ANNQUEST JULY 2020
ISSN:2321-3043

www.stannsannquest.com

\VACCINE TRIALS IN A NUTSHELL FOR NOVEL CORONAVIRUS

Syeda Nooreen Fatima
St.Anns college for women
Email-Id: syedanooreen981@gmail.com

Rachana Gowlikar
St.Anns college for women
Email-Id: rachna.gowlikar@gmail.com

ABSTRACT:

In this review, we identify opportunities for Vaccine development for the treatment of COVID-19. The vaccine development methodologies are aimed at discovering novel chemical & biological means targeting a shortlist of the host & viral entities (proteins) that should extend the multitude of anti-SARS-CoV-2 agents. Pharmaceutical companies around the globe are competing to produce an effective vaccine against the novel coronavirus. This will require a coherent strategy for vaccine development where pharmacologists play an important role. Evaluations of an inactivated whole virus vaccine in ferrets and nonhuman primates and a virus-like-particle vaccine in macaques induced protection against infection.

KEY WORDS:

SARS-Cov-2, SinovacBiotech, CanSino, Moderna, BCG vaccine, Pfizer.

INTRODUCTION:

Severe acute respiratory syndrome coronavirus- 2 is an infectious disease caused by a novel coronavirus. Patients carrying this disease can be either symptomatic/ asymptomatic thus creating a demanding situation to control this disease outbreak due to lack of a specific vaccine or treatmentthis makes the process of developing a safe and effective vaccine against COVID 19, a top priority among the public health sector.

Dr.Zhang Jixian, head of the respiratory department at Hubei provincial hospital reported to health officials in China that they found a person affected with symptoms similar to SARS, and that the disease caused by a novel coronavirus.
In the beginning, authorities suspected the virus rooted from something sold at a wet market in Wuhan which sold both dead and live animals including fish and birds.

However, some of the patients identified that they did not have any connection with the wet market (lancet).Before this on November- 17th 2019. A 55-year old individual from the Hubei province in China may have been the first person to have contracted the COVID 19 (SOUTH MORNING CHINA POST).

Bats were believed to be the original host were not sold at the wet market but may have infected animals including live chicken. Suchmarkets pose a heightened risk of transmission of zoonotic diseases its challenging to maintain hygiene standards. There are three possibilities to fight against the

COVID-19 they are:

1.Herdimmunity- communities develop immunity against the disease.

2. Invention- Repurposing the drug to control the disease

3. Reach for the vaccine.

What is a Vaccine?

Vaccines are biological products which are of various types such as subunit vaccine(a part of the virus), a live attenuated vaccine (totally inactivated virus), killed vaccines, nucleic acid vaccines (RNA is used as a vaccine), etc. These vaccines are injected into the body to act against toxins released by a pathogen. As a result, the immune system identifies the disease-causing pathogen and stores in memory which fightback in the most effective way. Research is happening all around the world at a rapid pace and some of the vaccines are now entering clinical trials. Scientists in Seattle announced a vaccine for the first human trial for which they are skipping any animal research to test its safety or effectiveness. The first human trial in Europe has started in Oxford,with more than 800 recruits. Pharmaceuticals giants Sinofi and GSK have collaborated to develop a vaccine. The first comprehensive pre-clinical trials involving animals have begun by Australian scientists by injecting ferrets with two potential vaccines.

What still needs to be done?

Potential vaccines have been designed by several research groups however, there is much more work to be done. The vaccine would not be useful if it caused more problems than the disease. Therefore, trails need to show whether the vaccine is safe or not. Clinical trials must ensure that the vaccine provokes an immune response that would protect people from getting sick.

There must be a way for producing the potential doses of vaccines that must be developed on a huge scale. It must be approved by the medicine regulators before it can be given. Inoculating most of the world's population will be challenging for the vaccine makers around the globe. Self-isolation and lockdown could make this process slower.

To know whether a vaccine works it requires vaccine trials to be done on a greater number of people. Injecting vaccines and infecting people (a double-blind study) helps to get sooner results, it seems too dangerous as there is no known treatment.

