SWAPAN MAHAPATRA/PTI

COVER STORY

CHALLENGE AND OPPORTUNITY

It would be premature to believe that the epidemic has burnt out and unpardonable to leave the population unguarded against a possible catastrophe. That is why the vaccine is so welcome, but there are many challenges in its administration. BY **T. SUNDARARAMAN**

AS THE YEAR COMES TO A CLOSE, THERE IS finally some good news on the COVID-19 front. The number of new cases has gone down quite dramatically, and a vaccine has become available. Both are highly awaited developments. But it is not yet time to celebrate.

At its peak, around September 11, 2020, India was recording over 97,000 new cases and 1,250 deaths a day. As of December 15, the figures dropped to 26,401 cases and 380 deaths a day.[1] What could be the reason for this decline? Could it be effective public health control, or just poor measurement, or has herd immunity crossed the threshold levels? Or is this just the lull before the storm—a deferred epidemic, the worst of which is yet to come?

Poor measurement is no doubt a problem. One has to account for the fact that the five or six top performing States in terms of traditional health indicators like maternal and child survival, and whose social determinants of health are clearly better, have the highest number of reported cases per million or of deaths. The degree of under-reporting was estimated in one study as about 90 missed infections for every detected case. While the two States, Delhi and Kerala, with the highest rates per million of the population missed about 25 infections for every detected case, the proportion of missed cases in States with weaker public health systems such as Uttar Pradesh and Bihar could be 300: 1.[2] Thus Kerala reports 19,034 cases per million and Uttar Pradesh reports only 2,436 cases, while the all-India average is 7,355 cases per million. On the other hand, the trend in the number of cases reported is likely to be more reliable than the absolute numbers. And there can be little doubt about a declining trend in the past two months.

CELEBRATIONS in the Christmas week in Kolkata. As people get back to normal lives and social interactions increase, a second wave of the infection is a possibility that cannot be wished away.

Better care and ability to handle the spread may have improved the ability to flatten the curve. Access to testing has also increased, and further after the peak crisis months of July to October, beds for hospitalisation also became easier to access. It is likely that isolation of sick cases, whether in COVID-19 hospitals, or in care centres or at home, is now more robust than in the first few months of the pandemic. High levels of stigma could also paradoxically contribute to more sick people and contacts staying at home.

Another contributory factor for the decline in COVID cases is that in select population clusters the proportion of those who have been infected (otherwise known as herd immunity) has reached a level where epidemic spread no longer occurs. Spread at a lower rate does, however, continue. We still do not know the exact threshold level of herd immunity required for preventing epidemic spread. The most frequently cited figure is 60 per cent, but that assumes a level of infectivity which may change with changes in behaviours as well as the spread of mutant strains.

However, as is typical of all diseases with epidemic potential, there would be many clusters where the proportion of non-immune population is high, and outbreaks in such clusters would continue to occur. It is in such circumstances that most nations in the West are experiencing a huge second wave. In this second wave, the regions that did well in the first round are likely to do worse simply because the proportion of unimmunised persons is higher. We can see that to some extent in Kerala, which did very well in controlling the disease in the first few months but slipped into high levels of case incidence in later months.

The second wave is not inevitable, and a robust disease surveillance system backed with active testing, contact-tracing, and isolation or quarantine, can prevent this—as many nations in the Asia-Pacific region have shown. But premature celebration, and the resulting complacence that the epidemic is behind us, could leave us vulnerable to an intense second wave. And second waves, as we know from the 1918 flu pandemic, could be worse than the first.

This is the big reason why the coming of the vaccine is so welcome. It would be premature to believe that the epidemic has burnt out and unpardonable to leave the population unguarded against a possible catastrophe. While the proportion of those with severe or fatal forms of the disease may be low, the absolute numbers are high enough to make this disease one of the leading causes of adult mortality in India. There has been one crore cases and 1.5 lakh deaths owing to this disease in 2020. Though it is possible that sub-clinical infections, undetected by the usual antibody tests, have provided herd immunity or that virulence of the virus has decreased, it is also possible that we would face a second wave with increased virulence. And even if herd immunity thresholds are adequate to break an epidemic spread, disease incidence and mortality may be high enough to cause serious public health concern. Good public health planning cannot rest merely on wishful thinking and a hope that the epidemic

will slow down by itself. It is not only the mortality rates that are a cause of concern. The lockdowns in the wake of the epidemic spread have severely affected economic activities across the world, and the introduction of vaccination would go a long way in reviving the economy. Even in the industrialised world, which has fairly robust, universalised social security networks and universal health care, vaccines are urgently required to open up economies. Just as an RT-PCR test has become mandatory for most international travel, a proof of vaccination is certainly going to become a mandatory requirement for travel soon in all developed nations.

In countries like India, as normal economic life resumes, the degree of social mixing will sharply go up and may result in new outbreaks and cycles of lockdowns and unemployment. This would affect large sections of the working population with no social security and the absence of a return to normalcy may itself curb demand in a major way.

It is, therefore, not surprising that almost every single political party in India has promised free and universal vaccination against COVID-19 as soon as vaccines are available. These promises are loudest just before elections. But in official pronouncements, there is much backtracking from earlier commitments to free and universal access to this vaccine. Clearly, there are many challenges that any programme of vaccine delivery would have to address. Important among these are determining the effectiveness and safety of the vaccine, organising procurement and delivery, building capacity for storage and distribution, and determining priorities for immediate distribution, while planning for ensuring access for all.

INTRODUCTION OF NEW VACCINES

The first challenge is the ability to innovate an effective vaccine that would be appropriate to the Indian context. Any vaccine that is introduced has to undergo clinical trials that demonstrate that it at least provides effective protection against severe disease and reduces mortality along with a high level of safety, since normal persons are being given the injection. The big change in December 2020 is that there are now five vaccines that are on the market or close to being so, and according to information circulated, the mid-term third phase of clinical trials have found these to be effective. These are the Pfizer vaccine, the Moderna vaccine, the Oxford-Astrazeneca, the Russian Gamaleya of Sputnik V, and the Chinese vaccine CoronaVac. Of these, only the Oxford vaccine's clinical trial data are published in a peer-reviewed journal.

