/H1N1 and B.[28,29] Such variation is likely due to differences in the immunogenicity of HA antigens.[30] Further, attack rates in Seattle children were double those seen in adults for a given HI titre,[29] suggesting the importance of unmeasured humoral and cellular immunity.[22,31,32] Broadly reactive 'recall' immune responses, seen within days of vaccination,[33] could explain the rarity of H1N1 infection in Seattle adults with low HI titres and a cohort history of exposure to a related strain 26 years earlier.[28]

Models incorporating immunity

Spicer and Lawrence modelled influenza in Greater London from 30 years of mortality data. Exposure to successive drift mutants was assumed to reduce the susceptible pool, which was replenished by births and the emergence of antigenically novel strains.[34] In a model for South-East Asia, Ferguson *et al.* assumed that 27% of rural households would be resistant to a novel strain of influenza as a result of recent contact with related antigens.[10] Other models

allow the risk of transmission,[11,35] or progression to disease given acquisition,[36,37] to depend on age, indirectly incorporating immune protection. Longini *et al.* explicitly calculated the influence of 'high' or 'low' antibody titres on influenza risk in children and adults from epidemic data, but could not refine their estimates.[38]

The simplest influenza models assume that a single episode of infection confers lifelong immunity. This cannot be true, especially for children, who can experience three or four clinical episodes in successive seasons.[28] Ferguson *et al.* modelled the combined effects of waning immunity and antigenic drift for inter-pandemic virus by assuming that a single exposure to influenza protected against related strains for 5 years, after which individuals were again fully susceptible. Less robust immune responses in the very young and elderly were modelled by shortening this duration of protection.[37]

In the absence of priming, immune responses to novel antigens can be insufficient to confer short-term protection, even in adults. This could explain the second wave of infections observed on Tristan da Cunha, in which 33% of islanders experienced a second (usually milder) attack within a month of the initial outbreak.[20] Repeat infections after a short interval have been reported in other outbreaks, as in the naval apprentice school at Greenwich in 1924 (Figure 1)[39] and the summer, autumn and winter waves of the 1918–1919 pandemic in England.[19]

Multiple-wave data from Tristan da Cunha and from the 1918–1919 pandemic in Royal Air Force camps in the UK (Figure 2) have been modelled to estimate R_0 as well as parameters for prior immunity, waning of immunity/antigenic drift, and subclinical infection, with consistent results (J. Mathews, personal communication).

Infectivity, transmission and subclinical infection

After experimental inoculation of adults with influenza, virus titres in nasal lavage fluid rise at 24 hours, peak with fever onset at 48 hours, and then decline over the next 5 days.[40,41] In children with natural infections, viral titres continue to rise 24–48 hours after symptom onset.[42] In one community-based study, 8·3% of children were still shedding influenza

virus into the second week of illness.[43] Elderly and immuno-compromised patients can shed virus for weeks or even months.[44] Conversely, of cases detected by seroconversion during epidemic influenza seasons, perhaps a third are asymptomatic[29,45] and of uncertain infectious potential.

Viral shedding is an imperfect guide to the risk of transmission. During influenza outbreaks, some infected individuals never infect anyone else, whereas in exceptional circumstances as many as 40 secondary cases have been reported.[46] R_0 thus represents a value averaged over different hosts and environments.[47] Experimental studies of influenza acquisition in humans[48] and animals[49] cannot capture subtle effects such as confinement on aeroplanes,[46] seasonal climatic variation[50] or altered conditions during wars.[51]

Epidemiological and household studies can provide insights into host factors influencing infectiousness. Preschool and school age children are more likely than other infected household members to produce secondary cases among contacts,[52] a phenomenon attributed to density rather than to the duration of shedding in modelling analyses.[53] Accordingly, influenza models incorporating age structure[36,54] do not explicitly allow for longer infectious periods in children. Although asymptomatic individuals are unlikely to be highly infectious, serological evidence of 'off season' transmission in families has been reported.[29] Models that allow for reduced infectiousness of asymptomatic cases have halved the infectious period[55] or lowered the probability of transmission.[10,56] Whether or not 'severe' cases shed more virus and are thus more infectious is questionable, as the host immune response plays a significant role in pathogenicity.[16,57,58]

