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Omicron: What Happens Now?

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The long-term trajectory of COVID-19 will see the disease becoming endemic with the occasional flare up and frequent booster shots having to be given. We must understand the consequences of this path and reach a consensus on the level of risk we can live with.

The novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes the disease COVID-19, infects people through the respiratory route, through small droplets that we emit while speaking or even breathing. As of 8 January 2022, there were over 304 million confirmed COVID-19 cases and almost 5.5 million deaths worldwide. Of these, over 35 million cases and 483,000 deaths have been reported from India. The actual numbers of cases and deaths far exceed these numbers, in India as well as globally. The pandemic has led to the second largest recession in history, with the global GDP shrinking by nearly $22 trillion as of January 2021. Longer-term losses are estimated to exceed $80 trillion for the period 2020 to 2025.

Viruses, immunity and variants

Biologists Jean and Peter Medawar wrote in 1977 that a virus is “simply a piece of bad news wrapped up in protein”. An outer membrane covering with three different proteins—spike (S), envelope (E) and membrane (M)— together with an inner protein core made of the nucleocapsid (N) protein protect the genetic material of SARS-CoV-2, a single ribonucleic acid (RNA) molecule. This molecule contains all the information the virus needs to copy itself once it enters a living cell. The RNA molecule itself is a sequence of four chemical units called the adenine (A), cytosine (C), guanine (G) and uracil (U). A string of these single-letter characters, arranged in a specific sequence, describes any RNA molecule. SARS-CoV-2 is represented by close to 30,000 such letters.

When a virus infects a living cell, it uses the information contained in its RNA sequence to make new virus proteins. Some of these copy the incoming RNA into thousands of new copies while others pack these into new virus particles (or ‘virions’) that escape the infected cell and go on to infect others. When we cough, sneeze or speak, these virus particles escape as droplets from our oral and nasal cavity. These can be ingested by others, thus infecting them. If such an infection results in disease, it can lead to inflammation, pneumonia, oxygen deprivation and even death.

Our immune system defends us against infections. An initial broad-based innate (or non-specific) immune response is followed by a specific adaptive response, which includes antibodies and killer T cells. Antibodies made by types of blood cells called B cells, recognise and attach to parts of the virus before it can enter cells. Killer T cells seek out and destroy virus-infected cells, removing the source of infection. Vaccines train our immune system to develop virus-specific antibodies and killer T-cells, and though both wane with time, long-lived memory B and T cells persist. These are recalled in future encounters with the same virus.

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To enter cells lining our nasal or oral cavities or the lung epithelium, the virus latches on to cells using the spiky structures that make up the S protein, especially its business end, called the receptor binding domain. These sites on the virus are also the target of ‘neutralizing’ antibodies, made in people with a history of prior infection or vaccination. But viruses mutate, i.e. the sequence which describes them changes with time. This happens because the process by which the genetic material is copied is imperfect and the copies made when the virus replicates are not exact. For example, the sequence “..AUG ..” could become “..ACG..”, which may alter the protein produced from it. Most of the time, these changes do nothing to the ability of the virus to infect people or cause disease. In some cases, however, the changed (mutant) virus can infect better depending upon what has changed and where it is in the virus. If, for example, key contact points for virus entry into cells are changed, this could alter the ability of the virus to infect target cells.

Sometimes, these changes can also allow the virus to escape being the target of neutralizing antibodies. Mutations accumulate with time if they give some benefit to the virus, such as immune escape. We periodically see the emergence of viral lineages in which some mutations come together. These are viral variants, identifiable by genome sequencing. Sometimes, by random chance, a variant can emerge that is more transmissible between people. The original Wuhan strain of SARS-CoV-2 that emerged in late 2019 acquired such

a mutation (D614G) by January 2020. As a result, this virus completely replaced the original one. All circulating variants today are its descendants.

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National and regional governments, and scientists, have so far provided almost 7 million genome sequences for SARS-CoV-2 in public databases. This allows scientists to map viral lineages and see how and when they emerged. The World Health Organization decides if any of these need to be watched closely, these then become Variants of Interest. Those that don't spread well are soon dropped from this list. But those that spread well, escape pre-existing immunity, or cause more severe disease, become Variants of Concern (VOC). There have been five variants of concern so far, each assigned a Greek alphabet – Alpha, Beta, Gamma, Delta and Omicron variants.

What is the Omicron variant?

The Omicron variant, called lineage B.1.529, was first found in Botswana. It was soon implicated in a spurt of cases in the Gauteng province of South Africa before it spread further. A number of those infected were children and young adults, who were in hospital for other reasons and showed no COVID-19 symptoms but tested positive under routine testing.

