ILLUSTRATION: ROHNIT PHORE

● COVID-19

Vaccine cos should take time

MAX NISEN

Bloomberg

Cutting corners on clinical trials boosts the risk of bad reactions as use expands

THE FAST PACE at which various laboratories are working on vaccines against Covid-19 carries both promise and peril. On Monday, Moderna Therapeutics Inc announced the first reported data from human trials, and they are positive. That is good news, and it arrived sooner than expected. But, the parts of the project that lie ahead will be harder to accomplish with speed.

Eight patients who received low and medium doses of the Moderna's candidate vaccine appear to have developed antibodies capable of neutralising the new coronavirus. The company didn't have detailed data on the rest of the 45 trial participants, but all generated at least some antibodies. It was early data from a small study, though, and the limited results don't prove that the vaccine provides broad and durable protection. Also, while there were no serious safety issues, three patients who received the highest dose of the vaccine briefly suffered modest "flu-like symptoms" after their second injection.

For this vaccine to succeed, tests ahead will need to demonstrate that it can indeed protect people from Covid-19 for an extended period, and that it will prevent substantially more harm than it causes. The bar is especially high for vaccines, because they are given to healthy people—a Covid-19 vaccine, in particular, could be given to billions of healthy people. Of course, there is pressure to move quickly. But, some parts of the vaccine development process simply cannot be rushed.

Moderna and other companies that have created vaccine candidates in record time have been able to speed early stages of the process—for instance, by compressing animal experiments—and they plan to keep hurrying by testing higher-risk patients earlier than usual and by starting more extensive efficacy trials while smaller safety studies are still running. The Trump administration's new Operation Warp Speed aims to help by building significant manufacturing capacity for candidate vaccines even before they prove successful.

But, there are limited ways to shorten the large randomised human trials that will be needed to assess any vaccine's safety and effectiveness.

One way to try to move faster is to use so-called surrogate endpoints—that is, to measure certain biomarkers of the drug's effectiveness rather than wait for hard data from patient outcomes. You might look, for example, at the number of antibodies that subjects generate after trying the vaccine. This evidence can demonstrate which specific candidates or doses are worth pushing forward. However, it isn't enough for approval. Only clinical data from a large and varied population can establish how much protection a vaccine can safely provide, and for how long.

Such trials take time, in part because so much needs to happen before the data are complete. It could take months for enough of the subjects who are given placebos to be infected with the coronavirus—to demonstrate by comparison the vaccine's effectiveness. And, public health efforts may inadvertently slow this process, if they are able to delay or minimise a second wave of the disease.

Human challenge trials, in which healthy volunteers are deliberately exposed to a virus in order to assess a vaccine rapidly, could also speed things up by identifying the most promising vaccine candidates. Even so, it makes sense to run trials on a diverse set of possible vaccines, ranging from Moderna's novel RNA-based option to more traditional inactivated viruses. Multiple good alternatives are going to be needed to meet the historic challenge of inoculating the world against Covid-19, and some will turn out to be easier to manufacture and distribute than others.

Vaccine studies need to be large especially to establish safety. Immune systems vary enormously from person to person, which means that it is easy for a mostly safe vaccine to provoke an occasional adverse reaction. Cutting corners on clinical trials boosts the risk that bad reactions could emerge as use expands.

Moderna's early safety data reveal nothing that would prevent broad use of its vaccine. In future trials, including a large pivotal test scheduled to begin in July, the company plans to use a middle-size dose, which should theoretically lower the risk of side effects. But, if this dose produces anything worse than scattered and transient unpleasant symptoms, the vaccine may not be approvable.

Regulators will need to determine exactly how much safety data is enough, based on input from both research scientists and clinicians. Despite the world's urgent need, this reasoning will need to be guided by the evidence as it comes in, not by any wished-for calendar date.

This column does not necessarily reflect the opinion of the editorial board or Bloomberg LP and its owners

ALOK SHEEL

RBI Chair Professor, ICRIER
Views are personal

● BEFORE COVID-19

A brief history of pandemics

The break between the epidemics of the past and today is provided by the public health revolution that followed, but did not coincide with, the Industrial Revolution that sharply reduced mortality from infectious diseases

THE COVID-19 CRISIS is a grim reminder of the negative externalities associated with globalisation. Influenzas are amongst the most 'virulent' diseases known to man, spread by little-understood entities that inhabit the twilight world between life and matter. They can lie dormant for long periods, mutate quickly and spread quickly from person to person, and through the air. In a highly mobile world, they spread rapidly across the globe, challenging the best public health systems as vaccines and antidotes take time to develop. Covid-19 is also the first pandemic played out in the full glare of social media, evoking panicked policy responses even where epidemiological patterns are very different and normal influenza mortality much lower.