Presymptomatic transmission

Viral shedding studies suggest that transmission could peak soon after the onset of illness in the index case. Ferguson *et al.*[37] and Fraser *et al.*[59] estimated that 30–50% of transmission occurred before symptom onset, assuming that illness would result in withdrawal to home. Some models incorporating household structure extend this idea, allow-
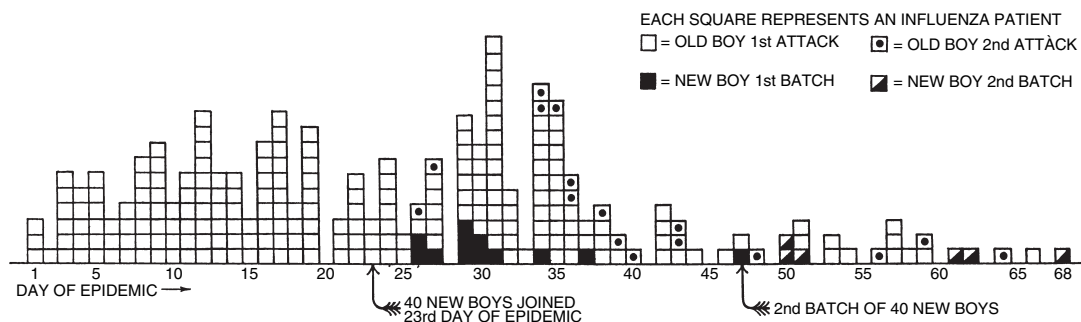

Figure 1. The 1924 influenza epidemic at the Royal Naval School, Greenwich. The introduction of new classes of (susceptible) students led to recrudescence of the outbreak with both 'new boys' and 'old boys' affected.[39]
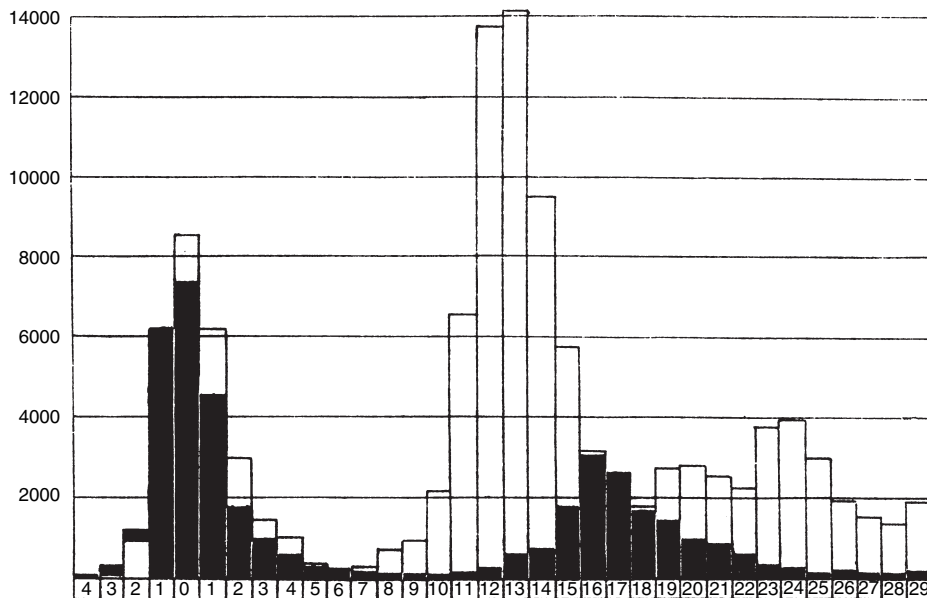
Figure 2. Incidence of influenza cases in Royal Air Force camps (black columns) and the city of Copenhagen (white columns) during the 1918–1919 pandemic.[19] Time-line units are in weeks measured from the maximum of the initial peak. Both curves display multiple waves, consistent with hypotheses of waning immunity and/or antigenic drift. De-mobilization at the conclusion of World War I could have prevented the third wave, visible for Copenhagen, from being registered in the Air Force camps.