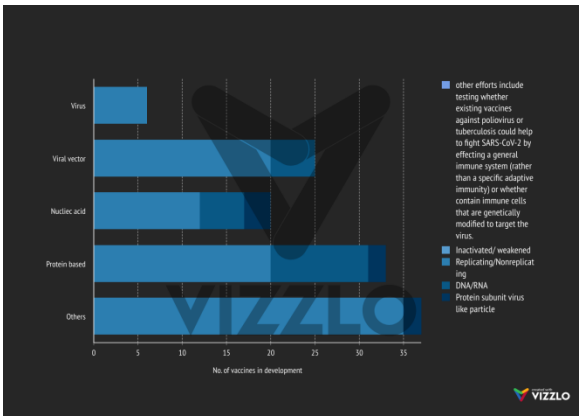


Fig (1): No. of vaccines in development

Source:nature analysis based on who covid-19 vaccine landscape/milken institute covid-19 treatment and vaccine tracker/t. thanh le et al. nature rev. drug. disc. http://doi.org/ggrnbr (2020)/f. amanat & f. krammer immunity 52, 583–589 (2020)/w. shang et al. npj vaccines 5, 18 (2020).

Over 240,000 deaths have occurred worldwide and more than 3.5 million people are infected from COVID-19. The race is to develop a vaccine to prevent infection in the first place followed by

finding new drugs to treat COVID-19 patients.

A research group from the International Union of Basic and Clinical Pharmacology says there will be no 'magic bullet' to treat the disease. According to them it takes almost 10-12 months to develop a vaccine to tackle the global pandemic. (When the immune system is fighting back to clear the infection, but in severe cases immune responses in the overactive stage it

leads to cytokine storm so this causes collateral damage to the organs).Professor Davenport from the University of Cambridge said that there are three key stages of infection: to prevent the virus from entering the host cells in the first place, stopping it from replicating if it gets inside the host cells, and reducing the tissue damage which in this case are the tissues of lungs and heart. He also mentioned that the main focus is on repurposing drugs that already have regulatory approval or are in the late stages of clinical trials.

Research teams across the world are developing vaccines (>90) against SARS -CoV-2. Different technologies that haven't been used in a licensed vaccine before are being trailed by the researchers. Volunteers in safety trials are being injected formulations by at least 6 groups of researchers.

AN ASSEMBLAGE OF VACCINES

As mentioned earlier vaccines do not cause any disease but will provoke an immune response that can kill or block the virus if a person become infected. Eight types of vaccines are being trialed against the novel coronavirus which relies upon different viruses or viral parts.Currently, there are ongoing clinical trials with both which relies upon different viral parts, and there are ongoing clinical trials with both investigational and approved agents.

VIRUS- (LIVE ATTENUATED VACCINES)

Vaccines are being developed by using the virus itself (weakened/ inactivated form) by at least seven research teams. Vaccines for measles and polio were also made in this way but they require proper safety testing.

