PERSPECTIVE

Pandemic Influenza: Imminent Threat, Preparedness and the Divided Globe

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With generic consensus on certainty of an impending influenza pandemic, concerns are mounting about its devastating global impact. Preparedness and preventive approaches adopted by the nation states are polarised between resource rich and resource challenged countries. India has, rightly, taken a middle path. It seems that the non-pharmaceutical interventions would be the only preventive modality available in large parts of world. Production of any pandemic vaccine would take a minimum of 6 months after isolation of novel virus, and antivirals may not be available where they are required most. Efforts to create a universal pool of resources and stockpiles of antivirals, antibiotics and vaccines for use in first affected countries need to be strengthened with urgency.

Keywords: *Bird-flu, Influenza, Pandemic.*

The global health leadership is preparing itself for the impending threat of an influenza pandemic. There seems to be a generic consensus on the certainty of a pandemic within a short period from now - and a substantive historical as well as epidemiological evidence supports this prediction(1).

WHAT LOOMS LARGE

Concerns are mounting that the epicenter of the outbreak could be the Asia-Pacific region(2). Widespread emergence of avian influenza virus (A/H5N1) for which humans lack immunity and the virus having shown replicability and disease causation in humans is seen as a prerequisite build up. Availability of an intermediate like pig, thought to be required to make H5N1 transmission to human beings, creates a genetic-reassortment vessel. The only missing piece in this ecological fuse is a virus-strain capable of efficient human to human transmission. Emergence of such a virus is widely accepted as a matter of time(3). We are already in a pandemic alert period (Phase 3). The protean nature of H5N1 genome could transform it into the source of next pandemic(4). Historically, there have been 10 pandemics of Influenza A in past three centuries. Today, with 6.5 billion world population - more than thrice that in early twentieth century - even a milder pandemic could kill several millions.

However, this apparent consensus is not without contest - at least in quantitative sense. Model based extrapolations of 1918-20 Spanish influenza (A/H1N1), which killed 30-100 million people worldwide (including 7 million in India), indicate that an estimated 62 million people would be killed by a similar pandemic this time(5,6) and 96% of these deaths would occur in developing world(1). Laboratory evidence suggests that a pandemic caused by current H5N1 strain is likely to mimic Spanish influenza of 1918 and could lead to 180-360 million deaths if we translate those mortality rates to current world population(3). On the other hand, it has also been argued that these projections are 'counter-intuitive' at places and the impact of pandemic may be lesser in those instances(7). Resource rich and technically proactive nations may fare better than they did in 1918. Contemporary pandemic can also be naturally more muted, as was the case with 1957 and 1968 pandemics. Predictive accuracy of modeling exercises has always had its

detractors, and it is argued that models only help us organize our data and thoughts - nothing more. At the most we can say that the possible effects of a contemporary pandemic influenza, when it happens, would have devastating consequences for the world.

THE RESPONSE

Preparedness and preventive approaches are polarized between resource rich and resource challenged countries. Commitment of the governments in most European and North American countries is strong and level of preparedness is broadly good(8,9). At the probable epicenter — the Asia-Pacific region, variance on account of strategies is quite visible amongst rich and 'not so rich' countries. China, Thailand, and Vietnam have set out a vision to strengthen future capacity in preparedness planning, while Australia, New Zealand, and Hong Kong are aiming mainly at harnessing available resources such as stockpiled antivirals and vaccines(2). On the other hand, many underprivileged countries in this region lack a future strategy or plan to deal with the looming pandemic.

Indian scenario

India has tried to take a middle path. Largely, its strategy is comparable to those of resource challenged countries but has also preserved stockpiling components. The 'Influenza Pandemic Preparedness and Response Plan' of India(10) emphasizes on phase-wise preparedness. Emergency Medical Relief division of Ministry of Health and Family Welfare is the nodal agency for planning, coordinating, implementing and monitoring of preparedness and response. The National Institute of Communicable Diseases (NICD), which has a dedicated Avian Influenza Monitoring Cell with round the clock call centre, conducts the surveillance. National Institute of Virology, Pune, a World Health Organization (WHO) reference laboratory, provides the laboratory support along with NICD. For the drug oseltamivir, preparatory work for bulk production and procurement is on - and though inadequate, about one million doses are in stock (procured-2006, expiring-2011). Serum Institute of India is one of the institutions identified by WHO for manufacture of vaccine for use during the pandemic.