The data of the others have been made available to national regulatory bodies, and different nations have provided "Emergency Use Authorisation" (EUA) for one of more of these. EUA is more of an early and temporary licensing method and only implies that the vaccine is likely to qualify for full approval once all the data are in. The World Health Organisation (WHO) itself has not certified any.

One concern regarding the clinical trials is that the end point used for measuring effectiveness is the reduction in symptomatic cases among those vaccinated as compared with the control population. While this is likely to be associated with reduced mortality, sample sizes are not as yet adequate to establish that. Post-introduction follow-up studies are needed to know for sure that it would be equally effective in the elderly and in persons with co-morbidities who are more vulnerable to fatality. The current sample sizes are too small even to establish safety adequately, and extensive post-introduction surveillance will be required.

Further, we do not know the duration of immunity these vaccines will provide, and though it could be life-long, it could also be as short as one year. We also do not know for certain that it will reduce asymptomatic infections and whether such individuals could continue to spread disease. Also, the vaccines till date need two doses spaced about a month apart to be effective.

All of this means that mass vaccination will need to be accompanied by extensive monitoring and surveillance. Thus, vaccination is not a one-off effort but has to be built into the structure of a comprehensive health systems approach with adequate outreach and surveillance. While digitisation of vaccination data could help to an extent, projection of such digitisation as a stand-alone or main solution and its use as a short cut to systems strengthening is insufficient and misleading.

VACCINE LOGISTICS

The next major challenge is addressing the requirements of vaccine logistics, and this includes procurement, storage, distribution and vaccine delivery.

In procurement, both costs and the ability to ramp up domestic production are important considerations. The Pfizer and Moderna vaccines are costlier at approximately $20 and $33 per dose and are not under production in India. Gamaleya is $10 and there is only one company licensed to manufacture this. Oxford-AstraZeenca is relatively affordable at $ 4, but this would still be costlier than any vaccine we currently use.[3] There is an Indian version of this vaccine, called Covishield, which is ready for manufacture in India by the Serum Institute of India (SII) under voluntary licensing with Astrazeneca, and potentially its production can be scaled up. But, there are no binding agreements as yet with the Indian government, though the SII has agreements for advance purchases with many industrialised countries and the international COVAX Facility. Nor has the government announced any budget on what it is willing to spend for such vaccination or even a White Paper outlining its proposed strategy.

When it comes to storage and distribution, the Pfizer vaccine, which requires minus 70 degree Celsius storage facilities, becomes an unviable option in Indian circumstances. Moderna's requirements are less (minus 15 to minus 25 degrees C), but still far in excess of Indian cold storage capacity. The Oxford-AZ vaccine and the Russian and Chinese vaccines, however, need only +2 to +8 degrees C temperature for storage. But, given the

Overview of soon-to-be-available COVID-19 vaccines

Platform	Manufacturer/Supplier	Route of administration	Doses	Cold chain requirement (°C)
Inactivated	Bharat Biotech (Whole virion) Sinovac	IM	2	2–8
Viral vector Adenovirus	Oxford/Astrazeneca/ SII Gamaleya Research Institute/ Dr Reddy's Laboratory, India	IM	2	2–8
Protien Subunit (recombinant)	Novavax GSK/Sonafi Biological E, India	IM	2	2–8
mRNA	Moderna Pfizer	IM	2	-20 at 2–8 x 30 days -70 at 2–8 x 5 days
Live attenuated virus	Codagenix/SII	Inhalation	1,2	2–8
DNA	Zydus Cadilla, India	Intradermal		2–8

IM: Intramuscular; SII: Serum Institute of India,
Source: Editorial by Rajesh Bhatia, Online version India and COVID-19, Part-IV, Indian Journal of Medical Research

volumes, even this would be a challenge. Existing vaccine supply chain requirements largely cater to children below one year of age, and to expand from that to vaccinating the entire population is a huge leap. Uninterrupted, safe and reliable supplies at tens of thousands of delivery sites also require well-functioning logistics management systems, and except in three or four States, these too are under-developed.

ADDITIONAL CAPACITY VS RE-PURPOSING

Increasing capacities to vaccinate a major part of India's population requires a substantial increase in storage infrastructure, equipment, vaccine transport vehicles, and, not least, a tremendous investment in human resources. This requires financial resources but it also needs the time to build the physical and organisational structures required.

Instead of investing in increasing infrastructure and human resources, the government would be tempted to simply re-purpose existing primary health-care capacity to take on this load. Such re-purposing displaces essential health services and can cause untold and unmeasured harm to people's health. In an earlier phase, the government created bed capacity for managing severe cases of COVID 19 by converting busy public hospitals providing a wide range of tertiary health care into dedicated COVID hospitals. This in effect was a cessation of essential public hospitals services, and the displaced patients were pushed into the high-cost private sector (often not even that, for the private sector was itself shut down).

There is a similar danger in initiating COVID-19 vaccinations through the existing public sector, without the necessary increase of infrastructure and human resources. If even a part of existing staff and infrastructure are simply re-purposed, other chronic diseases like tuberculosis and HIV (human immunodeficiency virus) infections are likely to see a huge rise, and hard-won achievements in maternal and child survival may face a setback. And other epidemic-prone diseases can flare up.

FOR A SECOND GENERATION OF VACCINES

In the coming year a number of new vaccines are likely to enter the market. Across the world, over a hundred vaccines are being developed and many of these could have advantages over currently available vaccines. India itself has an indigenously developed vaccine, Covaxin of Biotech, which has entered the third phase of trials. Fortunately, political pressures to prematurely certify this product have been checked, giving the researchers time to develop more evidence and credibility for the vaccine. Advantages that future vaccines could provide include a single dose requirement as compared with two doses currently; a longer duration of immunity; ability to store at room temperature; or easier ways to administer, such as drops. And the next generation of vaccines need to be even more affordable and be part of domestic manufacture, so that supplies are reliable and there is no drain on national revenue. The possibilities are immense.

