Pandemic influenza: interventions to reduce morbidity

An influenza pandemic is considered by many experts in the field to be a certainty. If not necessarily imminent, it is nonetheless certain because, as is the case with other natural disasters such as earthquakes and hurricanes, influenza pandemics have demonstrated themselves to be recurrent for centuries.

As with numerous other communicable diseases, there are several targets for which interventions can be developed. These can be divided into biologic, behavioural and social approaches.

On the biologic front, influenza pandemics were previously thought to arise uniquely due to the reassortment of genes from influenza of two different species (as seems to have happened in 1957 and 1968). It is now believed that pandemics can also occur due to changes in the genetic structure due to simple point mutations and following a process of adaptation as now appears to have occurred in 1918 (Osterholm, 2007).

Much effort is being placed in this current pre-pandemic phase to surveillance and rapid confirmation as well as subsequent containment of avian influenza in poultry and animals. The World Organization for Animal Health (OIE) is key in this regard, with support from the World Health Organization which coordinates similar efforts with respect to human infections. It is not expected that efforts at containment be successful.

Great strides in understanding influenza viruses have taken place in recent years, including the sequencing of the influenza genome. What is considered the best long-term solution is developing a vaccine; yet it is not known if H5N1 will be the virus to leads to a pandemic... A summary of H5N1 vaccine development efforts was published last month (http://www.who.int/csr/disease/avian_influenza/guidelines/H5VaccineVirusUpdate20080214.pdf). Ideally such a vaccine would be available early on in the course of the pandemic; more rapid production of “conventional” and “second generation” cell-culture based vaccines is thus actively being researched (see: http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/biofacts/panflu.html#_Surveillance_Considerations). Production of a “broad-spectrum” influenza vaccine would allow vaccination right at the onset of a pandemic but this is still several years away in terms of development.

Strategies for administering pandemic influenza vaccination have been modeled (Bansal, 2006). If transmission rates are high, a mortality-based strategy (targeting school-aged children and school staff) is suggested to be most prudent as herd immunity is maximized. If on the other hand transmission rates are lower, then vaccinating those at higher risk of complications (the elderly, infants, and caregivers) is proposed. Optimal, as compared to prudent, strategies could be formulated as data emerges during the pandemic.

Given hypothesized base reproductive numbers (R_0 in the absence of interventions) between 1.6 and 2.4, it has been estimated that in the U.S. there would be from 2.3M to 7.9M new cases per day at peak pandemic activity with between 86 and 52 days of over 100,000 new cases (Germann, 2006). Simulated numbers of ill people (cumulative incidence per 100) ranged from 32.6 to 53.7 but decreased to from 0.04 to 35.3 with some vaccination regimens.

Short of a vaccine (possible use of adjuvants to make a limited vaccine supply go further is discussed by the “writing committee,” 2008), antivirals are often seen as the next biologic line of defence. These can be used as prophylaxis or for treatment. As with current H5N1 vaccines stockpiling, such a strategy for antiviral has been brought into question, particularly as resistance seems to be emerging and that it is difficult to rotate the supplies (because legal clauses do not allow pandemic stock and yearly influenza stock, though *of the same antiviral*, to be used interchangeably). When used for targeted prophylaxis (as modeled by Germann, 2006, see above), the incidence ranged from 0.06 to 19.3 (though unrealistically considering an unlimited supply, with no resistance).

At the interface of biologic and social approaches, behavioural infection control measures such as masks and (hand) hygiene appear intuitive in some sense but the research is either contradictory, or at least so is its interpretation such that quite divergent guidelines are promoted in different jurisdictions. Part of the issue is that it is not fully established whether influenza is spread by droplets or is airborne. This is addressed elsewhere.

Several interventions are possible at a social level. Assuming a limited availability or efficacy of influenza vaccine and/or antivirals, such interventions will be even more critical. Taken individually, for a range of R_0, school closures were very effective with low base reproductive numbers, yet minimally so with higher numbers (Germann, 2006). Local social distancing and travel restrictions had little effect individually but, when used together, could have a moderate effect in a mild pandemic. As expected, these interventions where much more effective when combined with vaccination or propylaxis.

Voluntary self-isolation upon onset of illness is the cornerstone of the U.S. community mitigation strategies (http://www.pandemicflu.gov/plan/community/commitigation.html), to be used in all severities of pandemic. Quarantine (when exposed but not yet ill) is recommended only for moderate or severe pandemics.