ing continued exposure of the index case to family members while reducing community spread.[36,56] This assumption has significant consequences for outbreak control, which will be more difficult if most transmission occurs before index cases can be identified.[59]

Infectious period, serial interval and latent period

Observational studies of primary and secondary infections in households provide information about serial interval between cases. A mode of 2 days between the onset of symptoms in successively infected household members was reported by medical officers during pandemics in 1890[7] and 1918–1919.[19] The mean serial interval for Kelley's Island households in 1920 was 2·9 days, with a mode of 2 days (Figure 3).[60]

Later household studies during the 1957 pandemic in Cleveland and the 1968 pandemic in Kansas reported median serial intervals of 3[61] and 8 days[23] respectively. However, a mode of 2 days was again seen in Kansas,[23] and in subsequent studies of interpandemic influenza,[52] showing that the median is sensitive to censoring of the observation period. The average serial interval between cases could be longer for transmissions occurring in the community, if there is continuing access to susceptibles.

Elveback *et al.*[36] and Longini *et al.*[35,56,62] separate latent (1·9 days) and infectious (4·1 days) phases of influenza infection, with no transmission during the latent period.[56] Ferguson *et al.* allow for a similar mean latent phase of 1·48 days in their individual-based models, but shorten the

duration of peak infectiousness to give a serial interval of 2·6 days.[10,11] More recent work from the Longini group assumed a slightly longer generation time of 3·5 days.[63]

Assumptions about mixing

Opportunities for disease transmission differ by social situation, and location, as seen in the Kelley's island outbreak of 1920 (Figure 4).[60]

Hope-Simpson estimated a fourfold increase in influenza incidence among general practice patients exposed to a household case.[24] Children typically experience higher age-specific seasonal influenza attack rates than adults, often acquiring the infection from peers in day care centres, kindergartens and day schools.[25] For this reason they more frequently introduce illness into the family,[27,29] although in some previous pandemics an adult was as likely to be the household index case as was a child.[23,64] Family size and measures of crowding can further influence influenza risk.[27,60,64] Other residential settings in which large populations of susceptibles may become rapidly infected include boarding schools[19,65] and aged care homes.[66,67]

Indirect evidence about the role of social mixing in disease transmission is provided by the natural history of the 1919 influenza pandemic in Sydney. Following diagnosis of the first cases in late January, government acted to limit spread by closing institutions and meeting places and by requiring masks to be worn in public. Incident cases declined by mid-February, and restrictions were then
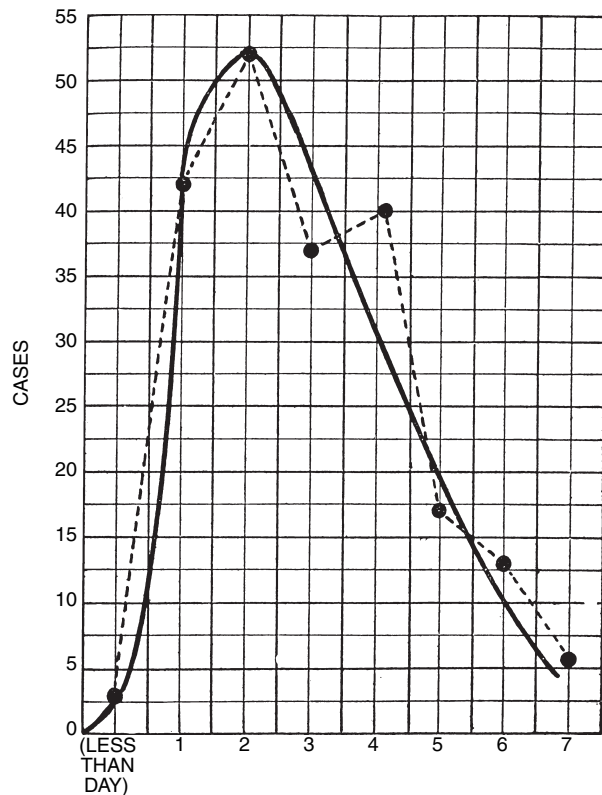
Figure 3. Distribution of the serial interval during the 1920 influenza epidemic on Kelleys Island, Ohio, USA. Interval taken to be the time in days between the first and subsequent cases in a household, assuming that the first case is the source of infection for other household cases.[60]

removed. A second epidemic wave followed in early March, after which regulations were reimposed.[68] Records from 1919 also reveal higher infection rates in occupations involving travel and frequent contact with the public.[68]