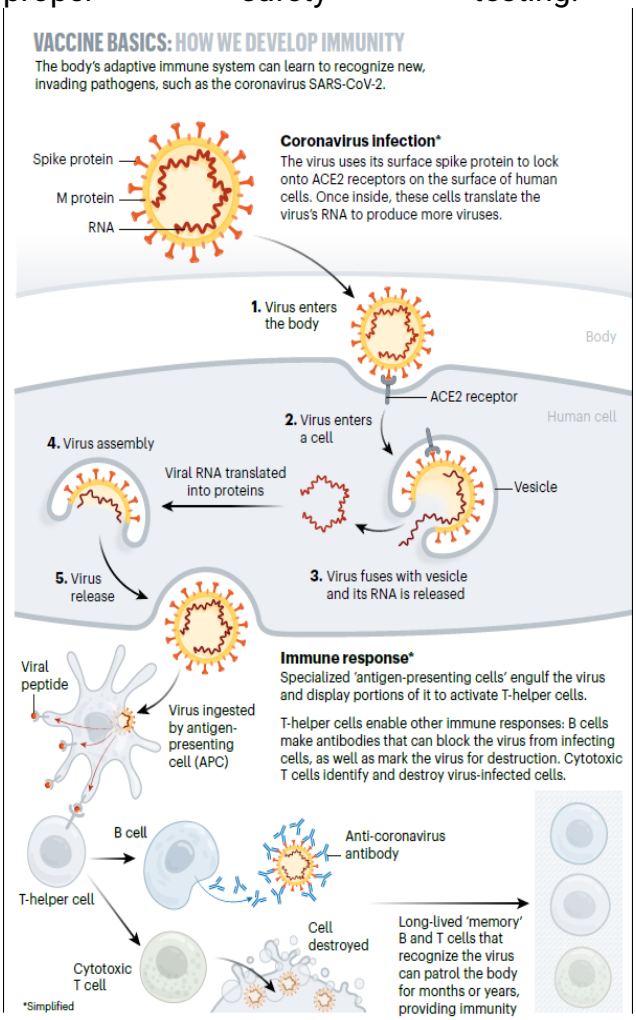


Fig (2): Immunity Development

Source: NATURE ANALYSIS BASED ON WHO COVID-19 VACCINE LANDSCAPE/MILKEN INSTITUTE COVID-19, TREATMENT AND VACCINE TRACKER/T. THANH LE ET AL. NATURE REV. DRUG. DISC. HTTP://DOI.ORG/GGRNBR(2020)/F. AMANAT & F. KRAMMER IMMUNITY 52, 583–589 (2020)/W. SHANG ET AL. NPJ VACCINES 5, 18 (2020).

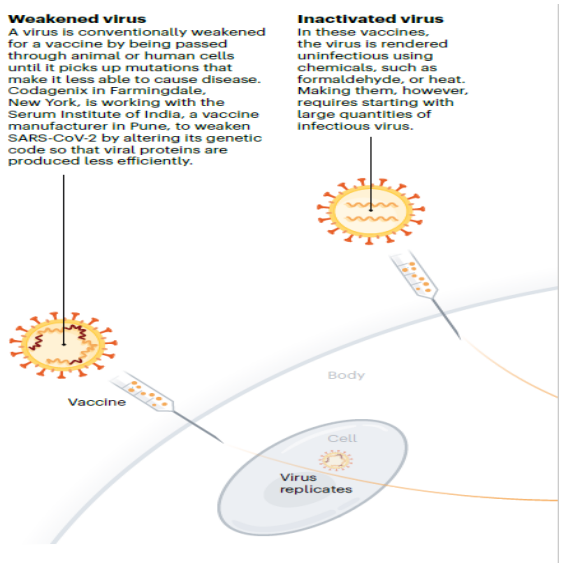


Fig (3): Weakened & Inactivated form of virus'
Source:NATURE ANALYSIS BASED ON WHO COVID-19 VACCINE LANDSCAPE/MILKEN INSTITUTE COVID-19 TREATMENT AND VACCINE TRACKER/T. THANH LE ET AL. NATURE REV. DRUG. DISC. HTTP://DOI.ORG/GGRNBR (2020)/F. AMANAT & F. KRAMMER IMMUNITY 52, 583–589 (2020)/W. SHANG ET AL. NPJ VACCINES 5, 18 (2020).

NUCLEIC ACID VACCINES

Genetic instructions in the form of DNA/RNA for a coronavirus protein are being used at least by twenty teams that prompt an immune response in an infected person. The human cells are inserted with the nucleic acid which amplifies the virus protein; which encodes the virus's spike proteins. To produce RNA and DNA based vaccines only the making of genetic material is required, not the virus. Licensed vaccines do not use this technology as it is unproven.

VIRAL VECTOR VACCINES

These are in the making process by around 25 research groups. To produce coronavirus proteins in the body, a virus such asAdenovirus or measles are genetically engineered. To prevent the disease these viruses are weakened. There are two types of weakened viruses- the viruses that can replicate within the cells and the viruses that can't replicate because the key genes have disabled.