Transnational strategy to contain the initial emergence of pandemic influenza

This is going to be an extraordinary public health intervention, if required, through international efforts and collaboration. WHO has recently come out with a protocol on rapid operations to contain the initial emergence of pandemic influenza(11,12). Under this, there is provision that concerned national authorities and WHO would jointly assess all relevant technical, operational, and political factors to determine if: (*i*) there is compelling evidence to suggest that a novel influenza virus has gained the ability to transmit easily enough from person to person to initiate and sustain community level outbreaks and, if so (*ii*) are there any compelling reasons why a containment operation should be deferred. Proposed strategy geographically divides the outbreak area into 'containment zone' and a surrounding 'buffer zone'. The containment zone would constitute geographical area and population harboring the 'index cluster', where widespread antiviral medications for treatment and prophylaxis, movement restrictions, and non pharmaceutical interventions (NPIs) would be used to restrict the virus from spreading beyond the zone. NPIs would include: isolation of ill persons, voluntary quarantine of contacts, social distancing measures such as school closures and cancellation of mass gatherings, other measures to minimize person density (e.g. staggered work and market hours), and community-wide practice of hand and respiratory hygiene. This would be to reduce the possibility that a noninfected person will come into contact with a person 'infected by' and 'infectious with' pandemic influenza. The buffer zone would be simultaneously subjected to an intensive active and complete surveillance for possible 'break-through' cases, to evaluate whether the containment operation is succeeding. In both zones, emphasis will be placed on containment communications to different stakeholders.

INHERENT RIDDLES

There are three distinct epidemiological domains requiring outbreak alertness and response - 'seasonal human influenza'; 'avian influenza in birds with spill over human infection'; and the 'pandemic influenza'. This creates a difficulty not only in risk

communication and community awareness but also at the levels of health care providers and multisectoral partnership. During the initial stages of pandemic, two things would be extremely critical: (*i*) the decision to launch rapid containment exercise, and (*ii*) the process of declaration of pandemic (phase 6). Containment would not be possible if the local authorities do not support the operation or it is not feasible because of security reasons(12). Besides this, determining the size and shape of containment and buffer zones would involve several operational factors such as natural and administrative boundaries, infrastructure, and essential supplies. Rapid containment is time sensitive and the window of opportunity is going to be narrow. Today's civil aviation carries more than 2 billion travelers a year, enabling the inter-continental transport of a novel virus in a matter of hours. We had a close shave with severe acute respiratory syndrome (SARS) in 2003, which cost Asian countries an estimated US$ 60 billion of expenditure and business losses, besides tremendous impact on health and health systems. Quarantine measures, which were extremely successful in SARS are unlikely to work here considering a much higher communicability of influenza(13). Models are heavily dependent on basic reproduction number (R_0) of the new virus for several predictions and the containment would be very difficult if the R_0 exceeds 1.8(14). The pandemic may last from one to three years, and we should be prepared for multiple waves. Subsequent waves may be deadlier than the first one and are likely to hit us when the health systems are exhausted logistically.

Distribution, spectrum and outcome of disease

In 1918, more than half the deaths occurred in largely healthy individuals of 18-40 years and were caused by virus induced cytokine storm leading to acute respiratory distress syndrome (ARDS)(15). Since this pandemic was also associated with the avian virus (A/H1N1), one is tempted to force old data to contemporary settings. However, epidemiological domains do not interact mathematically, and predictions on the course and outcome of disease would remain unreliable. Best we can do is to analyze information from recent human cases of avian influenza confirmed from Asia Pacific, Africa and Europe. With 391 total human cases and 247 deaths (till 16th December 2008), overall case fatality rate is more than 60 per cent. Majority of cases have occurred among children and below 40 adults, and the mortality was highest between 10-19 years. Primary viral pneumonia was the cause of death in most of the cases – not the superinfection with bacteria. This data too is unsuited for extrapolation in pandemic situation. The clinical spectrum of human cases of H5N1 is constructed on records of hospitalized patients. Frequencies of subclinical infection, milder illness, and atypical presentation (e.g., encephalopathy and gastroenteritis) have not been measured, but case reports indicate that each of them exists(16). There are some other worrisome realities to be factored in the equation. What shall be the impact of comorbidities such as malnutrition, diabetic mellitus, HIV, and tuberculosis, is only a matter of informed guess. Secondary bacterial pneumonia may still contribute significantly to the death toll. An equitable antibiotic supply will affect the impact of bacterial superinfection. A worldwide effort for antibacterial vaccination especially to achieve universal pneumococcal immunization has also been advocated(7). However, with present level of preparedness, this looks unrealistic.