Compared to the original virus, Omicron has the largest numbers of mutations in any variant lineage: 50 mutations overall, including 30 in the spike protein, of which 10 are in the key receptor binding domain. Every key mutation in other VOCs has come together in Omicron. Several of these mutations are associated with increased immune evasion and infectivity, as seen in laboratory studies. These aspects agree with population data from several countries, which monitor new infections as a function of vaccination and prior infection status.

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There are several hypotheses to explain how the Omicron variant may have appeared in the first place. The most plausible of these is that it emerged from a virus that persisted and accumulated mutations in an immuno-compromised person for a long period of time. A similar explanation was put forward for the emergence of the Alpha variant when it was first reported in southern England. Another variant with 46 mutations that lead to 30 amino acid changes, including 14 in the spike protein and called IHU or lineage B.1.640.2, was reported recently from southern France in a traveller from Cameroon. South Africa and Cameroon have high numbers of persons living with HIV, in a region that has low vaccine coverage. Could that be the trigger for development and emergence of highly mutated variants?

By the end of December 2021, the Omicron variant accounted for about 30% of global COVID-19 cases, but for about 80% of the cases found in Africa. The swiftness with which it is replacing the existing Delta variant is what is alarming. The number of countries reporting Omicron cases is currently 90 or more. The United States is seeing an unprecedented rise in cases, with over 800,000 new cases a day, as are several countries in Europe, particularly the United Kingdom and Italy. Most of these are likely to be Omicron infections. On 7 January, India recorded about 142,000 new cases, a jump from lows of about 6,500 barely two weeks before. These daily case numbers have now exceeded the maximum case count in the first wave and are moving quickly towards the numbers India witnessed in the second wave.

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But there are positives. Overall, from the experience of South Africa, while cases are rising, a similar rise has not been reflected in the need for hospitalization and critical care. It is thus possible that Omicron infection could lead to milder forms of the disease, with many who are infected showing no or very mild symptoms. Mortality in the Omicron wave in the South African province of Gauteng has so far been noticeably lower than in previous waves. However, especially since mortality is a lagging indicator, the true trend will only become apparent over a longer period. How disease severity is distributed across different age bands is also of great interest but is yet unclear from the available data.

What lies in store for India?

As of 8 January all major metros in India were showing a sharp increase in cases, in particular, Mumbai, often a bell-weather for what might happen later in the country. Test positivity rates in Mumbai have increased five-fold within just a two-week period; it is now at a staggering 30%. Cases are doubling over a period of two-three days. Much the same is playing out in Delhi and Kolkata. The reproductive ratio (R0), a measure of the rate of transmission, is already up to 2.69 according to an Indian COVID tracker model. Even more disturbingly, there are reports of large-scale infections of doctors, over 50% in some reports from a few Delhi-based hospitals.

What is crucial now is to understand the extent to which Omicron is truly immune evasive. Even if you show symptoms following an Omicron infection, will they be serious enough to send you to hospital if you have received two vaccine doses? Is hybrid immunity—a prior infection followed by a vaccination—strongly protective? This is an important consideration, since as many as 950 million Indians were already infected by the end of the second wave (by July 2021). Many of these exposed adults would have gone on to receive one or two doses of vaccine by now.

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There is by now considerable evidence that some fraction of those infected with the Omicron variant will go on to exhibit symptoms of the disease, even if they are mild. Vaccine-derived protection from serious disease is expected to be maintained longer than protection from symptomatic infection. But both wane with time. Acquired immunity, in the form of T-cell and B-cell response, appears to continue to be robust. All vaccines work, largely at the same level, at keeping someone infected out of hospital. From Mumbai, there are reports that over 90% of hospitalized patients who require oxygen are unvaccinated. Where different vaccines differ is in their ability to counter symptoms following infections. Indeed, it is really this that booster shots target.

From the South African experience it does appear that children are disproportionately at risk of infection, perhaps even of disease. However, whether this comes from a relatively lower probability of a prior infection or reflects the differential impact of vaccination programmes among the elderly versus the young remains to be seen.

There have been suggestions that Omicron infection might function as a natural vaccination, preventing infection by later (or earlier) variants. There is preliminary evidence that an Omicron infection might protect against a (re-)infection by the Delta variant, but there are many reasons why extending this argument to welcome infection by Omicron because it is potentially milder and provides protection, is incorrect. First, “mild” is relative, and depends as much on the response of the host as on the variant. We still don’t understand why an otherwise healthy 25-year-old might wind up in hospital while a 70-year-old does just fine.

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Second, the nature of long COVID is still ill-understood. It may arise from a re-activation of a dormant virus or from microscopic clots that form after an infection, or from a host of other possibilities. Finally, ensuring that health systems can cope with a sudden influx of patients is also crucial, as India learnt the hard way during the Delta wave. It is this last point that should worry us most in the immediate term. A small fraction of a very large number is still a large number, which can quickly overwhelm healthcare facilities, especially when frontline workers get infected and have to be isolated.