All of this will require research institutions in India and all over the world to press ahead with their research. But current global innovation regimes can be an impediment to the discovery of new and more appropriate drugs and vaccines. They have so far failed to deliver on any curative medicine for COVID-19 and failed to share information on or transfer technology for better vaccine development. Vaccine developers are working in silos in competition with each other, when the need is for shared information and collaborative work. To address this bottleneck, in one of the most significant developments in global trade policy since the Doha declaration, India and South Africa have sponsored a joint resolution calling for the suspension of a wide variety of intellectual property rights to enable research, innovation and transfer of technology for new COVID-19 products and for scaling up manufacture of existing products. This resolution has found support from most

VIJAY SONEJI

A VOLUNTEER undergoing Covaxin clinical trial at Civil Hospital, Sola, one of the hospitals selected for vaccine trials, in Ahmedabad on November 27.

developing nations, but predictably been opposed by the same few developed nations who support and profit from big pharma. But this is an opportunity for developing nations to push ahead with or without the waiver, to develop more relevant approaches to innovation and manufacture of essential medical products.

PRIORITISATION

Even in the best-case scenario, it is difficult to imagine going to scale with extensive vaccination programmes in India before the middle of 2021 and reaching a substantial proportion of those in need before the end of 2022. Therefore, the question of who will get priority access to free vaccines becomes all-important. WHO has already released two guidance documents to define the principles and goals that national and global policies should prioritise.[4]

In India a committee has been constituted (National Expert Group on Vaccine Administration for COVID-19, or NEGVAC) and plans have been drawn up, though such plans are far from transparent or participatory. What we do know is that the plans prioritise all health workers who are estimated at about one crore, then all front-line workers defined as including the police, armed forces and civil defence, and municipal workers estimated at about two crores. After this, it is the elderly and those with co-morbidities, estimated at 27 crores, who would be the priority.[5]

There are other important categories that are not mentioned. Two of the five principles that WHO spells out are equity, which is understood as reaching out to those more vulnerable for socio-economic reasons, and reciprocity, which is defined as "those who bear significant additional risk and burden of COVID-19 response for the benefit of society". By these criteria migrant workers who would be travelling across States and face high exposure owing to their working conditions, and who lack access to health care and social security should also be on the priority list. While those on international travel will be certain to access the vaccine as an entitlement, it remains to be seen whether working people and all sections that cannot practise social distancing will have an entitlement to get free vaccines. Only a commitment to universal access to free vaccination would ensure this.

Faced with financial, logistic and managerial constraints, it would be tempting for the government to adopt a policy where vaccination of a small part of the population is paid for and the rest is left to the private sector. It would be relatively easy for the government to get away with such a minimal intervention policy. Without a major health communication effort there is likely to be a lack of expressed demand for the vaccine in large segments of the population characterised by low health awareness. Stigma is already one of the big barriers for access to care in most under-developed regions. In such communities, herd immunity would soon decrease the rate of spread of the disease, and excess mortality could go unnoticed. Government inaction on the vaccine front could also get re-enforced by more modern forms of vaccine hesitancy in sections of civil society.

Finally, while vaccines may become available, recognition has to dawn that vaccines are public goods only if vaccination is a public good. Further, that universal vaccination will be feasible and justifiable only if it goes along with the strengthening of health systems in a manner that recognises the entire public health system as a public good.

Universal vaccination is not only the act of giving two doses of vaccine to all eligible individuals. It includes building up extensive disease surveillance systems which in turn requires extensive outreach services as well as testing capacity, and the ability to identify, manage and compensate those who develop complications, and continue with both public health measures and hospital care for some time to come.

The rising tide of people's movements should find in this crisis an opportunity to push the government to honour its political commitment to provide universal vaccination as part of ensuring the people's right to health and health care. □

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ENDNOTES

1. https://www.worldometers.info/coronavirus/country/india/
2. https://theprint.in/health/india-is-missing-about-90-infections-for-every-covid-case-latest-govt-analysis-shows/567898/
3. https://www.bbc.com/news/world-asia-china-55212787
4. These are "Values Framework for the allocation and prioritization of COVID-19 vaccination," and the "Roadmap for Prioritizing Population Groups for Vaccines against COVID-19".
5. https://www.livemint.com/news/india/who-will-be-on-priority-list-for-covid-vaccines-in-india-what-expert-panel-suggests-11607429290362.html

Light at the end of the tunnel

Developing a vaccine during the COVID-19 pandemic is an extraordinary feat of science made possible by of years of scientific work and investment in understanding two closely related coronaviruses, SARS-CoV-1 and MERS-CoV. But there is still a long way to go before equitable access to vaccines is ensured and COVID-19 is completely defeated. BY **GAGANDEEP KANG**

OLI SCARFF/AFP

MEMBERS OF STAFF DELIVER INJECTIONS of the Pfizer-BioNTech vaccine to invited patients at a drive-in vaccination centre in Greater Manchester of North West England on December 17.

PETER SUMMERS/GETTY IMAGES

BRITISH PRIME MINISTER Boris Johnson leaving 10 Downing Street after it was announced that the United Kingdom government had approved the Pfizer/BioNTech COVID vaccine for use, on December 2.

With the approval of the first vaccines for COVID-19, we can now project a future where this terrible time is behind us and the pandemic is under control. Getting this far, this fast has not been easy. It has meant compressing a decade of vaccine development work into less than 12 months—an achievement that has only been possible because of science and the collaboration between academia, industry, policymakers and funding.

The first emergency use authorisation for Pfizer/BioNTech vaccine, based on data that went beyond the originally projected endpoints, was issued on December 2, just 218 days after the clinical trials started and 326 days after the novel coronavirus sequence was released. For both the Pfizer/BioNTech and the Moderna vaccines, it was a matter of days to design the constructs that resulted in the two mRNA vaccines that have shown 90-95 per cent efficacy in protecting against disease and are now approved under U.S. emergency use authorisations, and in the case of Pfizer, in many other countries around the world.