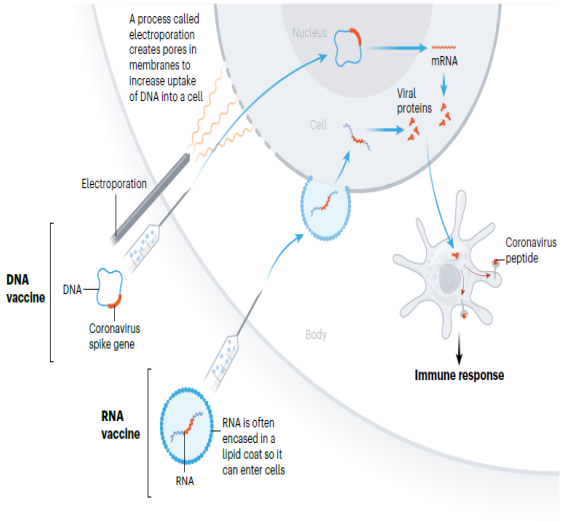


Fig (4): Nucleic Acid Vaccine'
Source:nature analysis based on who covid-19 vaccine landscape/milken institute covid-19 treatment and vaccine tracker/t. thanh le et al. nature rev. drug. disc. http://doi.org/ggrnbr (2020)/f. amanat & f. krammer immunity 52, 583–589 (2020)/w. shang et al. npj vaccines 5, 18 (2020).

PROTEIN-BASED VACCINES Protein shells that mimic the coronavirus's outercoat and fragments of proteins can also be used.
The drug that originally developed for the Ebola virus, Remdesivir is also being used against the novel coronavirus, and FDA has now approved it for emergency use. There have also been promising findings from studies of monoclonal antibodies, but this type of drug is expensive to produce and therefore less likely to be scalable.
Three drugmakers, Cansino, Moderna,

Inovia are in human trials. Chinese Biotech Cansino already is in phase 2 of

human trials in conjunction with the Beijing Institute of Biotechnology. US phase1 results are being carried out by biotech firm Moderna as well as US pharmaceuticals Inovia. US drug makers Moderna and Inovia expect early results in a few months. Beyond that other 67 pharmaceuticals are in their pre-clinical trials which means we are still months away from that vaccine. Researchers in AstraZeneca think an existing drug used to treat adult leukaemia has the potential to treat COVID-19.

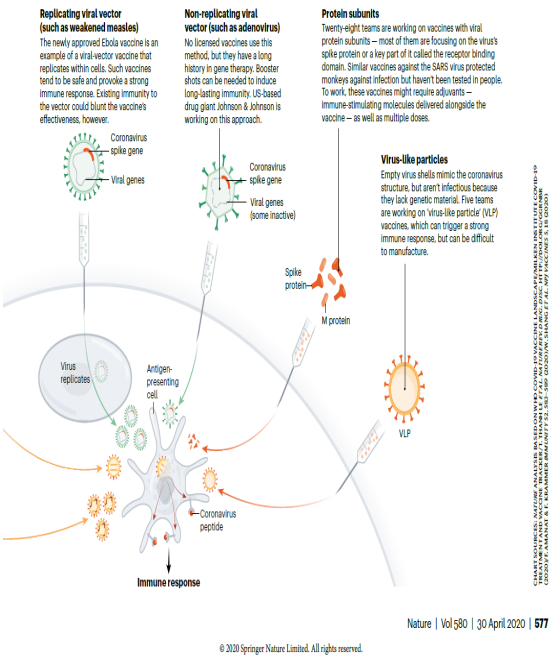


Fig (5): Viral vector & Protein-Based Vaccine'

Source:nature analysis based on who covid-19 vaccine landscape/milken institute covid-19 treatment and vaccine tracker/t. thanh le et al. nature rev. drug. disc. http://doi.org/ggrnbr (2020)/f. amanat & f. krammer immunity 52, 583–589 (2020)/w. shang et al. npj vaccines 5, 18 (2020).

Chloroquine and Hydroxychloroquine are also being used to treat COVID-19 patients. But, a small study in Brazil was halted due to concerns about the safety and impact the high doses of the drug can have on heartbeats in the heart. So, there are some concerns mounting in the medical community about these two drugs.

