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GUEST EDITORIAL

Will Coronavirus Pandemic eventually evolve as Pan-endemic?

The 2020 pandemic virus is called SARS Coronavirus-2 (SARS-CoV-2) to distinguish it from Severe Acute Respiratory Syndrome (SARS) coronavirus that scared the world in 2003 and also to highlight that the two are closely related. The disease caused by SARS-CoV-2 is coronavirus disease-2019 (Covid-19). It started in Wuhan city, in Hubei Province, China.

Covid-19 started as *zoonosis* (vertebrate-to-human transmitted infectious disease) sometime in late 2019. On 31 December China alerted the World Health Organization (WHO) about several cases of pneumonia in Wuhan, with tests for all known causes negative.

SARS had a similar history. It started from Guangdong, China, sometime in 2002, and later it reached Hong Kong, Viet Nam and Singapore. Its cause as coronavirus and spread as *anthroponosis* (human-to-human transmitted infectious disease) were soon deciphered.

SARS virus receptors are in lungs, none in upper respiratory tract. Therefore it was not an efficient spreader. Pathology was pneumonia; severe cases had acute respiratory distress syndrome (ARDS). WHO developed a protocol to contain its spread – screen travellers from infected countries on arrival using no-touch thermometers; quarantine and test anyone with fever. Fever came before infection was transmissible, a helpful sequence. India had three importations without secondary spread.

By diligent application of protocol by all countries, transmission was arrested in July 2003 after there were 8096 cases in 27 countries with 774 deaths – case-fatality rate was 9.6%. When WHO declared the influenza pandemic in 2009, India applied the same protocol but it did not prevent the importation of the pandemic virus. The protocol was not sufficient against *contagious* (easily transmitted during social contact) influenza, with virus receptors in upper respiratory tract.

On 7 January 2020 China informed WHO that the pneumonia in Wuhan was caused by a novel Coronavirus. Chinese scientists put the full genome sequence data and primer sequences for reverse transcriptase polymerase chain reaction (RT-PCR) for diagnosis, in public domain. International virus taxonomists re-named the virus, on 11 February, as SARS-CoV-2. It had 96.2% genetic similarity to a virus that was detected in bat faeces in a cave in Yunnan Province, China, in 2013. So, SARS-CoV-2 is a virus, jumping to humans through a not-yet identified intermediary animal. SARS had jumped to humans from bats through palm civets.

By 24 January China had reported 26 deaths among 830 disease-cases. By then infection had reached Thailand, Japan, Taiwan, South Korea, Viet Nam, USA, France, Australia, Singapore, Malaysia and Nepal.

On 30 January, infection was prevalent in all provinces of China and WHO declared the disease a 'public health emergency of international concern'. On 31 January, the Philippines, India, Russia, Spain, Sweden and UK documented virus importation. A *contagious anthroponosis* with virus spreading in 17 countries outside China-Hong Kong-Macau, was already an undeclared *pandemic* (global epidemic).

WHO declares a pandemic 'when the world's population would likely be exposed to a new infection with potential to make a proportion sick'. By 2 February infection had spread to 7 more countries; by end-February 70 countries were infected. WHO declared Covid-19 pandemic on 11 March. Countries depending on WHO guidance for mounting responses apparently mistook the delay as a message that the epidemic was not spreading rapidly.

Did WHO delay the coronavirus pandemic declaration? On 11 June 2009 WHO had declared influenza H1N1 as *pandemic*. That was the correct response. Fortunately H1N1 influenza turned out to be not very severe, with case-fatality of about 0.1%. The 1918 Spanish flu pandemic was by H1N1 virus which was replaced by H2N2 of 1957–58 Asian flu pandemic. All above 52 years had high probability of immune memory for H1N1.