These achievements, however, did not come from a standing start. The rapid acceleration of development of vaccines was only possible because scientists had been working to prepare for future outbreaks despite policymakers and governments dismissing their forecasts of future pandemics. In the wake of Ebola, the World Health Organisation (WHO) began to publish the Global Research and Development Blueprint which identifies each year the top 10 threats to public health, and always includes Disease X, the unknown pathogen that will come from an unknown place at an unknown time. The experience also led to many international consultations, which resulted in the establishment of the Coalition for Epidemic Preparedness Innovations (CEPI), a grouping of state and non-state actors who were committed to the development of early clinical stage vaccines for outbreaks, which would address the issues of 'market failure'.

'Market failure' refers to the idea that even though there is a need for certain types of vaccines, the companies that manufacture vaccines are not interested in making them because they do not see any commercial viability in such products. In other words, if a disease affects the poor who cannot afford to pay for a vaccine, who will make it for them? For an infectious disease outbreak, where the timing of the disease is unpredictable, the number of people needing to be vaccinated is unknown and if the disease occurs in a poorer part of the world, finding a company or group who will try to make a drug or preventive product like a vaccine is near impossible.

EXPERIENCE WITH EBOLA

This was certainly the case with Ebola, where a vaccine candidate had been developed at the National Microbiology Laboratory of the Public Health Agency of Canada a dozen years before the first West African urban outbreak, but there were no companies interested in clinical development. By the time the world got its act together to evaluate the vaccine, and turf wars between countries and agencies that all wanted to conduct vaccine research to control the outbreak were sorted out, Ebola cases were already trending down because of aggressive treatment and infection control measures. While developing vaccines that prevent disease are clearly a superior strategy in terms of lower human costs, we need to remember that with sufficient resources, spread of human-to-human infection can be controlled by separating the infected from the healthy, as we have seen with SARS-CoV2, even with the additional challenge of asymptomatic infections.

A COALITION AGAINST EPIDEMICS

CEPI arose from the idea that an essential part of preparedness for epidemics was to make and keep ready vaccines that could be used quickly in outbreak situations for diseases on the WHO Blueprint and also to try to develop new technologies for rapid response in case disease X emerged. CEPI, supported initially by the governments of Norway, Germany and Japan, and by the philanthropic organisations the Wellcome Trust and the Bill and Melinda Gates Foundation, had India's Department of Biotechnology as a founding partner, with Dr K. Vijayraghavan, then the Secretary of the Department of Biotechnology and now the Principal Scientific Adviser to the Government of India, chairing the interim Board. CEPI was formally established in Norway in 2017, and it raised about $800 million from governments and philanthropies to target Lassa fever, MERS and Nipah in 2018. In 2019, CEPI expanded its portfolio to also sup-

port development of chikungunya and Rift Valley fever vaccines and rapid response platforms, which included mRNA and viral vector technologies. Therefore, in 2020, when SARS-CoV2 clearly emerged as a potential global threat, CEPI was able to fund the first three vaccine candidates in January, and these included support for Moderna and the University of Oxford.

Shortly thereafter, others, particularly multinational companies, with and without vaccine development experience, and governments followed with support for vaccine development at multiple scales, particularly in the United States and Europe. The story of vaccine development during this pandemic, while incomplete, is a remarkable record of great speed, great science and cooperation on a scale we have never seen before. But the world has only been able to make such rapid advances because of years of scientific work and investment in understanding two closely related coronaviruses—SARS-CoV-1 and MERS-CoV. The National Institutes of Health in the U.S. house the Dale and Betty Bumpers Vaccine Research Center, which was established under President Bill Clinton to make a vaccine for the human immunodeficiency virus (HIV). While HIV vaccine development efforts have so far not been successful, the learning gained from understanding HIV has resulted in vaccine candidates against Ebola, the original SARS, chikungunya and many other viruses. That Moderna and Pfizer were able to design highly effective vaccines within days of the viral sequences being released was due to the fact that researchers had invested years in understanding how to target the spike protein that studs the surface of all coronaviruses. Work with SARS has shown that stabilising the structure of the spike in the shape before it fuses with the host cell is more likely to preserve targets for infection-blocking antibodies induced by a vaccine.

This exceptionally rapid progress on mRNA vaccines seen in 2020 reflects years of patient endeavour by scientists on new vaccine platforms. In all our approaches to vaccines from Edward Jenner onwards, the focus of vaccine development was to deliver the entire infectious agent, or part of it, in order to induce an immune response that was calibrated to protect without inducing disease or side-effects. With new technologies that focus instead on delivering the instructions for making a protein to host cells, scientists are trying to make vaccines that are safer, can be made much more quickly and can be adapted to a range of targets once the infectious agent is known. With viral vectors, RNA and DNA vaccines, the two essential components are the genetic cargo or the sequence that instructs our cells to make a protein, and the delivery vehicle, whether it is a virus that acts as a carrier or vector, a fatty nanoparticle that protects RNA from breaking down, or plasmid DNA that incorporates the sequence for a protein within itself. Once inside the cell, the genetic cargo essentially hacks into the same mechanisms used by SARS-CoV2 to replicate itself, but instead of producing the whole virus, a single protein in its three dimensions is produced. The immune system recognises the protein as foreign and musters all of its components to respond.

These revolutionary technologies have, for mRNA and viral vectors, been validated by phase 3 and give the world powerful new tools to radically accelerate the response to future disease threats. Even as we hear news of new variants, and the very real threats they pose, we have hope because we now have the tools that will enable us to respond effectively and rapidly.

These are landmark shifts in vaccine development. If

R.V. MOORTHY

CONSTRUCTION WORK in full swing for a COVID vaccine storage unit at the Rajiv Gandhi Super Speciality Hospital in New Delhi, on December 20, 2020.

a range of viral vectors can be validated, we will have options to choose from, depending on the rapidity and durability of the immune response to be induced, and whether it is to a single protein or multiple proteins. While the vector will remain the same, the genomic message they carry can be easily switched based on need. Viral-vectored vaccines can be easily and cheaply made, holding real promise for their use in low- and middle-income countries. The potential for much more distributed vaccine-manufacturing capabilities, at regional and country level, will promote future security of supply.