The global pandemic could come to an end if a vaccine that protects people from coronavirus is developed. But, finding one that works and manufacturing enough doses pose a great challenge. A cell line was used to develop an Ebola vaccine at the NRC. Cansino's vaccine against coronavirus is produced using the same cell line.

SINOVACBIOTECH: COVID-19 VACCINES PROTECT MONKEYS FROM NOVEL CORONA VIRUS

Scientists report that one of the many COVID-19 vaccines in development has protected an animal, Rhesus macaques, for the first time, from infection by the new coronavirus. The chemically inactivated version of the virus, an old-fashioned formulation- vaccine, produced no side effects in the monkeys, and human trials began on 16th April 2020. Two different doses of COVID-19 vaccines were given to a total of 8 Rhesus macaques by researchers from Sinovac- Biotech, Beijing based company.

The best response was given by the monkeys with the highest dose of vaccine: After a week researchercouldn't detect the virus in the pharynx or lungs of any of them. Sinovac team reported that animals with lower doses had a 'viral blip' but also appeared to have to control the infection. On the other hand, a high level of viral RNA was developed by four control animals in several bodyparts followed by severe pneumonia.

But Douglas Reed of the University of Pittsburgh said that the number of animals was too small to yield statistically significant results. The most severe symptoms that SARS-CoV-

2causes in humans do not develop in monkeys. The Sinovac researchers also acknowledge that the best animal model for studying the virus is not yet known.But when the unvaccinated Rhesus macaques were given the virus, mimics COVID-19 like symptoms.

Earlier vaccine experiments with animals related to coronavirus that causes Severe Acute Respiratory Syndrome (SARS)and Middle East Respiratory Syndrome (MERS) had found that when a pathogen is injected into the animal the low antibody levels lead to an aberrant immune response which enhanced the infection and caused pathology in their lungs. Vaccinated animals who produced relatively low levels of antibodies did not show any lung damage according to the Sinovac team.

SARS-CoV-2 seems to undergo mutations gradually which might pose a challenge for vaccine development. In test-tube experiments, the Sinovac researcher mixed antibody was taken from mice, monkeys, and rats given their vaccine with strains of the virus isolated from COVID-19 patients Italy, China, United Kingdom, Switzerland, and Spain. The strains which are widely scattered on the phylogenetic tree were potently neutralized by the antibodies. This gives evidence that the mutations of the virus are not resistant to a COVID-19 vaccine. Sinovac started phase-I clinical trials in 144 volunteers (Jiangsu Province, North of Shanghai) an aim to gauge safety and immune responses. Participants will receive high or low doses of placebo. Although placebos do not asses efficacy, they can help better evaluate the dangerous side-effects of the vaccines. Sinovac will seek to launch phase-III efficacy trials and join international vaccine trials being organized by The World Health Organization (WHO).

- **The Oxford University:**The University of Oxford has developed a vaccine candidate 'ChAdOx1 nCoV-19' in under three months. The vaccine candidate uses a weakened strain of common cold virus (adenovirus) and is combined with the genetic material of the SARS-CoV-2 (the coronavirus causing COVID-19).This will enable the body to identify the spike protein of the novel coronavirus. The vaccine candidate is now in a clinical trial phase-1 and healthy volunteers have already been injected to check its safety and efficiency.

- **Massachusetts-based Moderna vaccine:**In the US, the Massachusetts-based biotech company Moderna is developing an RNA based vaccine in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID). The vaccine candidate mRNA-1273 has already conducted phase 1 trials and is all set to begin phase 2 trials. The RNA vaccine works by entering the human cells and carries the molecular instructions to make the viral protein. Once, this viral protein is recognized by the body, the immune system of the body is triggered.

- **Beijing-based Sinovac Biotech**:Chinese scientists are claiming to have successfully tested a potential vaccine for the novel coronavirus in monkeys. To conduct this experiment, the researchers injected the monkeys with the potential vaccine

"PiCoVacc" which is made by Sinovac Biotech, a Chinese biopharmaceutical company. The monkeys were later exposed to novel coronavirus and it was found that those injected with a dose of the potential vaccine were largely protected from the virus. The vaccine is currently undergoing human clinical trials.