Compartmental models often stratify individuals by age to help capture the heterogeneity of contact opportunities in populations.[69] Ferguson *et al.* employ this method to characterize close mixing in schools and aged care institutions.[37] Longini *et al.* developed an individual-based model of a 'typical' American population[36] with 1000–2000 people in households of different sizes and age structures, with some attending day care centres and schools.[62] The probability of acquiring infections from the community has been estimated from epidemiological data,[70] with parameters refined to incorporate the influence of age[54] and prior immunity.[38] Analogous models for influenza spread in rural South-East Asia[10,35] and the developed world[11,63] have characterized community mixing patterns in a range of social settings.[35] Network type models consider explicit interactions between discrete nodes, with contact probabilities related to social rather than geographical distance.[71,72] Other models have simulated spread within and between

subpopulations to estimate the probability of local extinction of an outbreak, and subsequent reintroduction.[73,74] Incorporation of geographical distance and travel information has allowed modelling of the effects of travel on regional,[75] national[76] and international[76] influenza spread.

Modelling interventions

We discuss modelling approaches to three public health strategies that can limit influenza transmission: social distancing, use of antivirals and immunization.

Social distancing

Social distancing encompasses measures that limit person-to-person spread of infection. In the 1918–1919 pandemic, stringent quarantine of the island populations of American Samoa and Australia was of benefit,[18,19] although unlikely to be practicable in our age of international air travel.[11,77] Restrictions on social movement within communities in 1919 also appeared to limit disease spread.[68] A caveat is that self-imposed behavioural changes can influence the apparent efficacy of government interventions during any pandemic.[10,63]

The effects of school closures on community-wide influenza transmission are not well defined. During the 1920 influenza epidemic on Kelley's island, Ohio, school contacts were found to be important in disease spread. Further, a decline in incidence followed school closure (Figure 5).[60]

More recently, a 30% reduction in paediatric visits to healthcare providers coincided with a 2-week teachers' strike during the epidemic influenza season in Israel.[78] Historically, the likely benefit of closing schools was thought to depend on the household living conditions to which children would be returned.[19] Accordingly, models exploring this intervention are sensitive to assumptions about age-specific transmission rates in the school compared with rates in the home.[11,63]

