Influenza mixes its pitches: Lessons learned to date from the influenza A (H1N1) pandemic

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This note will appear towards the end of the 2009 baseball season, and the authors may perhaps be excused for resorting to a metaphor derived from that game. As Mike Stadler notes in *The Psychology of Baseball* (1), one of the fascinations of baseball to fans relates to the fact that professional players literally achieve the impossible on a daily basis. Major league pitchers throw a ball so hard, and have the ability to make the ball 'break' or swerve so sharply, that it is actually impossible for the eye of a batter to follow as it crosses the plate. As such, batters actually need to make decisions about whether or not to swing, and where to swing, before the ball has even left the pitcher's hand. If the pitcher's delivery didn't vary from pitch to pitch, presumably a good hitter would learn to anticipate the ball's placement, and would hit successfully often. But good pitchers mix their pitches: change the speed, change the degree to which they break or slide across the plate, and change the placement. No wonder the best hitters succeed only three times out of 10.

A reader who has been paying attention to both the baseball season and the almost perfectly coincident influenza pandemic, which emerged following the occurrence of disease caused by a novel swine-origin influenza A (H1N1) virus in Mexico in April 2009 (2), will anticipate what we are about to say next. Influenza, as an RNA virus with a segmented genome (3), accumulates mutations and recombines freely with other strains (eg, the current pandemic strain is a mixture of known swine, avian and human strains) (4). As such, the virological and epidemiological characteristics of a novel influenza strain represent the infectious disease equivalent of a well-thrown knuckleball, a pitch whose movements may be unpredictable even to the pitcher. As the infectious disease specialist 'batters', we nonetheless need to make rapid decisions about our actions regarding influenza: how and when should nonpharmaceutical mitigation strategies be used? How should the public be informed of risk? How should our limited supplies of antiviral drugs be allocated?

This problem is further compounded by our remarkably limited knowledge of the genesis and behaviour of influenza pandemics. Indeed, there are only three pandemics (including the present one) during which viruses were actually identifiable using laboratory diagnostic methods (with the characterization of earlier pandemics based largely on serological testing) (5). The degree to which prior influenza pandemics and

epidemics were identified 'indirectly' is exemplified by the work of Robert Graves, an eminent 19th century clinician (he of "Graves' disease" fame), who documented the presence of an influenza epidemic in 19th century Dublin by counting over 700 excess burials in that city's Prospect Cemetery (6). Infectious disease trivia buffs will know that *Haemophilus influenzae* is so named because it was mistakenly believed (as Pfeiffer's bacillus) to be the etiological agent of the 1918 influenza pandemic (7). In the 1957 and 1968 pandemics, diagnosis was achieved through culture and serological testing. Our current testing methods, which are largely based on nucleic acid amplification techniques, far exceed earlier methods in sensitivity, which reduces our ability to compare the epidemiology of earlier pandemics to the current pandemic directly. Our gap in understanding with respect to the molecular epidemiology of earlier pandemics and shift events is even greater: the number of influenza sequences available in the United States National Institutes of Health decreases markedly with time. For example, a July 31, 2009, search of the Genbank flu sequence archive (8) retrieved 1008 sequences for the influenza A HA genes from 2009 alone; by contrast, only 98 sequences for viruses circulating during the four decades between 1918 and 1957.

"PANDEMICS START IN ASIA"

Perhaps the most fundamental example of how little we understand of influenza, and how prominently this lack of understanding has figured in the most recent pandemic, relates to the presumption in recent planning documents that future influenza pandemics would emerge in Asia. For example, the Ontario Health Plan for an Influenza Pandemic states: "Most new influenza strains emerge in Southeast Asia where human populations have close interactions with pigs and domestic fowl. The probability of a new strain emerging in North America is relatively low" (9). But, of course, North America (Mexico) is precisely where this novel influenza strain emerged. This is an important reminder of the truly global nature of this disease, and the degree to which historical events (the 'Asian flu' of 1957, the 'Hong Kong flu' of 1968, and the recent circulation of highly pathogenic influenza A [H5N1] in southeast Asia) colour our expectations of the future.

For Canada, the emergence of a pandemic in Mexico rather than Asia likely had an impact on the initial dynamics and control of this epidemic: in part, North American ties that

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Figure 1) Association of Ontario influenza A (H1N1) 2009 specimen collection with history of Mexico travel: changes over time

resulted in Canadian cooperation with the Mexican authorities on outbreak investigation gave this country's public health community a few days of 'lead time' not available to those in other countries; however, the close economic and travel links between Mexico and Canada ensured that cases would emerge in Canada shortly after the identification of this disease in Mexico. Kamran Khan and colleagues (10) recently reported that approximately 80% of outgoing international flights from Mexico in March and April 2008 were destined for cities in the United States and Canada and the volume of international travel from Mexico to other countries was highly correlated with reported importations of novel H1N1 cases to those countries. The current influenza pandemic reinforces (as did the 2003 SARS outbreak) that the global connectedness of Canadian cities serves as an important driver of economic development in this country, but also necessitates ongoing investment in public health infrastructure related to mitigation of global disease threats, and awareness of emerging disease threats around the world by Canadian physicians and public health officials.