The world before the great age of European discovery was a very local one. The means of communication were slow, based on animal traction on land, wind traction on water, and limited in range. Most people were born and died at their place of birth. Epidemics right up to the end of the medieval period were localised affairs. Mortality rates could be high, generating panic that revived longstanding social prejudices like anti-Semitism, just as they do today. Pestilence, along with famine and war, were the three equilibrating devices that kept the pre-modern population in check despite high basal birth rates.

Bubonic Plague was in a class of its own. The first plague pandemic was the Plague of Justinian between 6th-8th century AD during the high tide of the Roman Empire. The second pandemic, the Black Death of the 14th century, was also in the pre-modern era. It was only the third pandemic of the mid-19th to the early 20th century that took place in the post-industrial age.

Plague, however, is a disease primarily of rodents. Ordinarily, humans cannot infect each other, except in the rare pneumonic form, or when the rat flea is looking for a new host following the death of its current host. Rat colonies thrived on coastal ships, and infected rats were transported from port to port. Once established inland, bubonic plague became a creeping epizootic, spreading only as fast as the underlying rat population travelled. Modern technology transformed plague epidemics. In the early 20th century, the epidemic spread fast in the Indian hinterland after landing by ship, being carried rapidly up the country through grain movements by railway with their complement of infected rats. It, however, reverted to the medieval creeping epizootic away from railway links.

Viruses present a grave threat to globalisation. Most viruses are either highly virulent, but relatively benign causing low mortality like seasonal flu or have been less virulent but deadly, like Ebola, SARS, MERS

As the means of communications improved, large numbers could now be transported over long distances. Maritime technology transited from coastal shipping to trans-continental oceanic voyages even before the engine age following new scientific inventions that heralded the European Age of discovery and imperialism from around the 16th century. As Europeans discovered and conquered new lands, they brought with them unfamiliar diseases against which the local populations had no herd immunity. In the Americas, the arrival of Europeans decimated 90-95% of the indigenous population through smallpox, measles, typhus, cholera, diphtheria, influenza and the like.

It is intriguing why a similar phenomenon did not occur in the East Indies and India. Europe and Asia was a single landmass with low-level long-distance links over centuries through the Indian Ocean trade extending from the southern coast of China, through the straits of Malacca and India, right up to the horn of Africa and terminating in Venice. Eurasia, therefore, shared a common pool of disease.

The first modern pandemic was cholera, imported into Europe from Asia in the early 19th century following the colonial link. Why cholera had not reached Europe earlier through the Indian Ocean trade route remains a mystery. Was this because the cholera pathogen could not survive long outside its warm moist tropical environment on long coastal shipping journeys and was transported to Europe only in the age of faster steamships invented towards the end of the 18th century?

The break between the epidemics of the past and today is provided by the public health revolution that followed, but did not coincide with, the Industrial Revolution that sharply reduced mortality from infectious diseases. One of the more interesting debates in English population history is centred on the spike in mortality in the immediate aftermath of the Industrial Revolution. This is attributed to the squalor in urbanised industrial counties and greater population movements. The decline in mortality followed the public health revolution. Likewise, mortality increased in India in the 19th century despite improved food security following modern developmental works like all-weather roads, railways and canals that also led to the rapid spread of malarial fevers, keeping population stagnant right up to 1921.

Viruses present a grave threat to globalisation. Most viruses are either highly virulent but relatively benign, causing low mortality like seasonal flu, or have been less virulent but deadly, like Ebola, SARS, MERS. But, now and then the perfect storm will occur, a strain both virulent and deadly with the potential of causing death on a mind boggling scale. The value attached to human life has changed over time, but a quarter-million deaths from Covid-19 to date is far from being a perfect storm. The Spanish flu a century ago claimed an estimated 40-50 million people globally. The first two plague pandemics claimed 30-50 and 200 million lives respectively, and the third 10-12 million in China and India alone. Over 40 million perished from cholera in the 19th century. It is only a matter of time when a perfect storm arrives again. Hopefully, with the experience gained with handling Covid-19, the world would be better prepared.

REGIONAL CAFE

Innovating for the Covid 19 era

Many South-based start-ups are finding opportunity in the pandemic

SUSHILA RAVINDRANATH

sushila.ravindranath@expressindia.com

MANY START-UPS THAT were looking forward to 2020 with optimism are now facing some seriously uncertain times. Downsizing and closures have already begun. To emerge relatively unscathed, these start-ups have to reinvent themselves. Some of their business models have lost relevance.