Transmission from infected individuals can be reduced by institutional or household quarantine. Household-based models of this strategy show a fall in effective reproduction rate, contingent upon the timeliness of tracing, the proportion of cases and contacts identified and their compliance.[11,79] Infection control measures, including hand hygiene and personal protective equipment, can also reduce the individual risk of respiratory infections.[80,81] Although aerosol spread of influenza can occur,[46] its importance, relative to droplet infection, is still controversial, with implications for the standard of protective mask needed to reduce exposure risk.[82,83] Importantly, experience of the recent SARS outbreak has shown that well co-ordinated institutional responses can protect healthcare workers far more than would be predicted from the additive effects of individual measures.[81]
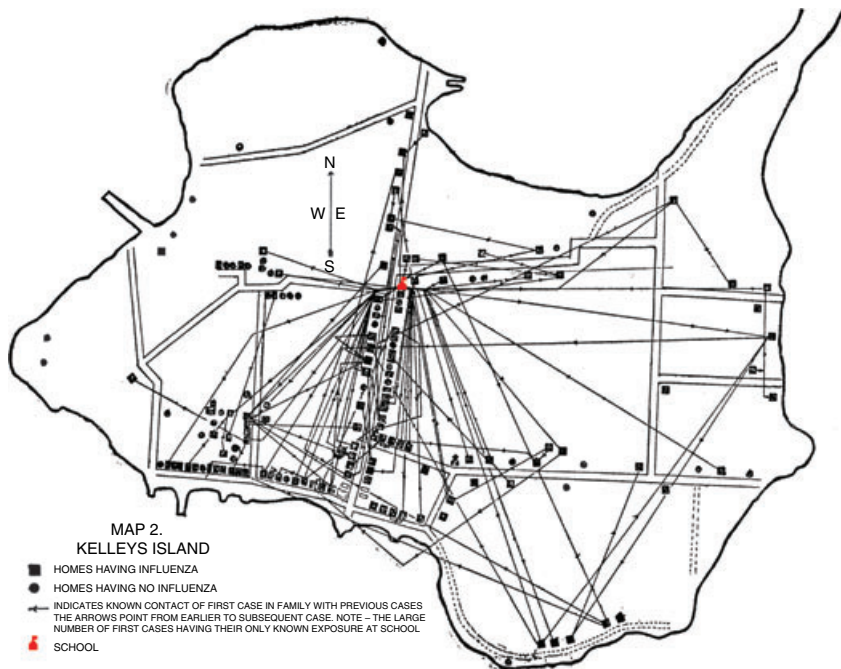
Figure 4. Map showing the location of influenza cases on Kelleys Island, Ohio, USA, during the 1920 epidemic.[60] In this small population, relatively isolated from the outside world, it was possible to reconstruct likely networks and hubs of disease transmission. Paths and arrows indicate a known contact between a first case in a family and a previous case. Note the large number of first cases having their only known exposure at the island's school (indicated).
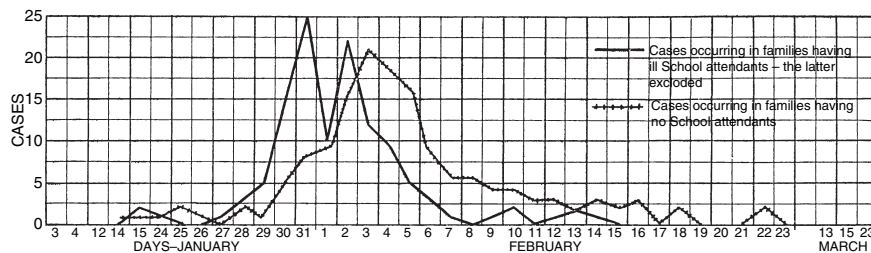

Figure 5. Daily incidence of influenza cases on Kelleys Island, Ohio, USA, during the 1920 epidemic for (1) cases occurring in families having school attendees and (2) cases occurring in families having no schoolchildren. The peak incidence for (1) occurs 3 days before the peak for (2) showing the effect of mixing in school on earlier transmission to households. The island's school was closed on 31 January.[60]

Antivirals

The neuraminidase inhibitors (NAIs) zanamivir and oseltamivir antagonize the action of neuraminidase (NA), thereby impairing release of virions from host cells.[84] Although effective in prophylaxis and in reducing the severity and duration of symptoms in interpandemic influenza, the use of these drugs has produced little benefit in H5N1 influenza,[85] possibly because of treatment delay,[85] which reduces efficacy,[86] or higher viral loads.[87]

Data from clinical trials with interpandemic influenza show that NAI treatment within 48 hours of symptom onset in virologically confirmed influenza reduces viral shedding by 40–70%.[85] Effects begin within 24 hours,[88] with total suppression of virus achievable by day 2–3 of illness.[89] NAIs have less impact on shedding in children,[90] but a 1-day reduction in symptom duration is achievable regardless of age.[91,92] Prophylaxis with NAIs can reduce the risk of infection in household contacts, measured by seroconversion or viral isolation, over and above treatment of the index case,[93] with efficacy of 60–80%.[85] Breakthrough cases on prophylaxis are less symptomatic.[93]

