



Editorial

Pandemic Flu, 1918: After hundred years, India is as vulnerable

The year 2018 marks the centenary of the 1918 influenza pandemic. Then, India had the largest number of deaths in any single country (10-20 million) as well as highest percentage of excess deaths (4.39%) in the world^{1,2}. The estimated total global death toll was 50-100 million. A modelling exercise has shown that if an influenza pandemic with a similar severity were to happen in 2004, the world is likely to have around 62 million deaths. And sadly, India again would top the countries with maximum deaths (approximately 14.8 million)². Even in 2018, the situation is unlikely to be any different. However, we can and should stop the history repeating itself.

Influenza A and B cause seasonal flu outbreaks. Influenza A virus also occurs naturally in aquatic birds, which serve as the reservoir. It also infects poultry, and animals such as pigs, horses and dogs. Reassortment of human and avian/animal viruses happens occasionally resulting in a major shift in their antigens, producing a novel reassortant virus. Moreover the virus can also jump from one species to another; for example, from poultry to humans. If these viruses adapt to the human beings, person to person transmission of infection starts. The stage is set for an epidemic.

As the virus is continuously changing, the composition of seasonal vaccines needs to be annually tailored to match the circulating strains. The seasonal flu vaccines therefore provide protection only against the circulating strains. This is one of the reasons why vaccinations against seasonal flu are needed every year. When a pandemic strikes, a new vaccine matching the pandemic strain is developed. With the existing technology, it takes around six months for the manufacturers to produce a new vaccine.

When the first pandemic struck in 1918, our knowledge on influenza was a clean slate, in fact, some believed that the pandemic was caused by a bacteria - *Bacillus influenza*³. There were no

vaccines, no antivirals and no antibiotics to treat the superadded infections. Today, we have a slew of public health measures for influenza. One category is of pharmaceutical interventions that include vaccination and the use of antiviral drugs. Second is of non-pharmaceutical interventions that include the implementation of measures at individual, household and societal levels. It is expected that when used appropriately, these would slowdown the speed and spread of the outbreak that would buy time for preparation and implementation of other measures such as vaccination. These measures are expected to help reduce the total number of cases and deaths. Development of antivirals has been promising, these are recommended in the short therapeutic window, and for prophylaxis when either a vaccine is not available or vaccination is inadequate, but their use is threatened by emergence of drug resistance⁴. Although the vaccines may not give full protection, these remain the best line of defence and play a vital role in the prevention.

In 2014, there were 115 World Health Organization (WHO) Member States with influenza immunization policies in place⁵. A survey of the these countries indicates that those which have an influenza vaccination policy are high income or upper middle income countries, have introduced new and underused vaccines (like the birth dose of hepatitis B virus, PCV, human papillomavirus), have a strong routine immunization programme (measured by DPT3 coverage and achieving maternal and neonatal tetanus elimination) and functional National Immunization Technical Advisory Group⁵. With India launching the Intensified Mission *Indradhanush* to improve the routine immunization coverage among the unreached children⁶, India's score on the fully immunized newborns is targeted to be more than 90 per cent by end of 2018⁶; India checks on almost all these boxes but does not have a seasonal flu immunization/vaccination policy.

Every year, on an average, 3-5 million cases of seasonal flu and 290,000-650,000 deaths are reported globally⁷. In high-income countries, deaths occur in elderly (65 and older) while in the low and middle income countries like India, 99 per cent of deaths are in children under five with influenza-related lower respiratory tract infections⁷. However, the low and middle income countries hardly use the vaccine. In 2015, of the 486 million doses distributed to 201 countries, 95 per cent were shared among the Americas, Europe and western Pacific WHO regions and only five per cent were distributed among South-east Asia, eastern Mediterranean and Africa WHO regions⁸. When a country does not buy and use the vaccine in 'peace time', it gets a low priority even if it were to pay for the vaccine when a pandemic strikes as happened during the 2009 pandemic⁹.

Influenza A/H1N1 2009 virus emerged in April 2009. Within weeks, the virus spread across 30 countries. On June 11, 2009, the WHO declared it as a global influenza pandemic^{10,11}. In four months, infection was reported from 122 countries with 134,000 laboratory confirmed cases and 800 deaths. By August 2010, when the pandemic was declared to be over, 214 countries had reported confirmed cases and 18,449 deaths¹². The first pandemic vaccine to be approved was in September 2009. Eleven pandemic vaccines were manufactured and prequalified for use during the course of the pandemic. The manufacturers of seasonal flu vaccine (of which more than 80% doses are produced by seven large manufacturers located in USA, Canada, Australia, Western Europe, Russia, China and Japan) switched over to making pandemic vaccines⁹. There were reports that the developed countries had placed large advance orders for the 2009 H1N1 vaccine and bought all that the vaccine manufacturers could produce, leaving very little or nothing for the rest of the world. As a result, no pandemic Influenza A/H1N1 vaccine was available in majority of the low resource countries before January 2010 - more than eight months after the WHO declared the pandemic.