Assessment and planning for surge capacity

Whether we would (or would not) have a surge capacity for health care, food and other supplies is not going to be a simple question of low income and high income countries. Pandemic situation may act as a leveler. Even in the USA, most patients needing ventilator would not have access to it(3). Health care providers would fall sick and die at similar rates, or even higher than those in general public. Immune survivors of initial wave among the health workers may be the only trained personnel left. Going by the experience with SARS, some health workers would not show up for duty. Mass voluntarism may be the last rescuer but if not suitably trained well in advance, this highly motivated, quasi-informed and largely uncoordinated cadre may even end up creating a chaos.

Antivirals

In spite of an apparent agreement on stockpiling the

antivirals, the jury is still out on their efficacy, formulary and modality of deployment. WHO recommends their judicious use(17), while a *Lancet* editorial opines that the antiviral drugs are expensive and not effective enough(13). Some experts suggest that as long as resistance does not become a major issue, prompt use of neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir) should substantially reduce mortality(18). In the light of emerging evidence that H5N1 can develop resistance to oseltamivir, it is proposed that stockpiling an alternate antiviral could provide a second line of defence(19). How big should be the stockpile of antivirals has also been a matter of intense debate. If the R_0 of the new virus is below 1.8, a Thailand-based model predicts that a stockpile of 3 million courses of antiviral drugs should be sufficient for containment. Effectiveness will depend critically on quick detection of clinical cases and the speed with which antivirals can be made available to the geographical area and target subjects(12). Stockpiling the items that have a shelf life - like medicines and vaccines-demands an ongoing systems support. Most vaccines would expire in 1-2 years and most antivirals in 5 years. This would require periodic replacements of stockpiles and may also result in heated political and public debates on perceived 'wastage'.

Vaccination

Immunization may be tactically used by some resource rich and technically proactive states but for the low and middle income countries (LMICs), this is not going to be an available option. Production of the present seasonal influenza vaccine is based on conventional egg-based manufacturing process, where we need more than 6 months and 350 million chicken eggs to supply 300 million doses(3). This process needs to be urgently replaced with cell culture technology for a higher and faster antigenic yield. Moreover, H5 and H7 subtypes cannot be made by standard methods since they are rapidly lethal to chick embryos. A suitable immunological priming of the population might be a useful strategy in impeding the genesis of a pandemic, and this creates the need and utility of a 'pre-pandemic vaccine'. Those prepared from earlier strains and stockpiled might be poorly matched to a novel virus because of antigenic diversity of currently circulating H5N1 viruses. Effective adjuvants might offer an answer. A trial of MF59-adjuvented subunit H5N3 vaccine has demonstrated the third dose induced cross-reactivity to a range of H5N1 variants. It remains to be investigated whether whole-virion vaccines can induce broad cross-reactive responses(20,21). Production of a 'pandemic vaccine' would take a minimum of 6 months after isolation of the circulating novel virus. Given the combined capacity of all international vaccine manufacturers, production during next 6 months would be limited to less than a billion monovalent doses. Since two doses would be required for protection, it would immunize only 500 million people-approximately 14% of world population(3). Over 85% would remain unimmunized - even after a year of pandemic.

Non-pharmaceutical interventions

Since a pandemic vaccine may not be available for initial 6 months, and the antivirals may not be accessible in required quantity, the NPIs would be the only intervention available at most of the places of outbreak. This is going to be the most likely scenario in India. Available evidence suggests that NPIs can delay the disease transmission, blunt the peak of epidemic and head off the pandemic by decreasing the overall burden(22,23). However, there is no India specific data from previous pandemics to determine which of the several NPIs would be most effective. All feasible NPIs will have to be deployed together.

Suppose there is no ground zero or distinct epicenter - the way we wish to see it in war-games!