Published models of scenarios using antivirals to limit the spread of pandemic influenza have used estimates of prophylactic efficacy based on such data.[10,11,55,56,63] The maximal achievable reduction in infectiousness as a result of treatment has been estimated at 28%.[10] Models allow exploration of a range of targeted scenarios for antiviral use, from treatment of cases and household contacts,[11] to prophylaxis of institutions or geographical regions where disease has been identified.[10,35,63] The importance of early case detection is paramount,[11] with the size of the antiviral stockpile as another major constraint. In the containment phase of a pandemic, an aggressive combined approach to treatment and prophylaxis of incident cases represents optimal use of a limited resource.[94]

Influenza virus resistance to oseltamivir is of potential concern,[95] but at present can be demonstrated in less than 0.5% of strains worldwide.[96] Mutants arising *in vitro* can have mutations in both HA and NA genes,[97] whereas those from treated immunocompetent patients show single mutations in the NA region.[98] Transmissibility of most resistant strains is greatly reduced,[99] but exceptions occur,[49] leaving no room for complacency.[100] Nine of fifty children treated with oseltamivir carried resistant strains within 4 days, with persistent shedding of both resistant and wild-type virus to day 7,[97] possibly related to the high viral loads observed in childhood.[101] The rarity of clinical zanamivir resistance[102] may relate to the poor *in vitro* viability of strains with this mutation.[103]

Models exploring the population impact of antiviral resistance confirm that the transmissibility of resistant strains, relative to wild type, and the rate of emergence of such strains are most important as determinants of outcome.[37] Intriguingly, a high rate of production of poorly transmissible mutants could aid, rather than hinder, outbreak control (J. McCaw, personal communication). Models comparing the likely impact of treatment or prophylaxis on the emergence of drug resistance are critically dependent on underlying assumptions. If as much as half of all transmission occurs before case detection, prophylaxis-based strategies favour selection of mutant strains,[37] whereas if transmission continues for several days after case detection, treatment has a greater impact on resistance profile.[55]

A potential concern is that antiviral agents could blunt the immune response to influenza, leaving treated cases susceptible.[85,104] Recurrent influenza infection has been reported in one small paediatric case series,[105] but there is no consistent evidence from adult studies to give cause for wider concern.[106,107] Re-infection has also been observed in untreated children, possibly because of immunological naivety or immaturity.[108] Furthermore, adult clinical trials of antiviral agents consistently show that virologically confirmed cases are prevented more effectively than serologically confirmed cases,[89,106,109] indicating sufficient exposure for seroconversion without illness.

Pandemic vaccines

Inactivated split virion vaccines based on recent H5N1 isolates from humans are currently under phase I trial. As H5 is novel to humans, high concentrations of antigen,[110,111] incorporation of adjuvants[112] and booster doses[110–112] have been necessary to achieve immunogenicity. Some monovalent vaccines against novel HA antigens have maximized yield by using reactogenic whole virus formulations.[113,114] Candidate H5 vaccines have afforded protection in neutralization assays[115] and animal models against variant H5 viruses.[116,117] Such 'best guess' vaccines can be stockpiled for possible use in priming critical subpopulations such as front line healthcare workers.[115] Nevertheless, if a pandemic occurs there will likely be substantial delays in production and supply shortages of strain-specific vaccines due to limited global manufacturing capacity.[118]

There is uncertainty about the best correlates of protection for interpandemic influenza vaccines,[119] let alone for a novel strain. Early observations showed that high titre (1:30–1:40) HI antibody is predictive of clinical protection,[17,120,121] although this measure is subject to considerable inter-laboratory variation.[122] For licensure in the EU, The Committee for Proprietary Medicinal Products (CPMP) requires documentation of HI antibody responses in terms of: post vaccine seroprotection rate (HI titre ≥1:40), mean fold increase and response, and seroconversion rate.[123] Interpretation is complicated, as fold rises will be smaller for individuals with pre-existing immunity, although protection will often be improved.[124] Reduced protection against heterologous influenza strains has been shown in challenge studies,[125,126] which could explain why some immunogenic vaccines perform poorly in the field.[127] Heterosubtypic vaccines providing broad protection against different sub-types offer theoretical advantages, but their efficacy is yet to be demonstrated.[128]