Models for India show that cases will continue to rise sharply, likely peaking by end-January or early February for the major cities and states where cases are currently increasing sharply. These models also suggest that healthcare systems will be under severe strain, comparable to or exceeding those in the second wave and that the main contribution to severe cases will come from the unvaccinated and partially vaccinated. They are based on the little information we have about the progress of the disease in South Africa and the UK, Indian demographics, and the vaccination status of the population in each state, and many assumptions about the protective effect of vaccines and prior infections. These numbers should be refined in the days to come, but appreciating the limitations of models and the difficulties of predicting complex human behaviour is always important.

What are we doing and what should we do?

Is rigorous science guiding policy in India? Despite early problems, the ICMR and AIIMS guidelines on testing and clinical management largely follow the science and are well-written. However, the situation regarding data availability remains the same. India contributes to global COVID-19 genome databases at a slow rate. We still do not have a system in place to correlate clinical, demographic and vaccine status information with infection, disease manifestation and virus sequence. Our public policy response seems

sometimes more targeted to demonstrating that something is being done, rather than ensuring that what is done makes epidemiological sense. Individual states have placed restrictions on the movement of those from other states based on little concrete evidence, striking at the heart of India's existence as a federal union.

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The Indian experience contains lessons for the world. In a remarkable achievement for a country of India's means, over 1.5 billion doses have been used to fully vaccinate 65% or more of our adult population, while providing at least one shot to more than 90%. A diverse set of vaccines are being produced in India. Cities such as Mumbai, with their war-room approach, have set an example for how good health systems function during a pandemic. Our testing and vaccination enterprise rests on the shoulders of ASHA workers and others, who have toiled with little compensation in an exceptionally challenging situation.

Last year's Delta wave was fuelled by state elections and the Kumbh Mela that acted as super spreader events. Omicron comes at a time when five more states in India are going to elections. This includes Uttar Pradesh, the most populous state, where barely 30% adults have received two vaccine doses. Huge rallies continued unabated until the Election Commission banned rallies until 15 January.

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India continues to fail on transparency. That the most trusted data on Indian cases and deaths continues to come from a voluntary crowd-sourced effort and not from government sources is disappointing. There is no doubt that deaths in India have been seriously undercounted, as documented extensively by public-spirited journalists and scientists outside the government system. Yet, there has been little to no government acknowledgement of these figures. What inputs the government takes, based on which it decides policy, remains opaque. An onerous non-disclosure agreement, valid for 10 years, stymies attempts at understanding why government-appointed committees made the decisions they did. Government communications have been bland, if not outright misleading at times, for example in repeatedly highlighting the entirely meaningless statistic of the total fraction of recovered patients.

More than ever, the world relies on science. We are now able to customize tests for specific variants and to mass-produce them within a month. We have a basket of vaccines, across multiple, novel platforms, both authorized for use and in the pipeline. Detailed randomized control trials have demonstrated that a number of initially popular treatments, such as Ivermectin, are not more helpful than placebos. We understand far better the implications that SARS-CoV-2 has animal hosts, thus making repeated spillover events possible and perhaps even inevitable in driving COVID-19 into endemicity.

> *As a society, we must reach a consensus on the levels of risk we can be comfortable with, since an endless procession of lockdowns and closures is plainly not sustainable.*

The biggest challenge we see globally are current levels of inequity in vaccine distribution, where existing stocks are used to provide booster shots in high-income-countries even as low and middle-income countries languish with abysmally low levels of coverage. Against such a background, the rise of new, even more transmissible variants than Omicron, seems inevitable. A second challenge is maintaining non-COVID health related services, including routine immunizations and the care of patients with chronic diseases, amidst the current wave and potential future resurgences of the COVID-19 pandemic. A third challenge is to reconfigure our homes, workplaces, schools and public spaces with the specific aim of improving ventilation, reducing the risks of COVID-19 spread. This is possibly the single most neglected public health intervention. A fourth challenge is simply reopening schools; they have been shut far too long in India. This has long-term repercussions. A fifth challenge is understanding the long-term consequences of a COVID-19 infection for those who have recovered from it.

As a society, we must reach a consensus on the levels of risk we can be comfortable with since an endless procession of lockdowns and closures is plainly not sustainable. A situation where COVID-19 becomes endemic, where vaccinations and booster shots must be taken at regular intervals, and where occasional flare-ups might require specific localized measures, will most likely be the long-trajectory of the disease in India and across the globe. We must understand and accept the inevitable consequences of this trajectory. It is now time to discuss this openly.

The views expressed here are personal.