Most of our strategies are based on certain assumptions and they largely revolve around a hypothetical ground zero or epicenter. What if it doesn't happen the way we foresee it? We need to take cognizance of the fact that stopping the development of a pandemic may not be possible in such a scenario. For instance, a newer virus may emerge simultaneously in several loci-making containment operations quite unattainable. This is also anticipated that no single measure can be applied successfully everywhere and in all the

KEY MESSAGES

- There seems to be a generic consensus on the certainty of an influenza pandemic, in a short period of time from now, with devastating global impact.
- Response and strategic approaches are polarized between resource rich and resource challenged countries. India seems to have, wisely, taken a middle path.
- If the pandemic were to occur tomorrow, it will savagely expose the class divide of the modern world instead of forcing a global solidarity.
- Since a pandemic vaccine - the best possible intervention - may not be available for initial 6 months, and antivirals may not be accessible in required quantity, the non-pharmaceutical interventions would be the only preventive modality available at most of the places of outbreak.
- There is a need for strengthening efforts to create a global pool of resources and stockpiles of antivirals, antibiotics and vaccines for the first affected countries.

events, no single containment measure by itself will be sufficient to stop the spread of novel virus. Nonetheless, these combined measures applied together could retard the genesis of a pandemic.

Dynamics between health, veterinary and agriculture sectors

Most communicable diseases of human beings that have emerged in last two decades have had an animal source. Therefore, the streamlining of the knowledge transfer and operational coordination between the departments of veterinary sciences, animal husbandry, wildlife and health is going to be absolutely crucial while developing early warning system and response. Such coordination can not be taken for granted even in the developed countries. The failure to prevent the outbreak of bovine spongiform encephalopathy (BSE) in Japan is a case under scanner where bureaucrats in each of these ministries, while ignoring the common objective, fiercely protected their own turf. Blame-game was in plenty, without enough exchange of information(24). Strengthening of these linkages is even more crucial in LMICs. Mass culling of poultry birds also raises several issues. Of them, spot or early compensation and local supply of food substitutes need to be immediately addressed to ensure people's support for the interventions.

THE CLASS DIVIDE

Mathematical models may prove to be inaccurate, but their home work certainly underscores the fact that glaring health inequity is hardly any lesser now than in 1918, and the technical advances of a century are unlikely to help much of the developing world in any contemporary pandemic. Sufficient stocks of antibiotics, antivirals and pandemic vaccines would not be available to most of the resource challenged countries. We are comparing the impact of a future pandemic with that of one in early twentieth century - and even the war-game results are an indictment of global inequity in health care(18). Stockpiles of vaccines and antivirals may expire and go waste in countries where they are not urgently required but are unlikely to be available to people who would need them the most. Politics and governance of LMICs along with their civil society movements must also share a significant portion of this blame.

Need for strengthening the global pool of resources for use in first affected countries

It is not that the solutions are not available. If we were to arrest or slow down the earliest outbreaks, delivery of the antivirals and vaccine stockpiles to the first sites - regardless of the domestic resources of affected countries-would be in everyone's interest. Respective governments of the resource rich countries need to realize this, while strengthening WHO's efforts to maintain a global pool of antiviral stockpiles and real time knowledge transfer on pandemic vaccine(11,12). We also need to have a properly mandated international protocol to this effect, besides having nation specific plans. New International Health Regulations (IHR) may have a substantive role to play. It is to be ensured that, in

global crisis, major political actors are driven by people's interest - not by power and privileges of select classes and regions. However, considering the present policies on oseltamivir stockpile and pre-pandemic vaccine, a positive public health internationalism doesn't seem to be evolving fast enough. NPIs may be the only available modalities of control for most of the people in most parts of the world, cutting edge medical developments of a century notwithstanding.

Forced optimism would be an insult to evidence

The author is not informed enough to punctuate such open issues with conclusions or certitude. Nevertheless, possibilities paint a scary picture. If the pandemic were to occur tomorrow, it will savagely expose the class divide of the modern world instead of forcing a global solidarity. Causal factors and context might have changed but on the score of access to quality care and empowerment, we are the way we were in 1918. Science and civil society have taken several people to places but for a vast majority of the world, the more things changed the more they remained the same. In such a milieu, for a person on the street in Asia, cynicism may well be a rational idea. Forced optimism would be an insult to evidence — and a sacrilege to science itself.

Funding: None.

Competing interests: None stated.

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