A Letter Report by the Institute of Medicine (2006) reviewed several other modeling research programs. Social-based interventions were grouped and analyzed together. Such approaches included school and work closures, social distancing of various age-groups, home isolation and quarantine, etc. As might have been expected, as the R_0 increased, the model predicted the need for increasing social distancing measures to reduce attack rates overall.

This same Letter Report describes another study that compared two groups, both of whom used as a baseline general hand hygiene, respiratory etiquette, surgical masks, domestic travel restrictions, voluntary self-isolation, N95 respirators, other personal protective equipment (PPE), surveillance, rapid diagnosis. To this was added, either an intense combination of contact tracing, cancelling of community events, school closures, workplace closures, voluntary quarantine, mandatory isolation, and limited mandatory quarantine; or simple social support. Interestingly, it was the latter (simply adding social support) which proved (from a modeling perspective) to be most effective in 97% of the simulations that were run. Social support was suggested to encompass provision of home food delivery, access to prescription medication, and assistance with legal and banking services as well as coping with loneliness.

Looking specifically at self isolation (Haber, 2007), it was estimated that if people voluntarily did so quickly when they first became ill, there could be a substantial reduction in overall rates of illness and death. Both Meltzer (2008) and Davey (2008) looked at when to later allow people back to school or back to work. Theoretically, the time to return could be optimized such that minimal further transmission occurred yet personal impact from the isolation be lessened. The main problem was that, once lifted, a ban (voluntary or compulsory) would be expected to be much more difficult to institute a second time.

Finally, once ill, patients have three options: home / self-care, family practice / OPD / triage centre, or hospital. If we count that the very ill will self-triage to hospital and that hospitals will be over-burdened (a big push for greater surge-capacity and skill-based cross training needs to happen), the majority of the ill will be cared for at home, hence communication in order to mobilization and train will be paramount in reaching the greatest number of ill.

SUMMARY	*Strategies to minimize impact of pandemic*	*Comments*
Biology		
	Surveillance and containment	Will eventually fail
	Vaccination (development, manufacturing, distribution)	MOST PROMISING but time-consuming
	Antivirals (prophylaxis, treatment)	Uncertain role, growing resistance
Infection Control		
	Masks	Controversial, depending on setting
	Hygiene (cough, hand)	Individual level, difficult to evaluate
	Contact tracing	Valuable in early stages only
Social Measures		
	Closures (schools, events, workplace, etc)	Depending on severity of pandemic
	Voluntary self-isolation	RECOMMENDED
	Quarantine	Recommended for mod-severe pandemic
	Simple social support (providing food, regular medications, banking, legal, and emotional support, etc)	As or MORE EFFECTIVE THAN contact tracing, school / work closures, mandatory self-isolation and quarantine combined
Health Care		
	Surge capacity	Essential
	Home Care	Much mobilization and training still needed

Much research remains to be done and planning for greater community resiliency is still needed. When it comes time to enter an EOC for the next pandemic, no matter where we are at in the "emergency preparedness" game, four areas will need to be addressed immediately: 1) coordinate vaccine manufacturing and, depending on apparent severity of pandemic, determine focus of distribution; 2) finalize antiviral distribution mechanisms to essential workers as a part of comprehensive surge capacity plan; 3) implement a cohesive communication strategy to instruct population regarding non-hospital-based care, voluntary self-isolation, and mobilization for 4) simple social supports through existing community groups and networks. And before long, though it will feel like "forever," it will be time to start focusing on recovery and emotional healing for, to quote Michael Osterholm:

> The world will experience another pandemic, and it will get through it, as it has all previous ones. The challenge is to figure out now how to minimize the number of deaths and the economic and psychological devastation it will cause. It is a particularly complicated problem because preparing for a pandemic challenges the very basis of the global just-in-time economy. [...]Finally, the long-term goal must be to develop universal influenza vaccines. The impetus must come from an initiative as bold as the man-on-the-moon agenda that President John F. Kennedy articulated in May 1961. The fact that no world leader has called for such an effort reflects a lack of comprehension about the devastation an influenza pandemic would wreak. The opportunity to save millions of lives cannot be passed up. Even if such efforts come too late to stave off the next pandemic, at least they would help in the one after that (Osterholm, 2007).

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