The mRNA approaches are even more of a paradigm shift. Unlike traditional vaccines which are dependent on biological manufacturing, which is often tricky and temperamental, mRNA vaccines are actually chemical compounds and the processes for chemical synthesis are well understood and easily replicated. While we still have to work through regulatory processes that have not yet dealt with platform technologies, there is at least hope of a future rapid response strategy.

A LONG HAUL, STILL

In the meantime, though, we still have a long way to go to defeat COVID-19. As an example, the U.S., which is the country most hit in terms of lives lost and the burden borne, is also the country with greatest access to vaccines because it invested $10 billion in making and testing candidates. While vaccine development is usually a risky process, with up to 90 per cent of the candidates failing, the availability of the best science, testing technologies, manufacturing methods and clinical testing platforms meant that the U.S. was able to mitigate the risk of failure for vaccine companies and able to deliver on both speed and scale. Vaccines are now being rolled out in high-income countries, in small numbers at the moment but expanding rapidly. Although other prevention strategies of masking, distancing and re-aligning to prevent congregations may need to continue, high-income countries have a light at the end of the tunnel.

In less well-endowed parts of the world, CEPI, the Gavi Alliance, the WHO and other partners have come together for Access to COVID-19 Tools (ACT) Accelerator that is seeking to make available at least 2 billion doses of vaccines for countries that participate in the COVAX facility. The COVAX facility has over 190 countries participating and is the largest multilateral undertaking after the Paris Agreement on Climate Change. Vaccines provided through COVAX are calculated to be sufficient for the participating countries to vaccinate at least 20 per cent of their populations. This is much better than what the world was able to do for H1N1, the last pandemic, but it is also clear that for most countries access will be slower than for countries that have made bilateral deals with vaccine manufacturers or countries like India, Brazil and Indonesia that have their own vaccine-manufacturing capability.

We need to understand that in a connected world and with a virus capable of asymptomatic spread, no country is safe until everyone has a chance of protection. The failure to promote access to vaccines around the world will ensure many more unnecessary deaths, further suffering and disruption of essential health services, and a slower global economic recovery.

It is estimated by the RAND Corporation that high-income countries would lose about $119 billion a year if the poorest countries are denied COVID-19 vaccines. RAND also estimates that the high-income countries that paid for vaccines would get back about $4.8. for every $1 spent.

We are in a good place now, but our work is not done. We have proven products, but they are insufficient for the global need and have challenges of storage, supply and distribution. For example, it is unlikely that mRNA vaccines can be widely used in India because of their requirements for cold- and ultra-cold storage. We will need vaccines more suited for all parts of the world, with less cold chain requirements, single dose and with long-term protection. Further, while India's immunisation programme is the largest in the world, it has no experience of adult immunisation. The logistics support, training, documentation strategy and safety monitoring systems are being built by the government by repurposing or building on existing strategies, but how well they will do, will be known only when vaccines are rolled out.

Although the acute phase of the pandemic may end in a year or so, SARS-CoV2 is likely to be here to stay. It will continue to circulate and evolve. If long-term protection is feasible, then we may not need booster doses, but otherwise we will have to vaccinate and update vaccines regularly. We need to be investing now in research and development so that we can plan for the long-term management of SARS-CoV2. This is actually a huge opportunity for investments in health and in vaccines for India because we have many viruses in our own and the global landscape, such as influenza, dengue, chickenpox and chikungunya that are all vaccine-preventable but have been largely unaddressed so far.

Known and unknown viruses will continue to be a threat. The COVID-19 pandemic will be repeated, even if we do not know when. We were lucky that that SARS-CoV2 is not a virus that has as high a fatality rate as SARS-CoV1 or MERS. With collaboration and incredible efforts, the world has developed vaccines that hold the promise of rapid control, even though there is much to be done for their manufacture and delivery. India may not have been the first to develop vaccines, but what matters more is that we are likely to be very large suppliers to the world, with the vaccines that will become available in 2021.

Looking to the future, in the wake of COVID-19, many countries will make national or regional investments in pandemic preparedness, and India should not be left behind. With investment in research, scientific solidarity, industrial partnerships and an enabling environment, we can develop vaccines for ourselves and the world at scale and speed. □

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Virus variants

A global second wave of infection spread with the new UK-variant is possible unless the usual precautions are strictly adhered to and other restrictions on movement are strictly enforced, particularly on international travel between the affected countries and others. BY **R. RAMACHANDRAN**

WITH THE IMMINENT ROLL-OUT OF VACCINES for protection against the novel coronavirus SARS-CoV-2 in large parts of the world, and a couple of them already deployed in a few countries for emergency use among select cohort groups, it seemed that the world would soon be on top of the COVID-19 pandemic. As in the separate article Professor Gagandeep Kang (page 9) has described, scientists and industry have worked together to use advanced science and technology to achieve what would have seemed impossible only a few years ago of delivering efficacious vaccines in less than a year's time, a process known to take a decade or more.

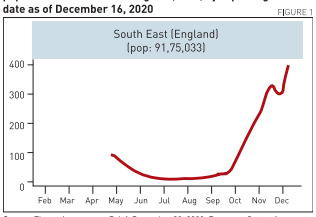
Because of the raging pandemic, the normal time frame for vaccine development was greatly squeezed. There has been a total paradigm shift from the traditional approach in clinical trials, approvals for public deployment and subsequent production. Investments towards R&D have poured in from multiple quarters, trial

REUTERS

AT A SPECIAL WARD in Arwyp Medical Centre in Kempton Park, South Africa, on December 25, 2020.