Strategic vaccine use

An efficient use of pandemic influenza vaccines would be to control transmission through herd immunity. Immunization of pre-school children in day care is known to significantly protect their families.[129] A more modest reduction in respiratory infections is seen among parents of vaccinated school age children,[130] and in teachers and classmates where institutional coverage is high.[131] In Tecumseh, Michigan, vaccination of schoolchildren prior to the influenza season in 1968–1969 prevented an epidemic similar to that in the comparison city of Adrian.[132] More dramatically, when mandatory influenza vaccination of Japanese schoolchildren was stopped in 1994 there was a sharp increase in pneumonia and influenza mortality in the elderly.[133] Likewise, immunization of carers in aged care institutions predicts a reduction in all-cause mortality among elderly residents in the UK[66,134] and Japan.[67]

In the simplest models, immunization moves all vaccinated susceptibles to the removed/recovered class.[72] However, vaccination is more likely to provide incomplete protection for most of those immunized. This critical distinction determines not only the threshold size of an epidemic,[135] but the optimal vaccine coverage required for disease control.[136] Vaccine effects can be characterized further within subgroups of interest identified from clinical trials.[137] In addition, the time to maximal immune response can be a critical consideration in outbreak settings.[36] As most models assume that vaccination reduces

both acquisition rate in those exposed, and viral shedding in established cases, it follows that vaccines will be useful even when efficacy is partial.[35,37,63,138]

Several models have explored the theoretical effectiveness of targeted immunization for pandemic control, showing optimal benefit from vaccinating children of school[63,138] and preschool age.[137] Britton and Becker concluded that influenza could be controlled most efficiently by targeting immunization to families with three or more members.[139] Such model conclusions depend upon underlying assumptions about population susceptibility and transmission in heterogeneous circumstances. For example, using assumptions based on age-specific attack profiles from the 1957 and 1968 pandemics, Patel *et al.* obtained two very different estimates for the optimal proportional distribution by age group of a limited number of vaccine doses.[140]

Conclusions

Historical and contemporary data show that the transmissibility and pathogenicity of influenza viruses depend on complex interactions with host populations. The emergence of H5N1 as a threat to the poultry industry has undoubtedly been influenced by a very rapid increase in numbers of caged birds in developing countries. Likewise, the risk of a new human pandemic can be linked to both the emergence of avian influenza, and to the large numbers of people on the planet, any one of whom could be host to viruses undergoing a pandemic mutation or recombination event.

Host immunity, which plays a crucial role, has clear specificity for influenza sub-type and strain. However, cross-reactive immune responses are needed to explain some otherwise anomalous observations.[21,22] In particular, there is reason to believe that clinical attack rates for influenza are not often constrained by low values for R_0, but rather by pre-existing immunity, and by subclinical infections which can immunize without causing symptoms.

With such complex interactions, making precise predictions about age-specific attack rates, morbidity and mortality due to a novel pandemic strain is near impossible. Nevertheless, mathematical models do provide a useful framework for pandemic scenarios to explore the potential benefit of public health interventions. As all models have to oversimplify complex biological systems, they should be interpreted with great caution. In particular, models are exquisitely sensitive to underlying assumptions about susceptibility, subpopulations and modes of transmission – all of which must be inferred, rather than being quantified by direct observation.

Model assumptions and predictions should be tested against as many real-world observations as possible to test the sensitivity of the model to different contexts. By validating model outputs against multiple data sources, investigators can tease out which of the parameters determining disease spread are more likely to vary between contexts, and which are relatively constant. To encourage such work, and to make relevant data sets more easily accessible, we have developed an on-line publicly searchable archive (FluWeb: http://influenza.sph.unimelb.edu.au), which includes rare historical documents from the 1889–1891 and 1918–1919 pandemics giving individual and group level data on influenza morbidity and mortality. By maximizing our use of historical evidence, we hope to more confidently predict the future.

Conflict of interest

J.D.M. is an active member of the National Influenza Pandemic Advisory Committee (NIPAC). He has advised the Australian Government on influenza and other public health matters as an employee (1999–2004) or occasional consultant (2004–2006) and in these roles has access to information restricted by confidentiality considerations. He has no involvement with professional organizations that may benefit financially from the conclusions of this review.

Acknowledgements

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