Notably, the linkage between novel influenza A (H1N1) virus case status and recent travel to Mexico was lost in Ontario within two weeks of initial identification of cases, suggesting that community transmission was already occurring in the province by the time the epidemic was identified (Figure 1). Sharp reductions in travel between Canada and Mexico (11), and aggressive disease mitigation strategies (including school closure and cancellation of public events) instituted by Mexican authorities (12) may also have contributed to the loss of linkage with Mexico travel. The rapidity with which the 'source region' ceased to contribute to disease risk is consistent with mathematical models projecting limited effectiveness of travel restrictions for the prevention the global spread of a novel influenza strain, and confirms yet again that the widespread impulse to 'secure the borders' in the face of global infectious diseases is neither a practicable nor a useful response to the worldwide movement of diseases.

ATTACK RATES VERSUS VIRULENCE: WHAT IS A 'MILD' PANDEMIC?

An important source of confusion in the current pandemic has involved conflation of the concepts of attack rate and

virulence in the discussion of severity. An influenza virus may be associated with very low attack rates (eg, highly pathogenic avian influenza A (H5N1), but substantial virulence (estimated case fatality ratio [CFR] 75%), or high attack rates with low virulence. The limited CFR associated with novel H1N1 has led some knowledgeable commentators to suggest that the World Health Organization made a mistake in declaring an influenza pandemic (13). The catastrophic pandemic of 1918 apparently represented a confluence of virulence and transmissibility, but pandemic strains with limited virulence are nonetheless capable of causing substantial disruption due to high attack rates that result from limited population immunity to the strain. For example, a current working estimate of case-fatality rates for novel influenza A (H1N1) virus in Ontario is somewhere in the range between 1/10,000 to 5/1000. Assuming that the lower estimate is correct, should we cease pandemic planning efforts and use our resources elsewhere? Likely not: consider the fact that a novel influenza virus may attack 30% of the population, even in the face of disease mitigation efforts. In a province with a population of approximately 13,000,000 persons such as Ontario, the combination of a 30% attack rate and 0.01% CFR would result in over 30,000 deaths. Consider the fact that these deaths would be expected to play out over only a few months, that many individuals who died would require prolonged intensive care unit care before death, and that Canadian intensive care units operate at near capacity in the absence of a pandemic, and you understand why planners are concerned about the potential impact of novel H1N1 on Canada's critical care system. It is interesting to note that Robert Graves, writing in 1864, understood the difference between virulence and attack rates. As he wrote: "Influenza is not by any means so severe or so rapidly fatal a disease as cholera; but the mortality which it has produced is greater, as it affects almost every person in society..." (6).

ANTIVIRAL DRUGS AND THE BATTLE OF BUNKER HILL

The newly emerged influenza A (H1N1) strain appears, at least at the moment, susceptible to the neuraminidase inhibitors oseltamivir and zanamivir (14). Until a vaccine is developed, antiviral drugs represent an important tool for control of influenza epidemics and pandemics. Models suggest that without resistance, early use of drugs could contain influenza pandemics caused by flu strains with low basic reproductive numbers (15). (Sometimes denoted R_0 , the basic reproductive number of a pathogen is defined as the number of secondary cases per primary case in a nonimmune population in the absence of intervention) (16). Canadian pandemic mitigation strategies focus largely on the use of antiviral drugs for treatment of infected individuals (9), though mathematical models suggest that their use for postexposure prophylaxis of contacts of individuals with influenza could also slow an influenza epidemic (15,17).

However, influenza viruses acquire resistance rapidly, making strategic use of drugs crucial for the preservation of these agents as resources for pandemic mitigation during the expected autumn wave of the epidemic (18,19). Models suggest that the early, aggressive use of antiviral drugs in a pandemic would be likely to produce a pandemic of antiviral-resistant infections (18,19), and that widespread use of antiviral drugs for mitigation of the epidemic should not be initiated until infection is

widespread, ('don't fire 'till you see the whites of their eyes'). At the time of writing, influenza A (H1N1) 2009 strains resistant to both oseltamivir and zanamivir have been reported from a variety of geographic locales (20,21), and the degree to which these drugs will remain effective for the treatment of novel influenza A (H1N1) 2009 in the coming months is an open question.

WHAT'S NEXT? PERILS OF PROGNOSTICATION

From a policy and planning point of view, it would be desirable to know with a high degree of accuracy how severe the next wave of the current influenza pandemic will be. Some experts have already suggested that the H1N1 pandemic is already in decline, and that further waves are unlikely (22), and indeed, that is precisely what happened to the 1977 'Russian flu' epidemic, which had caused outbreaks in younger individuals around the world but failed to become a true pandemic (23). It seems more likely that a fall influenza wave will occur, as it did in 1957 (during an influenza A [H2N2] pandemic that bears many remarkable similarities to the current pandemic [24]).

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