Contagious infections have transmission dynamics based on *reproduction number* and *generation time*. In order for the microbe to survive, one infection must generate at least one new infection. The *effective reproduction number*, R, should be 1 for a stable endemic infection. $R > 1$ is outbreak, and, $R < 1$ is infection declining. For endemic diseases like seasonal influenza, R fluctuates between <1 (low season) and >1 (high season), but average will be 1 over time.

The *basic reproduction number*, R_0, denotes how many would be infected by one infected person, if all contacts were non-immune and susceptible. For endemic infections

many contacts would be already immune, hence non-susceptible; so $R = 1$ means that among all exposed contacts, at least one was susceptible and successfully infected. The number of persons whose doors were knocked, so to say, is the *basic reproduction number* R_0.

For a pandemic the world population has to be non-immune to a new virus – hence for a time R would approximate R_0. For both pandemics, H1N1 and SARS-CoV-2, R_0 is about 2. The flu was declared pandemic about three months after emergence was recognized in Mexico. The starting date of SARS-CoV-2 is unclear. Already in December 2019 infection was widespread in Wuhan and the whole province of Hubei. Recently it was reported that infection had been confirmed in mid-November by studies on stored specimens.

The speed of spread of H1N1 flu was faster than that of SARS-CoV-2; whereas flu had reached nearly all countries of the world in three months, the coronavirus had reached only a little over one-third countries of the world, by early March. Perhaps this slower speed of spread might also have made WHO experts think twice, and be sure, before declaring pandemic.

The slow expansion of infected countries in spite of $R_0 = 2$ is no surprise for SARS-CoV-2. The reason lies in what we call *generation time*. The incubation period of flu is about 2 days and that of COVID-19 is about 10 days (range 3–14): we assume that it takes 6 days for an infected person to become infectious. Flu spreads fast – one case to two in 2 days; 2 to 4 in 4 days; 4 to 8 in 6 days; 8 to 16 in 8 days; 16 to 32 in 10 days. SARS-CoV-2 spreads slower, one case to two in 6 days; 2 to 4 in 12 days; 4 to 8 in 18 days; 8 to 16 in 24 days; 16 to 32 in 30 days.

When flu expands from one to 32 cases in 10 days, SARS-CoV-2 expands from one to 32 in 30 days. From early March to mid-March the expansion had doubled, reaching about 140 countries. Had experts understood the differences of transmission dynamics between the two, the seriousness of the multi-country epidemic would have been obvious weeks before the declaration of pandemic.

This pandemic is an avalanche, gathering momentum as it grows. Virus receptors are in upper respiratory tract and lungs – so infection spreads easily and is more virulent than flu. Most infections cause mild disease; <20% have severe disease. Case-fatality is 1–3%, depending on host factors as well as healthcare quality. Data from other countries show that case-fatality in children and young adults is <1% but in older adults, especially those with chronic diseases, it is 3–8%. The nation's response so far has been slow, reactive and incremental. We are moving a step or two behind the cusp of advance, instead of being wise and proactive, moving two steps ahead. The crucial expertise of *epidemiology intelligence* is missing in India's health management system.

Health management must use epidemiology intelligence to forecast probabilities. If pandemic flu H1N1 settled down as *pan-endemic* (globally endemic) after it reached all countries during its expansion phase, is it not likely that SARS-CoV-2 will also evolve similarly?

Why should we ask this question so early in the expansion phase of the epidemic in India? Our projection of how the epidemic will grow will depend upon our understanding of the future community–virus interrelationship. Will this virus infection die out or persist in humans? There is no precedent for a pandemic die-out by hara-kiri.

If it is likely to become endemic, it is likely to near-saturate the population in due course. For the flu H1N1 pandemic we neglected epidemiological monitoring. We do not know what proportion of population, by age, season and geography, got infected during the peak. We are not measuring the magnitude of H1N1 even now, after it evolved as pan-endemic and perennially seasonal.

SARS-CoV-2 infection may peak only after a few months, giving us breathing time to strengthen the health management system to cope with the burgeoning disease burden.

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