

Pandemic (H1N1) 2009: Priority Areas for Research

The 2009 influenza pandemic has affected most countries of the world within a short span of time.¹ Though at present the pattern of illness does not differ from that of seasonal influenza, the sheer volume of cases that is expected to occur could easily overstretch already fragile and overburdened health services, especially in the developing countries, and cause considerable suffering in human populations around the world.²

Outbreak analysis in different parts of the world show that like seasonal flu great majority of the cases have mild and self-limiting illness; only few require hospitalization.⁴ However, in some cases, the clinical course can deteriorate in matter of hours, leading to severe complications and eventually death. The risk of complications has been reported to be higher in those who have pre-existing diseases such as asthma, heart disease, kidney disease, and among pregnant women. In Europe, attack rates in the range of 20%–30% have been estimated.⁴ In Australia and New Zealand, where the regular flu season is coming to an end, an attack rate of 20% has been assumed. With regard to severity, the disease is labelled as mild to moderate as only 1%–2% of the cases require hospitalization. The case fatality rates in the USA and United Kingdom (UK) have been in the range of 0.3 and 0.4%. Taking into account cases that may not have reported to healthcare facilities, the case fatality rate could possibly be in the range of 0.1%–0.2%.⁵ Most of the epidemiological information has emerged from the developed world.

Due to differences in the environmental, socio-demographic, and health system, the epidemiology in developing countries could vary. Hence, an Informal Meeting held at WHO SEARO, New Delhi on 2 September 2009 identified following priority research areas. It concluded that though response activities are a priority and most of the staff is involved in these activities now. However, resources should also be committed to analysis and research. Quick analysis of the available epidemiological, clinical, and virological data can be of immense help in making the response activities focused to save more lives.

Research Areas:

1. Epidemiology

- 1.1. Analyze cases and deaths by person, place, and time
- 1.2. Study the risks of infection, disease, severity, and death, and identify risk groups and risk settings
- 1.3. Conduct sample survey of selected communities (schools, work-sites, households) by telephone or home visits and if possible find infection rate by sero-survey.

- 1.4. Follow up of sample populations (schools, work-sites, households) to measure communicability, i.e., attack rates, secondary attack rates, serial interval etc.
- 1.5. Establish surveillance for influenza like illnesses (ILIs) and severe acute respiratory infections (SARIs)
- 1.6. Estimate disease burden and effect of interventions by mathematical modeling using the parameters derived from above studies.
- 1.7. Establishment of an early warning system by monitoring absenteeism in schools, and workplaces
- 1.8. Extend the influenza surveillance (category A, B, C) into Integrated Disease Surveillance Program by involving public and private sector
- 1.9. Set up sentinel sero-surveillance sites in the voluntary and replacement blood donor.
- 1.10. Study the role of fomites and faeces in transmission
- 1.11. Find the determinants of variability in case fatality rate in different settings and different time periods.
- 1.12. Web-based surveillance system

2. Clinical

- 2.1. Clinical profile of cases and deaths- symptoms, severity, co-morbidity
- 2.2. Biomarkers of severity in people without any co-morbidity
- 2.3. Effectiveness of oseltamivir according to the timing of therapy initiation after onset of symptom
- 2.4. Impact of early oseltamivir therapy in reducing case fatality rates
- 2.5. Based on available hospital data, construct a profile of cases that are likely to have a severe disease and progressively deteriorate in a short period of time and die who; these cases will benefit from early antiviral treatment
- 2.6. Simple community-based measures of monitoring oxygen saturation
- 2.7. Effects and side-effects of different doses of oseltamivir
- 2.8. Effect and side-effects of combining oseltamivir and probenecid
- 2.9. Development of additional drugs, i.e., Star anise/Shikimic acid

3. Viral, Laboratory Diagnosis and Vaccine

- 3.1. Development of simple diagnostic test for clinical use (point of care) and a marker of infection (dried blood spot) for epidemiological use
- 3.2. Virus survival in environment in different climatic conditions
- 3.3. Virus excretion in faeces
- 3.4. Monitor changes in virus- antigenic shift and drift in humans and pigs
- 3.5. Set up surveillance system to monitor resistance to antiviral drugs
- 3.6. Develop vaccine against pandemic (H1N1) 2009 strain

4. Social, Behavioral and Communication

- 4.1. Monitor knowledge, attitude and practices (KAP surveys) in the community
- 4.2. Evaluating effectiveness of Non Pharmacological Interventions such as social distancing measures (school closure etc.)
- 4.3. Efficacy of masks in different climatic conditions
- 4.4. Social and economic impact of the epidemic

5. Health system

- 5.1. Monitor treatment prescribing practices in private sector
- 5.2. Assessment of surge capacity at various levels of health care
- 5.3. Scaling up of drug delivery through – public system (PHCs)/DOT/ART centers/ Private hospitals/selected Chemists
- 5.4. Delivery of vaccine- which vaccine, to whom and how