Fourteen-day COVID-19 case notification rates per 1,00,000 population in South East England, U.K., by reporting date as of December 16, 2020

FIGURE 1



Source: Threat Assessment Brief, December 20, 2020, European Centre for Disease Control (ECDC)

protocols have been shortened, approvals hastened and the industry too has taken a huge step of investing large sums to set up production infrastructure even before the trials were completed and regulatory approvals obtained. There was belief in the science behind these novel vaccines in the academia, the governments and the industry, and that hope had become a reality just a few weeks ago with the launch of a few vaccines.

But the light at the end of the tunnel which was bright until less than a month ago has dimmed slightly with the emergence of two new variants of the virus, in the United Kingdom and South Africa respectively, which have been found to be more highly transmissible than the original version from Wuhan (and other biologically and epidemiologically inconsequential genetic variants thereof) that the world has braved since December 2019.

SPIKE IN CASES IN U.K.

In the past couple of months, Britain had seen a rapid increase in COVID-19 cases (Fig. 1), particularly in South East England, with Kent being the most affected. Between the 41st week and 50th week, it increased from 100 cases per 100,000 population to 400 per 100,000 population, the reason for which was immediately unclear. Enhanced epidemiological investigations and genomic analysis were launched to find the basis for this unexplained sudden local spike in the number of cases.

Genome sequencing of virus isolates from these new cases found that over 50 per cent of the isolates had genomes belonging to a new single evolutionary grouping, technically called a phylogenetic cluster. This distinct variant has been named SARS-CoV-2 VUI 202012/01 (Variant Under Investigation, year 2020, variant 01) and is also sometimes referred to as 'lineage B.1.1.7'. In its COVID-19 monitoring and surveillance programme, the U.K. has put in place what is called "genomic epidemiology" in which epidemiological data is linked with sequencing data of isolates from a significant percentage of COVID-19 cases. Overall, the rate at which the U.K. has been analysing genomes of COVID-19 cases is around 5-10 per cent, which is quite high compared with most other countries. When the variant was detected, the rate in the region around Kent was about 4 per cent.

To date, for a total of over two million cases, the U.K. has analysed 126,219 genomes (6.3 per cent). This is over 45 per cent of the total of about 275,000 genome sequences submitted to the global genome database called GISAID (Global Initiative on Sharing All Influenza Data). The fraction of the new VUI isolates in the weekly number analysed by the body called COVID-19 Genomics UK Consortium (COG-UK) steeply increased from the 40th week, and is currently over 12 per cent (Fig. 3).

The United States, on the other hand, has a total caseload of over 17 million and has analysed only 51,000 genomes (0.3 per cent). South Africa, which has also detected a new more infectious variant and has 912,500 total COVID-19 cases, has released 2,730 genome sequences (0.3 per cent). India has an abysmally low rate of genomic sequencing of virus isolates from patients. With a total number of cases at over 10.1 million, India has released sequences of only 6,370 genomes (0.06 per cent) so far.

The U.K. perhaps was able to pick up this variant given its very high rate of genome sequencing, which is linked to the epidemiological surveillance system in place. It is quite possible that significant variants (perhaps including this) have been circulating in other populations around the world but missed detection because the genome sequencing rate has not only been low in most countries but also not dovetailed to their COVID-19 epidemiological data gathering, especially when there are sudden local spikes in the number of cases, which have occurred in India, for example.

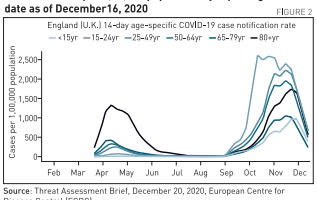
While surveillance and genomic analyses of the new cohort of recently infected patients in the U.K. (predominantly from South East England) have certainly demonstrated that this new variant is more transmissible, and hence more infectious, answers to other questions about the variant's biology, such as whether it causes more (or less) severe disease and whether it can evade human natural and/or vaccine-induced immune response, are uncertain. Extensive laboratory and clinical studies are required to unequivocally answer those questions, which undoubtedly will take time.

According to the COG-UK, which carried out the genomic analysis on the new cases of infection, this particular variant is growing in the U.K. about 70 per cent faster than the strain(s) that we have lived with until now. On the basis of this data, the New and Emerging Respiratory Virus Threats Advisory Group (Nervtag) of the U.K. has reportedly said that it is "moderately confident" that this new variant is substantially more transmissible. The fact that the variant was growing exponentially even during the lockdown period gave the Group that moderate confidence to declare that it demonstrated a substantial increase in its transmissibility compared with other variants (carrying mostly harmless genetic changes or mutations) that have appeared during the pandemic. In addition, it also said that the variant had the potential to increase the parameter R-nought (R_0), which is a measure of the number of persons that each infected case passes on to, by 0.4 or more than the values observed before this new variant came to light. The higher (than 1) the R_0 is, the more widely the virus spreads. As of December 15, over 1,600 individuals had been infected with this variant in the U.K., the earliest case being traced to September 20.

Until now there is no evidence of increased severity of the disease among those infected with this new U.K.-variant. According to a report of the European Centre for Disease Prevention and Control (ECDC), investigations into the properties of this new variant are ongoing and the U.K. has not so far reported adverse clinical observations, such as higher mortality or particularly affected groups. Cases with this variant were, however, seen predominantly in people younger than 60 years (Fig. 2), and it is these cases that are chiefly driving the increase of overall COVID-19 cases in the U.K. as well (Fig. 2). Modelling studies too have shown a strong correlation between the cases with the new variant and the overall increase in the caseload. In Wales, which too has seen a similar spike due to the new variant, the median age of the cases is 41 (range 11-71 years). But as the ECDC report points out, the current assessment that it does not seem to cause severe disease is also questionable because the affected age group is known to be less likely to develop severe disease. So, more clinical studies are necessary to firmly establish this.