Bengaluru-based MyGate, launched in 2016, is a platform that provides security management services for gated communities. Residents can use the app to communicate with neighbours, discuss matters on forums, manage visitors, maintain attendance record and salary payments of daily help, discover services and pay maintenance bills, among other things. These communities are beehives of activities. Abhishek Kumar, co-founder & COO, says, "We are a VC-backed company and have been growing rapidly year after year."

After the lockdown, very few people can either go in or come out of the gates of these huge complexes. The app is not needed at the moment. The company has figured out a way to help residents of these communities and also expand its activities. "MyGate is collaborating with various service providers to restore essential services for residents. We started identifying the pressing needs of our gated communities, and are using our multi-city workforce to find feasible partnerships across the board", says Kumar.

The start-up has collaborated with Grofers and ITC. It has also partnered with Swiggy, Zomato, Dunzo and Licious to offer contactless deliveries, and has tied up with telemedicine companies to provide free consultation from home. MyGate is the tech partner for the Karnataka State Police's Clear Pass, which issues curfew passes. So far, over 1,85,000 curfew passes have been given to 30,000 essential service providers for critical travel during the lockdown.

Another service it provides is the delivery of news. Over 3,00,000 app users access at least one of the 17 newspapers (with 50 regional editions to choose from) on offer. Users spend 6:08 minutes reading news on the website. MyGate hopes to add more services, they have not monetised any yet.

Hyderabad-based Ozonetel, founded in 2007, is a pioneer in providing on-demand cloud communication services in India. The solutions are KooKoo CloudAgent and KooKoo Interactive Assistant. Chaitanya Chokkareddy, CIO, says, "These solutions are perfect for companies looking to shift work to home as Covid-19 has triggered the world's largest work-from-home (WFH) experiment. However, not all jobs can be executed at home. For instance, is it possible for call centres to switch to a WFH model?"

Keeping this in mind, Ozonetel is offering cloud-based solutions to its clients to switch to a WFH model easily. Cloud telephony moves your business phone system to the cloud, allowing you to manage your business calls without compromising on quality and cost. With the help of the offline mode, companies can temporarily switch their call centres to a WFH model. This can be executed without compromising on security and privacy concerns of businesses.

Chokkareddy explains, "BigBasket is one of our clients. Delivery boys can move around. Agents gather the information from call centres, which are shut. Now, with our server, it is being done from home. The number of calls to call centres hasn't come down."

"We are the first company to establish a call centre on the cloud. We were ahead of the US", he adds. Set up by three technocrats returning from the US, with no backers, Ozonetel has quietly grown by client recommendations and word-of-mouth publicity.

GoFrugal, a Chennai-based SaaS company promoted by Kumar Vembu, has decided to help *kirana* stores. Vembu says, "As the country battles Covid-19, neighbourhood stores have emerged true heroes by being there for consumers during the crisis. To stand by them, we are offering free subscription of our bundled solutions till September 30."

These will help set up online ordering and a delivery management app. With OrderEasy, retailers can set up an exclusive branded Android app. Orders are automatically processed, making it easier for retailers to measure and improve service capability.

The GoDeliver app provides retailers with a platform to manage deliveries efficiently. It gives complete control to retailers by streamlining deliveries, sharing the most optimum routes with their delivery staff, tracking delivery, location and even rescheduling or cancelling. Retailers find managing the logistics of delivery easier and efficient and can serve more orders than usual.

Vembu says that in the last 4-5 years a lot of these neighbourhood shops have become supermarkets. They are, however, still small and social distancing is not possible, and customers cannot go inside. In this period, shops are open only for a few hours. By receiving orders through WhatsApp, shopkeepers are able to serve better.

GoFrugal has 30,000 customers across 70 countries. Of these, 6,000-plus are *kirana* stores. The company has seen a 30% rise in customers since lockdown, receiving an average of eight requests per day, and have on-boarded more than 220 customers.

Chennai-based Inthree Access Services was founded in 2013 on the belief that rural India is more than willing to buy branded white goods. It pioneered the concept of assisted commerce in rural space with Boonbox. "People don't understand that rural customers are aspirational and they have disposable income to buy consumer products," said Ramachandran Ramanathan, CEO, and one of the three founders, a few months ago.

"We believe this is a great opportunity to go beyond consumption commerce and work on the larger rural ecosystem," he says. Boonbox will tie-up with small farmers, SHGs and retailers via a digital platform.

"The post-Covid-19 scenario is a great time to accelerate digitisation in rural areas; that could be the single catalyst to a more prosperous rural ecosystem. Considering that all elements of the ecosystem are already prevalent across most of India, but in silos, Boonbox will be the integrator of the ecosystem," adds Ramanathan.

Those that are nimble and innovative will emerge as survivors and winners.