In developing countries several factors such as population density, level of under nutrition, care seeking from informal sector, and delays in management of cases could affect the attack rates, severity, and case fatality. Hence, establishment of surveillance in schools or worksites for recording absence due to influenza like illnesses (ILIs), and in sentinel hospital for admissions due to severe acute respiratory infections (SARIs) can help in characterizing the risks of clinical disease, severity, and death, and in identifying the risk groups and risk settings. The ratio of symptomatic to asymptomatic infection can be estimated by conducting sample survey of selected communities (schools, work-sites, households) combined, if possible, with a sero-survey; sentinel surveillance in voluntary blood donors can also be an alternative. Follow up of sample populations needs to be done to measure communicability, i.e., attack rates, secondary attack rates, serial interval etc. These epidemiological parameters can then be used in mathematical modeling to estimate disease burden and effect of interventions.⁶

In the USA and UK, the risk of complications has been higher in those who have pre-existing diseases such as asthma, heart disease, kidney disease, and among pregnant women; obesity has also been identified as a risk factor for severe disease.^{7,8} The profiling of symptoms and signs can give better case definition for surveillance, and clinical profile of cases and deaths by severity and co-morbidity, could identify important risk factors such as under nutrition which are relevant in developing countries.

Oseltamivir is the recommended drug of choice.⁹ Does the effectiveness of oseltamivir vary according to the timing of therapy initiation after onset of symptom, or does early oseltamivir therapy or a combination of oseltamivir and zanamivir help in reducing case fatality rates? Based on available hospital data, a profile of cases that are likely to have a severe disease and progressively deteriorate in a short

period of time need to be studied to identify cases that will benefit from early antiviral treatment including the study of side-effects of different doses of oseltamivir.⁹

Currently, confirmatory diagnostic tests can be done only in specialized laboratories. Reverse-transcriptase polymerase chain reaction (RT-PCR) provides the evidence of infection.¹⁰ At present, there is no validated rapid bedside diagnostic test (including so-called 'point-of-care' diagnostic tests). Commercially available rapid tests for seasonal influenza have uncertain sensitivity (between 10% and 60%) and lack specificity. Samples for laboratory tests are taken from the deep nasal passages, nasopharynx, throat or bronchial aspirate. It is not yet known which clinical specimen gives the best diagnostic yield for this infection. Development of simple low-cost diagnostic test for clinical use (point of care) and a marker of infection (dried blood spot) for epidemiological purpose will be immense help at this stage.

The climatic conditions vary a lot in various regions of South-East Asia. Virus survival studies in the environments of different climatic conditions, and specially duration of virus shedding in respiratory secretions and excretion in faeces are required to have specific recommendations for isolation and quarantine. Virus needs to be monitored for changes - antigenic shift and drift in humans and pigs including setting up a surveillance system to monitor resistance to antiviral drugs.

Currently, there is no vaccine against the pandemic H1N1 2009 strain. Antivirals are also available in limited supply. Vaccine against pandemic (H1N1) 2009 strain will help in tackling the second wave of the pandemic which could have higher severity. Effective personal preventive measures include protective coughing or sneezing, frequent hand-washing with soap, social distancing, and voluntary isolation by symptomatic individuals. Efficacy of masks in different climatic conditions also is not known. The knowledge, attitude and practices (KAP) surveys should be done in the community to find out the effect of mass media campaigns that have been launched by the governments. Evaluating effectiveness of Non Pharmacological Interventions such as social distancing measures (school closure etc.) is a priority. There is data to suggest also that the non-pharmacological interventions were useful in preventing deaths in the 1918 epidemic in parts of the US where these were implemented.¹² However, the feasibility of effectively implementing these measures and their acceptability by the population needs to be considered in the present context. In Japan, school closer has been effective in terminating the outbreak in the schools but was not effective in preventing community outbreaks. Social and economic impact of the pandemic also needs to be studied.

At present the pandemic virus is causing a mild disease, however, the next wave may be more severe. Hence, treatment prescribing practices should be monitored in public and private sector as only few drugs are at present effective against the virus, and resistance can develop if drugs are prescribed

inappropriately. Assessment of surge capacity at various levels of health care particularly the scaling up of drug delivery through – public system (PHCs)/DOT centers/ Private hospitals/selected chemists need to be explored. Whenever the vaccine becomes available, policies related to the vaccine delivery will be needed, i.e., which vaccine to choose, whom to give and how to deliver it etc.

Uncertainties still remain about the extent to which this virus may eventually spread. This will, we believe, depend on three factors: communicability of the virus as measured by attack rates, its virulence or severity as measured by case fatality rates, and implementation of an effective national response, in particular, ensuring proper case management measured by the surge capacity of the health or medical services.

It is clear that the influenza pandemics of 1918 and 1957 both began as mild but subsequent waves were more severe. Whether the current one which is considered as mild or moderate in severity will be more severe during the second wave remains to be seen. But policy makers and health authorities must consider seriously setting up of a task force for outbreak data analysis and research as a part of national preparedness and response to the ongoing pandemic. The overall impact of the pandemic in the twenty-first century could be determined by factors such as the availability epidemiological information, antiviral agents, potential for vaccine development and modern communication technology to spread prevention and control messages, each of which can possibly attenuate the effect of this pandemic on human life and the world economy.

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