- **Pfizer and BioNtech vaccine:**US-based Pfizer pharmaceutical company and its German partner BioNtech are working together on four RNA vaccine candidates. They also began clinical trials of their vaccine candidate BNT162. Their vaccine candidate is based on specially designed messenger RNA (similar to the Moderna vaccine) and the trials for testing the vaccine are taking place in the USA and they plan to test the potential vaccine on 360 healthy volunteers.

- **DNA-based vaccine by InovioPharmaceuticals:**Inovio Pharmaceuticals, a biotechnology company received 5 million dollars aid for developing a vaccine for the novel coronavirus. Located in Plymouth Meeting, Pennsylvania, the pharmaceuticals have developed a potential vaccine in its San Diego lab and are all set to begin Phase 1 trial at the University of Pennsylvania. The vaccine is named INO-4800 and each volunteer will receive two doses of the relatively novel DNA-based vaccine candidate, four weeks apart to check its efficiency and safety.

- **The BCG vaccine:**The Bacillus Calmette-Guerin (BCG) live-attenuated vaccine candidate is in phase 2/3 and is used against tuberculosis to boost the immune system. Clinical trials are being conducted to test the effectiveness and safety of this vaccine candidate in protecting people against COVID-19.

WHAT IS THE ROLE OF INDIA IN MAKING VACCINES FOR CORONA VIRUS?

Along with Bharat Biotech, Serum Institute of India (SII), and Zydus other mid-rung companies such as the Gurugram-based Premas Biotech, Ahmedabad-based Hester Biosciences, and start-ups Neuberg Supratech and Mynvax are also racing to develop coronavirus vaccine.

India can leverage its ability to mass manufacture the COVID-19 vaccine, for the leading international bodies like the Bill and Melinda Gates Foundation and the World Health Organization.

The Ahmedabad-based Zydus group is also developing the Covid-19 vaccine through its research arm in Europe, Etna Biotech.

Premas Biotech specializes in creating recombinant protein for vaccine development. The proteins on the SARS-CoV-2 virus: The spike protein, Envelope protein, and Membrane protein are targetted by these proteins.

Premas Biotech stated that the most immediate need and role for India to play right now is to enable large scale manufacturing, rapid approvals, guidelines and collective wisdom to deliver the appropriate vaccine.

Coronavirus vaccines for all strains like those of SARS, MERS, and even

common cold, have been notoriously hard to develop due to their rapid mutation, still, vaccines prove to be the best long-term strategy to combat pandemics. Therefore, vaccines are expected to be refined each year to cope up with the mutation.

Indian Biotech companies have collaborated with academia, research organizations, universities, and virologists to develop vaccines in core support.

Oxford University has collaborated with SII and plans to produce up to 400 million doses of COVID-19 vaccine, next year if all goes well.

SII is in partnership with the US-based biotechnology firm Codagenix to produce a vaccine that was among the earliest candidates in the pandemic to reach the preclinical stage of animal testing.

Bharat Biotech has partnered with the University of Wisconsin, Madison, and the US-based company FluGen to develop a vaccine, Coro-Flu. The vaccine is built on "M2SR", an existing flu vaccine that contains the weakened live H3N2 influenza virus. Gene sequences from SARS-CoV-2 would be inserted into M2SR so that the new vaccine will also induce immunity against the coronavirus.

CONCLUSION

Microorganisms such as bacteria and viruses, continue to evolve and evade our immune systems and the history of pandemics contributed to the decline and fall of civilization.