England (U.K.) 14-day age-specific COVID-19 case notification rate with cases per 1,00,000 population by reporting date as of December16, 2020

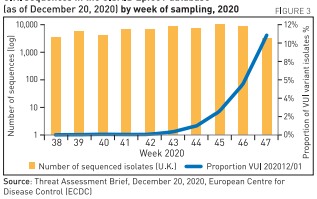
FIGURE 2



Source: Threat Assessment Brief, December 20, 2020, European Centre for Disease Control (ECDC)

Total number of SARS-CoV-2 sequences from the U.K. and proportion of VUI 202012/01 variant sequences among all U.K. sequences in the GISAID EpiCoV database (as of December 20, 2020) by week of sampling, 2020

FIGURE 3



Source: Threat Assessment Brief, December 20, 2020, European Centre for Disease Control (ECDC)

INTERNATIONAL SPREAD

While these above cases were concentrated in Kent and in the wider South East England, including regions of London and East England, there are indications of a wider spread across the U.K. and also reports of a few cases in other countries. In Wales, as of December 14, 2020, 20 individuals had been identified with this virus variant. Denmark apparently has identified nine cases, the Netherlands one, and Australia one. There are also media reports of four cases in Belgium.

According to the ECDC report, three sequences from Denmark and one from Australia, from samples collected in November 2020, cluster with the U.K.-variant in the phylogenetic tree. This indicates that international spread has most likely occurred already, although the extent remains unknown, the report says. Besides, of course, there are cases arising from the South African variant. This variant has recently also been seen in a few cases in the U.K. But detailed information about whether its lineage is the same as the UK-variant (lineage 3.1.1.7) and the number of people infected with the SA-variant within South Africa and globally is, however, not immediately available. We will return to the SA-variant later.

Pertinently, as the ECDC report notes, "the [U.K.] variant has emerged at a time of the year when there has traditionally been increased family and social mixing". So, what seems imminent, given the continuing rapid increase of these variants among the newly infected in the U.K. and South Africa, is that the pandemic is unlikely to die away anytime soon. If it spreads 70 per cent faster than the current variant, it will, in all likelihood, become the dominant form of infection and disease. Even a global second wave of infection spread with this new variant is possible, unless the usual precautions are strictly adhered to and other restrictions on movement are strictly enforced, particularly on international travel between the affected countries and others. This is already happening with the announcement of travel bans between some European countries and the U.K.

Viruses frequently undergo mutations, which occur due to random errors in copying the viral DNA or RNA as they multiply in the host, and these errors accumulate over time. The SARS-CoV-2 undergoes about two mutations (which are generally of the single nucleotide substitution type in the genes coding for amino acids, which are the building blocks of proteins in any organism). But this cluster differs by 29 nucleotides from the original Wuhan strain, according to its preliminary genetic characterisation. This means that the accumulation rate of mutations in this variant has been higher than two substitutions per genome per month.

As mentioned earlier, most nucleotide substitutions are harmless and, therefore, not of concern as they do not change the amino acid that the gene codes for. But when a substitution results in the change of the coded amino

acid, the functionality of the corresponding protein may change, and if that is a critical antigenic region of the viral genome, it is concerning. For instance, the flu virus accumulates mutations at such a rate that a new vaccine is required every year. The amino acid substitutions that have no effect on the protein functionality are called "synonymous" mutations and those that do alter the protein function are called "non-synonymous" mutations.

Genetic analysis of the new variant from the U.K. has revealed an unusually large number of mutations in its genome, which include changes that could potentially impact patients' response to pharmaceutical interventions to the disease. There are in all 23 mutations in this UK-variant, 17 of which are non-synonymous. Over half of these (nine) have been found to be across the Spike protein. S-protein is the stud-like protrusion in the outer envelope of the virus which the virus uses to gain entry into the host's cells and use the host biochemical machinery to replicate and infect the host. This fraction (9/17) is much higher than what is expected from random mutations, according to the ECDC report. These nine mutations are, in fact, thought to define the variant because, while many of these mutations individually have been observed in other variants as well and have been found to change the functional behaviour of the virus, but not in this combination. So this rare combined effect of these mutations on the S-protein could have a significant health impact.

It would be recalled ("How a Virus Evolved in a Pandemic", *Frontline*, May 22, 2020) that, during March-April 2020, we had already witnessed the emergence (from Europe) of a new lineage called A2a, with a dominant and defining 'non-synonymous' mutation called D614G (where the amino acid Aspartic acid (D) at site 614 in the Receptor Binding Domain (RBD) region of the S-protein was substituted by the amino acid Glycine (G)). The variant having Glycine (G614) was found to be more infectious than the original with Aspartic acid. However, it was also found that the body's innate immune system was able to produce antibodies against this variant as well. That is, the variant did not evolve to evade the immune system. In fact, the 614G variant was found to be more vulnerable to the neutralising antibodies. In the current new variant, however, studies with other viruses suggest that some of them could be what are called "escape mutations"—those which evade the immune system—and hence the concern for the new variant's possible significant impact on the pharmaceutical interventions to the disease and thus on the pandemic. The defining nine mutations of the UK-variant which are on the S-protein are: deletion (of gene) at position 69-70, deletion at position 144, N501Y, A570D, D614G, P681H, T7161, S982A and D1118H.

POTENTIAL BIOLOGICAL EFFECTS

Based on previous studies on other SARS-CoV-2 variants, three of these mutations are known to have potential biological effects, according to the preliminary genomic characterisation of the UK-variant by the COG-UK consortium:

1. Mutation N501Y, in which the amino acid asparagine (N) has been replaced by the amino acid tyrosine (Y). Like the mutation D614G, it is also located within the receptor-binding domain (RBD) of the S-protein and has been previously identified as increasing affinity to the ACE2 receptor on the host cells to which the virus binds and enters the cell. That is, this mutation could enable the virus to bind more tightly to the human cells. It is unknown whether tighter binding translates into any significant clinical or epidemiological differences. According to the U.S. Centres for Disease Control (CDC), this mutation has been associated with increased infectivity and virulence in a mouse model.

2. The double gene deletion at position 69-70 of the S-protein has been seen many times before and is likely to lead to conformational (or shape) change in the spike protein, according to the CDC. Perhaps due to this shape change, it has also been described earlier to aid evasion of human immune response in terms of antibodies in some immunocompromised patients.