India reported the first case of Influenza A/H1N1 in May 2009¹³. The first peak of the pandemic was in September 2009. The Government of India had imported 1.5 million doses of a pandemic flu manufactured by a multinational company to vaccinate selected population among the high-risk groups, healthcare and emergency service personnel¹⁴. The vaccine was provided to various States. Barring few

States, the acceptance and utilization of vaccine was disappointing¹⁴⁻¹⁹. The Government also supported three Indian vaccine manufacturers to produce the pandemic vaccine by providing ₹ 100 million each as advance market commitment. It placed an order of 625,000 doses from each of these companies. However, for various reasons, the vaccine could not be used and had to be destroyed. By end of 2010, India had recorded 38,730 cases and 2024 deaths²⁰. Due to limited testing facilities, this is likely to be an underestimation of the true number of cases in India²¹.

From the above, the following are obvious:

- (i) Because of its better economic situation, India is not eligible for receiving the donated vaccines, it needs to get its own vaccine;
- (ii) No foreign country vaccine manufacturer would be able to sell the vaccine to India unless its domestic requirements are fulfilled;
- (iii) Even when India pays for the vaccine, it may arrive too late to have an impact on the raging pandemic;
- (iv) Our health systems are not geared to deliver the flu vaccine; and
- (v) India has more than one vaccine manufacturers which have the skills and infrastructure to produce sophisticated influenza vaccines.

What should India do?

One, the burden of seasonal influenza is not recognized in India. Absence of data does not mean absence of disease. It is known that influenza disease exists in India, the types and subtypes of strains circulating in the country and the seasonality of annual outbreaks are also known²². There are limited data on the burden of severe influenza disease in India. It has not been characterized adequately, in terms of hospital admissions and excess deaths especially among the high-risk groups such as children under five years, pregnant women, people with comorbidities and the elderly. We need information on cost benefit and cost-effectiveness studies of using vaccines. Such information would be essential for the government to consider policies to vaccinate high-risk groups using seasonal flu vaccine.

Two, having the capabilities to produce pandemic vaccines is not enough. These companies cannot start manufacture and/or scale-up influenza vaccines production overnight. To maintain and expand current production capacities, demand for seasonal influenza vaccine is critical. Ensuring market for seasonal flu

vaccine will ensure that the infrastructure is able to switch over to pandemic vaccine production in the event of a pandemic erupting. Moreover, a vaccine produced in India would definitely be more economical than the one bought from any foreign manufacturer.

India has the highest under-five mortality rates in the world, in 2016 approximately 0.9 million children under five died²³. Using data from a study at Ballabgarh, Haryana²⁴ (field practice area of the All India Institute of Medical Sciences, New Delhi) and assuming that data are broadly representative of India, it has been calculated that 6.5 per cent of all paediatric acute lower respiratory infection deaths in India were associated with influenza in 2006-2008²⁵. With vaccination programme against the three major killers already introduced (*Haemophilus influenzae*-related invasive disease, rotavirus diarrhoea and pneumococcal pneumonia), influenza-related deaths are likely to become visible. We need to protect the vulnerable population.

We suggest two actions on priority. Information, education and communication programmes should be developed targeting general public and healthcare workers to raise awareness about influenza and dispel myths and misconceptions about vaccines. Second, seasonal influenza vaccination may be made mandatory for healthcare workers as they are at higher risk compared to the general population due to nature of their work. They can transmit to and also get influenza infection from patients. At the minimum, physicians and the nursing staff who take care of the infants, the elderly, those who are immunosuppressed (for example who have received organ transplant) or have other chronic conditions must be immunized against influenza, as has been recommended by the WHO²⁶.

Imagine the devastation a 1918-like pandemic would cause today in India when we are more interconnected. The cities are denser. The speed of travel has increased. Conditions that favoured the spread of influenza in 1918 are still prevalent. Given the widespread presence of influenza virus in nature, the probability of emergence of a reassortant flu virus which adapts to start human to human transmission is high. What is also certain is that India would not be spared. What is uncertain is how seriously does India perceive this threat and take action.

Conflicts of Interest: None.

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