The current pandemic could only be controlled by continuous trials of the rapid development of safe and efficacy vaccines. To date no vaccine has been successfully produced to protect against human beta coronaviruses such as those causing SARS and MERS. In contrast, numerous viral diseases have been successfully controlled by pharmacological agents. Viruses like HIV-AIDS and hepatitis-C virus with high mortality, morbidity, and variability and still be treated with direct antiviral agents allowing the elimination of the virus in a

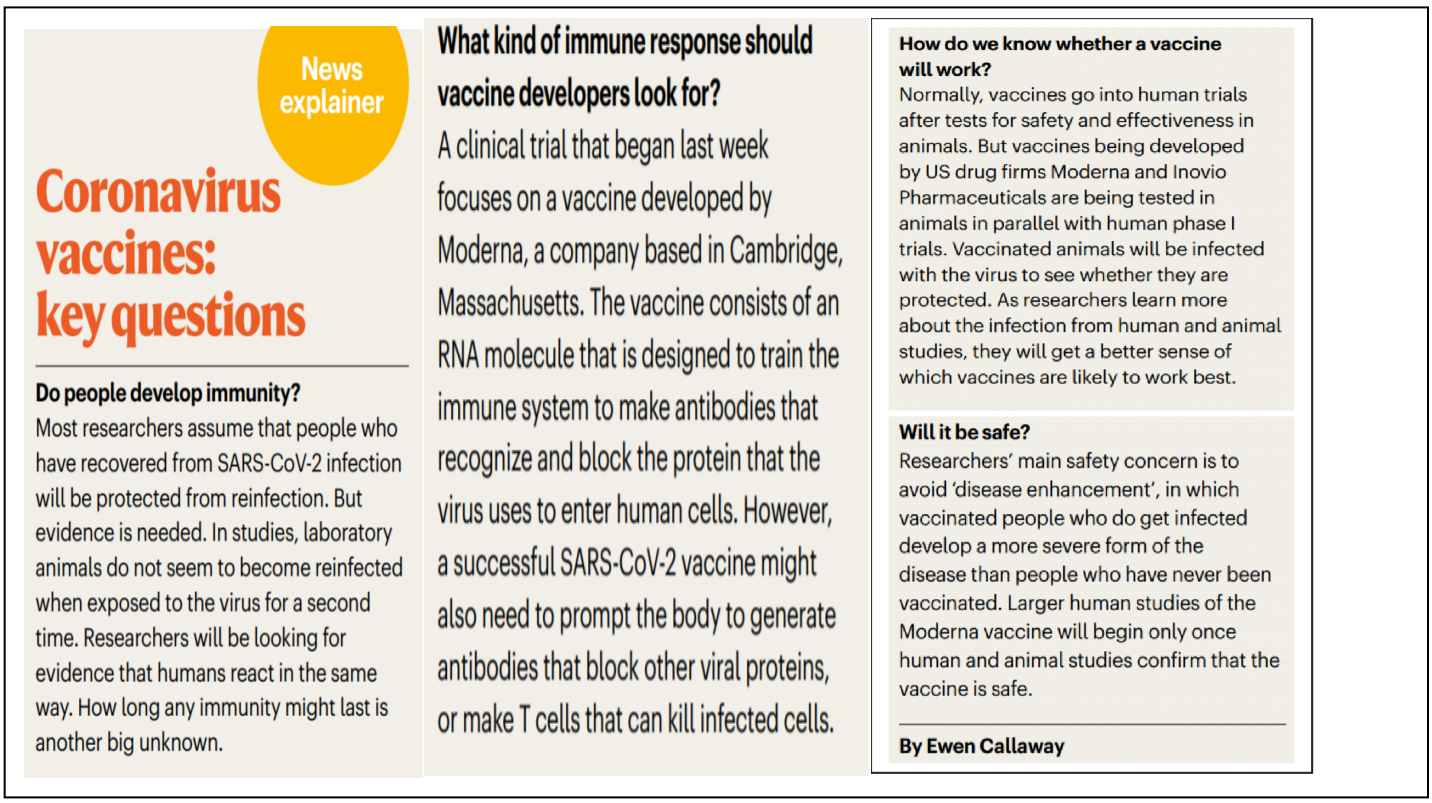
very high proportion of those treated. This evidence provides some relief from COVID-19 and (Indeed for viral threats yet to come).