3. Mutation P681H is immediately adjacent to the site of cleavage of the S-protein into its S1 and S2 subregions (a feature absent in other coronaviruses) by the human enzyme furin, which facilitates fusion of the virus with the human cell. So this mutation may have a locational advantage of interfering with the immune system's bid to prevent virus binding and fusion.

Says the COG-UK report: "Given the experimentally predicted and plausible... consequences of some of these mutations, their unknown effect when present in combination and the high growth rate of [the variant] in the U.K., this novel lineage requires urgent laboratory characterisation and enhanced genomic surveillance worldwide."

Challenges in vaccination against COVID-19

Category	Challenge
Political	Prioritisation of vulnerable populations. Selection of vaccine based upon efficacy and cost. Timely procurement of vaccine and ethical distribution.
Programme management	Augmenting health system to reach out to target population. Making available sufficient and functional cold chain up to last mile.
Technical	Monitoring efficacy, persistence of protection and safety in community phase and launching Phase 4 safety surveillance.
Operational	Timely procurement and efficient distribution. Managing cold chain. Enhancing capacity for efficient response. Data management. Community engagement including response to adverse reactions.
Epidemiological	Monitoring progress of pandemic and adjusting vaccination plans.
Research	Response to availability of second generation of better vaccines.
Financial	Mobilisation of financial resources from within the country or through international development partners.

Source: Editorial by Rajesh Bhatia, Online version India and COVID-19, Part-IV, Indian Journal of Medical Research

THE SOUTH AFRICA VARIANT

Is this new UK-variant related to the newly emergent variant in South Africa? The variant seems to have emerged in a major South African metropolitan area and was first detected in October. In its press statement of December 18, the South African Health Minister stated that a particular variant had increasingly dominated the findings of samples collected in the past two months. In addition, the statement said that there was evidence of a shift in the clinical epidemiological picture; in particular, a larger proportion of younger patients with no comorbidities were presenting with critical illness. The Minister also claimed that it was South Africa which alerted the U.K. authorities about the new variant which triggered the discovery of the U.K-variant.

While the UK-variant seems to have only caused an increase in the number of cases among younger adults, there was no evidence of increase in severity of the disease in any age group. However, in the South African scenario severe illness was also being observed in young adults. "The evidence that has been collated," he said, "strongly suggests that that the current second wave we are experiencing is being driven by this new variant." The SA-variant too carries the same critical mutation N501Y, which, scientists believe, may be responsible for the increase in the virus's greater infectiveness in both countries. Does this lead to severe disease in young adults? Only more studies on the variants can tell. The exact impact of its tighter binding to human ACE2 receptor is, however, not properly understood yet. However, according to Andrew Preston of the University of Bath, the mutation has been seen in other variants as well that have not been associated with increased transmission. "So, the picture is complex."

Genetic analysis of the SA-variant has shown that it also has an unusually large number of mutations like the UK-variant. But the key mutation, N501Y, occurs in combination with other mutations that are not seen in the UK-variant. So, in all likelihood, it emerged completely independently of the U.K. strain and is not related to it. The SA-variant is characterised by N501Y, E484K and K417N mutations, two of them (N501Y and E484K) within the RBD, and the strain has been now called '501Y V2'.

VACCINES EFFECTIVE

Despite the above concerns in the behaviour of the two new variants from the U.K. and South Africa, scientists believe that there is no reason to think that the vaccines being rolled out or under development will be less effective. According to the Centres for Disease Control (CDC) of the U.S., the U.S. Food and Drug Administration (FDA) authorised vaccines are 'polyclonal'; that is, they produce antibodies targeting several parts of the spike protein. The virus would likely need to accumulate several mutations in the spike protein to evade immunity induced by vaccines or by natural infection, the CDC says.

However, in a recent study by Paul Axelson and others from the University of Pennsylvania Perelman School of Medicine, which was posted on the bioRxiv web preprint repository on December 13, 16 naturally occurring mutations on the S-protein, including the N501Y mutation, were investigated to determine whether these were able to prevent antibody binding and maintain the ability to bind to the ACE2 receptor and viral infectivity.

Significantly, the authors concluded that "SARS-CoV-2 with mutated forms of the spike protein may retain the ability to bind to ACE2 while evading recognition by antibodies.... It seems likely *that immune evasion will be possible* regardless of whether the spike protein was encountered in the form of infectious virus, or as the immunogen in a vaccine. Therefore, it also seems likely that reinfection with a variant strain of SARS-CoV-2 may occur among people who recover from COVID-19, and that *vaccines with the ability to generate antibodies against multiple variant forms of the spike protein will be necessary to protect against variant forms of SARS-CoV-2* that are already circulating in the human population" (emphasis added). Whether all vaccines already developed or under development are really of this nature is not known.

CHALLENGES

There are already several challenges that the rapid roll-out scenarios proposed for public use must confront (Table 1). The emergence of new uncertainties due to the somewhat unusual virus mutations seen during a pandemic adds another dimension. Among the various concerns about the impact of the new variants, the ability to evade vaccine-induced immunity would likely be the most concerning because once a large proportion of the population is vaccinated, there will be immune pressure that could favour and accelerate emergence of such variants by selecting for "escape mutants". There is no evidence that this is occurring, and most experts believe escape mutants are unlikely to emerge because of the nature of the virus, says the CDC.

In the Indian context, the only viable vaccine currently is Oxford-AstraZeneca's adenovirus vectored-vaccine, which is the most easily deliverable vaccine given its easily manageable cold chain logistics. Vaccination prospects in India are, therefore, currently dependent entirely on its British approval. Following that India is likely to approve for use here immediately. But the vaccine's approval in the U.K., in the light of the emergence of this new variant and its rapid spread, may not come soon. The U.K. health authorities may want to see its efficacy against cases with the new variant(s) before. So, Indian roll-out plans should actually speed up trials and approvals for home-grown vaccines, but approvals must take into account all the new lessons being continually learnt from the virus variants' infecting potential. □