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GUEST EDITORIAL

COVID-19: India's endemic phase heralds the beginning of the end of the pandemic

The editorial 'Will coronavirus pandemic eventually evolve as pan-endemic?' (John, T. J., *Curr. Sci.*, 2020, **118**(6), 855–856) predicted that the COVID-19 pandemic would end by transitioning into endemic prevalence globally (pan-endemic).

At that time there was a widespread hope for the pandemic to end with SARS-CoV-2 transmission getting interrupted due to 'herd immunity'. This was due to the extrapolation from the natural history of epizootics in herds of farmed cattle, in the days before modern diagnostics and antimicrobials. The epizootic would naturally end after a large proportion fell ill, among which some died, others recovered, but the rest never fell ill. The transmission of epizootic agent had ended and its driving force was called 'herd immunity'. It was extrapolated to the pandemic.

A herd is a confined population, like an island community with very little in-migration and small birth cohort. Herd immunity's classical example was in Faroe Island in North Atlantic, where measles had died out after an epidemic in 1806. When re-introduced by sailors in 1846, all below 40 years were susceptible but all above 40 were immune. The virus had been absent for 40 years. Such a situation has no precedent in continental populations, in which new birth cohorts are sufficiently large to continue transmission chains at sub-epidemic frequency, in other words endemic state.

Using vaccination we could interfere with natural disease epidemiology. Theoretically it was predicted that at high level of immunization we could build up herd immunity and interrupt virus transmission – that level was termed 'herd immunity threshold' (HIT). There was a simple formula to derive HIT, namely 1 minus $1/R_0$ of the disease agent, R_0 denoting the basic reproduction number of the microbe. The teaching was a virus species would have R_0 as its basic property, not varying much in spite of mutations that result in minor phenotypic changes within the species.

During 2020 no COVID vaccine was available. The editorial predicted that the epidemic would transition as endemic when the HIT of coronavirus was reached. The basis of prediction was experience with pandemics of influenza viruses – H_2N_2 (1957), H_3N_2 (1968) and H_1N_1 (2009), all of which became endemic as the pandemics ended. The similarity between the Corona and Influenza viruses was in the transmission modality – inhalation of droplets and aerosol. The prediction has come true in India – our epidemic ended by 8 July 2021 and the endemic phase has been sustained for over 22 weeks.

Epidemic and endemic are descriptive terms coined by Hippocrates some 2500 years ago. When a graph of daily case numbers is drawn, epidemic is seen as a bell-shaped curve, with steady rise, a peak and decline. When the graph continues after decline as a roughly horizontal line, parallel to the *X*-axis, sustained for more than four weeks, with no more than minor fluctuations, the pattern is endemic. With COVID, we notice that endemic level begins with daily case number at or below 10% of the peak. India's second wave peaked on 6 May with 414,433 cases and rapidly declined to below 42,000 on 8 July 2021. Thereafter the level has steadied, with very slow decline – below 30,000 (25 September), below 20,000 (9 October) and continues below 10,000 (since 22 November).

The first epidemic wave would have provided approximately 30% herd immunity which was sufficient as HIT appropriate for the then virus variant (Wuhan-D614G). In human disease epidemiology, the term herd immunity had been adapted to mean the proportion in the population that is immune, either due to infection or immunization. The advantage is that it can be measured by immunity prevalence surveys, illustrated by periodic national level SARS-CoV-2 antibody surveys conducted by the Indian Council of Medical Research (ICMR).

Extrapolating from influenza viruses, which mutate frequently resulting in 'antigenic drifts', but without increasing R_0, an assumption was made that any new virus variants of SARS-CoV-2 should have relatively stable R_0. Since HIT had been reached, epidemic resurgence by way of another wave was not anticipated.

However, after 10 weeks of endemic pattern the second wave took off, this time with *delta* (B.1.617.2) variant proving the assumption of stable R_0 wrong. The *delta*

variant has many-fold higher R_0 than that of Wuhan-D614G variant, with the resultant HIT of about 85–90%. The fourth antibody survey by ICMR coincided with the pre-endemic time (June–July, 2021) and it showed overall 67.6% immunity prevalence with relatively even urban–rural distribution. In 6–9 year age group it was 57.2%; in 10–17 age group 61.6%; in 18–44 age group 66.7% and in 45–60 age group it was 77.6%. Those who got two doses of a vaccine it was 89.8%. Since then more people are infected every day, and also vaccinated daily, enhancing herd immunity levels very high. In the face of such high immunity prevalence, another epidemic wave by a new variant of the same virus is quite unlikely.

Nearly one year has passed since the *delta* variant emerged but no further variant with higher R_0 emerged until now. Very recently, a variant named *omicron* (B.1.1.529) has emerged in southern Africa and its rapid spread in South Africa suggests that it may have both higher R_0 and greater antigenic drift than *delta*. These properties have not been confirmed, but are likely to be confirmed; so we must be alert and cautious in case the *omicron* variant springs surprises.

Already the *omicron* variant has been detected in 57 countries, including India, attesting to its high transmission efficiency, hence very high R_0. It is likely that *omicron* may rapidly become globally prevalent. Fortunately *omicron* does not seem to be more virulent (pathogenic) than other variants. Moreover early indications are that the antigenic drift can be overcome with high antibody levels consequent to booster dose of any currently approved COVID vaccines. With these signals, India's response should focus on rapidly increasing vaccination coverage – second doses to all who have taken one dose and booster doses to all with second dose taken 6 or more months earlier.

We must also expand the age range for vaccination below 18 years in order to retard any spread of *omicron* among them. Left unvaccinated, they may become a virus reservoir leading to high frequency community spread.

After India, Taiwan reached endemic prevalence with daily case numbers below 15, on 6 August 2021 and has remained so during the last 18 weeks. Taiwan's epidemic profile was most unusual with only one major wave that was due to *delta* variant; it peaked on 25 May 2921 with 597 cases.

Japan reached endemic phase as on 1 October 2021. Japan's fifth wave with *delta* variant peaked with 26,184 cases on 22 August and then fell below 2000 on 1 October, below 1000 (on 8 October), below 500 (20 October) and below 200 (10 November). Thus Japan is in endemic pattern for more than 10 weeks.

The fourth country reaching endemic prevalence is Israel. After the peak of Israel's fifth wave on 2 September with 11,347 cases, the daily number fell below 1000 on 24 October, and below 500 since November 10. Israel meets the definition of endemic phase with over 6 weeks of low and stable case numbers with only minor fluctuations. In Israel, Japan and Taiwan, vaccination with two doses of various COVID vaccines reaching nearly three-fourths of their populations contributed significantly to reach the HIT of *delta* variant – hopefully *omicron* will not cause another wave.

The trend of epidemic transitioning to endemic in four countries will become the norm in all other countries, until COVID becomes pan-endemic. The in-country Coronavirus importations and beginnings of epidemic were staggered in various countries over several months – therefore we must anticipate the epidemic-to-endemic transition also similarly staggered. The predominant variant of pan-endemic COVID is likely to be *omicron*.

[Note: All data are from Worldometer Corona and Our World in Data (Corona). The daily numbers described are 7-day moving averages.]

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