Even after a new vaccine candidate has been shown to offer immunity against the coronavirus in humans, it needs to be tested in larger numbers of people to ensure it is safe to use. Manufacturing and distributing a vaccine at the scale needed to tackle this pandemic will also present significantchallenges.

Some of the vaccines may not work, so the more drugs that can be tested and the more we know about the targets, the more likely we are to get something which is effective.

The very specificity of vaccines means they are limited in which viruses they can neutralize. The lessons we learn and the drugs we generate will hopefully provide a greater degree of protection, not just against the COVID-19 virus, but also against the next viral threat." Professor Davenport is a member of the Department of Medicine, University of Cambridge, and a Fellow at St Catharine's College

.



News explainer

Coronavirus vaccines: key questions

Do people develop immunity?

Most researchers assume that people who have recovered from SARS-CoV-2 infection will be protected from reinfection. But evidence is needed. In studies, laboratory animals do not seem to become reinfected when exposed to the virus for a second time. Researchers will be looking for evidence that humans react in the same way. How long any immunity might last is another big unknown.

What kind of immune response should vaccine developers look for?

A clinical trial that began last week focuses on a vaccine developed by Moderna, a company based in Cambridge, Massachusetts. The vaccine consists of an RNA molecule that is designed to train the immune system to make antibodies that recognize and block the protein that the virus uses to enter human cells. However, a successful SARS-CoV-2 vaccine might also need to prompt the body to generate antibodies that block other viral proteins, or make T cells that can kill infected cells.

How do we know whether a vaccine will work?

Normally, vaccines go into human trials after tests for safety and effectiveness in animals. But vaccines being developed by US drug firms Moderna and Inovio Pharmaceuticals are being tested in animals in parallel with human phase I trials. Vaccinated animals will be infected with the virus to see whether they are protected. As researchers learn more about the infection from human and animal studies, they will get a better sense of which vaccines are likely to work best.

Will it be safe?

Researchers' main safety concern is to avoid 'disease enhancement', in which vaccinated people who do get infected develop a more severe form of the disease than people who have never been vaccinated. Larger human studies of the Moderna vaccine will begin only once human and animal studies confirm that the vaccine is safe.

By Ewen Callaway

REFERENCES

* https://bpspubs.onlinelibrary.wiley.com/doi/epdf/10.1111/bph.15094
* https://www.cam.ac.uk/research/news/repurposing-existing-drugs-for-covid-19-a-more-rapid-alternative-to-a-vaccine-say-researchers
* https://doi.org/10.1111/bph.15094
* https://www.sciencemag.org/news/2020/04/covid-19-vaccine-protects-monkeys-new-coronavirus-chinese-biotech-reports#
* https://www.hindustantimes.com/india-news/covid-vaccine-development-sees-unparalleled-

ANNQUEST(9)-1:1-9

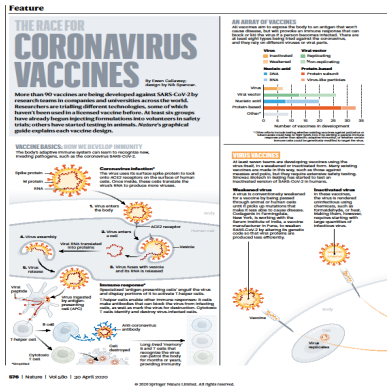
progress/story-PtAQIKRHB9omEFWbdUfJKI.html?

* https://www.ncbi.nlm.nih.gov/books/NBK554776/

* https://www.hindustantimes.com/india-news/covid-vaccine-development-sees-unparalleled-progress/story-PtAQIKRHB9omEFWbdUfJKI.html?jwsource=cl (source: video)

* https://theprint.in/india/how-india-can-be-a-world-leader-in-making-covid-vaccine-and-keeping-it-cheap-too/414701/

Coronavirus vaccines: key questions



Feature

THE RACE FOR CORONAVIRUS VACCINES

Feature

CAN THE WORLD MAKE ENOUGH CORONAVIRUS VACCINE?

Researchers warn production constraints and hoarding could limit SARS-CoV-2 vaccine supplies. By Roxanne Khamsi