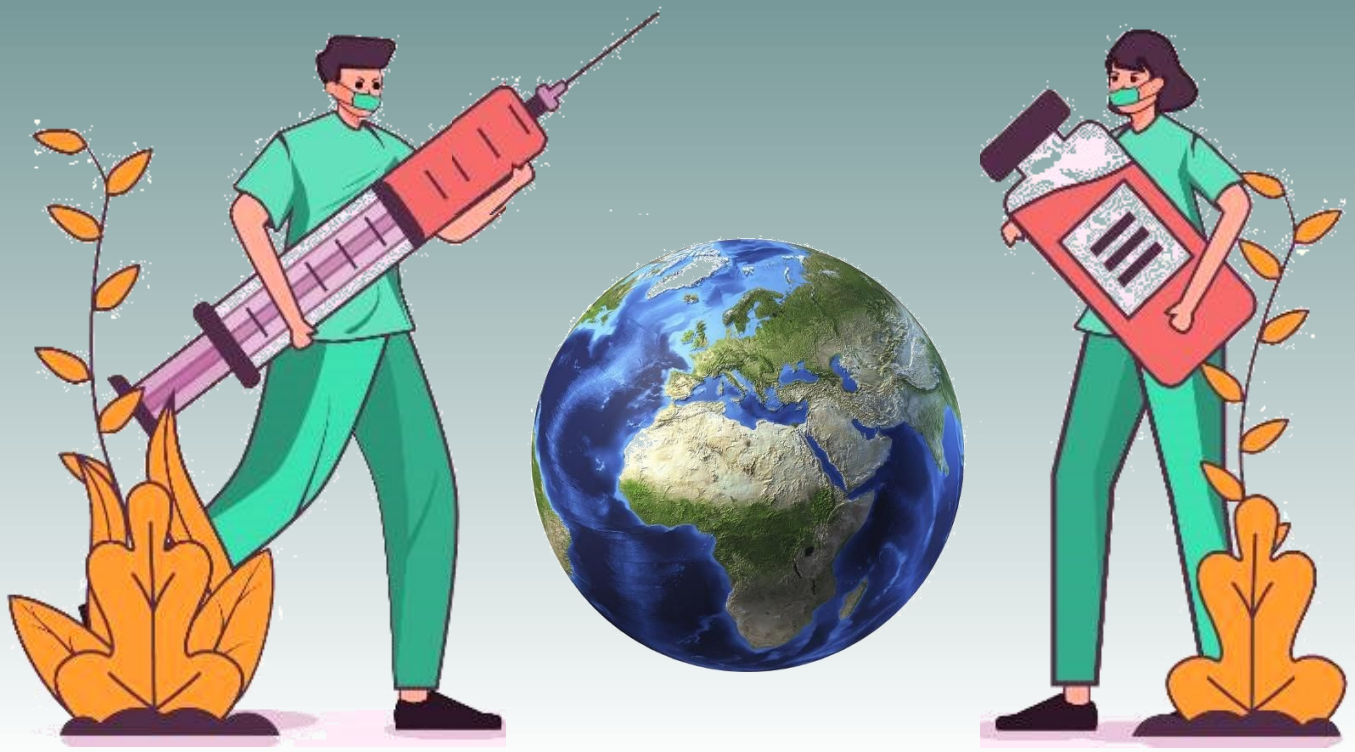
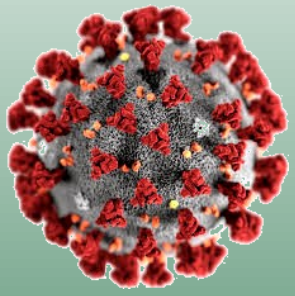
Kuwait Pharmacy Bulletin

DRUG INFORMATION FOR THE HEALTH PROFESSIONAL



Beginning of the end?



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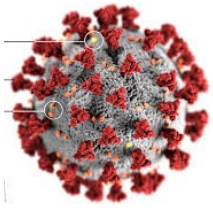
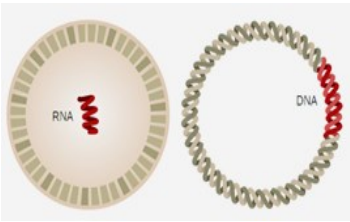
The race for COVID-19 vaccines -a fast shifting landscape



The coronavirus disease 2019 (COVID-19) has spread rapidly across the globe affecting every society and every age group taking not only a severe toll of human lives but has decimated every economy as countries struggle to control infection rates by introducing draconian lockdown measures. At the time of writing, it has now infected in excess of 60 million people with near to 1,400,000 recorded deaths (2.3% mortality rate); increasing daily. Better understanding of the etiology of the disease as well as preventive measures against airborne infection and use of anti-inflammatory steroids for supportive care, has had limited impact. However, numerous private and public enterprises have been engaged, operating at an unprecedented furious pace, in developing a safe and effective vaccine, which is widely considered to be the ultimate solution to halt this viral pandemic. This review will focus on the most widely publicised efforts under development by Pharma (big and small) in collaboration with universities and research institutes across many countries. In addition to all the considerable scientific challenges, attention is also turning to the no simple task of transportation and administration, particularly repeat dosing. This review summarises the current situation with the major vaccines which are in *phase 3 trials* with the greatest chance of eventual success.

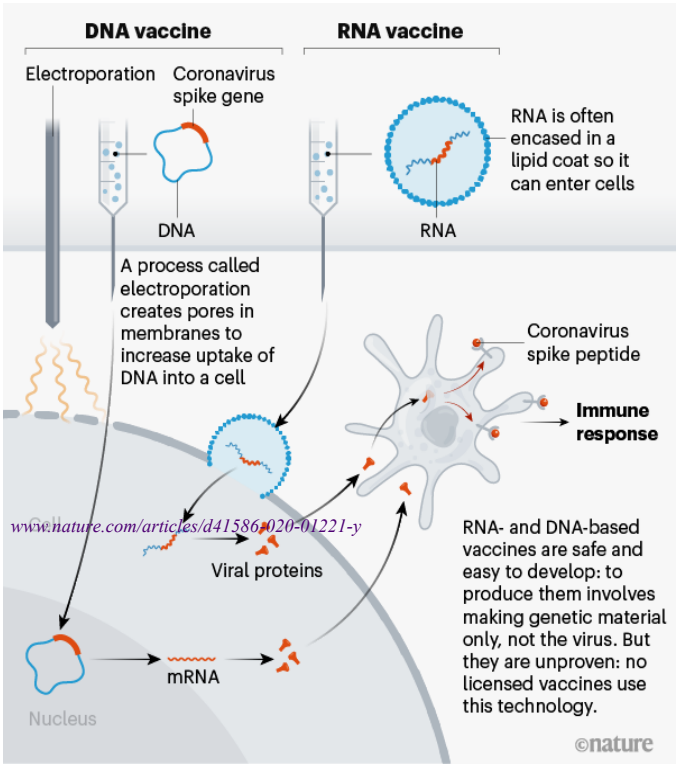
moderna

Develops vaccines based on messenger RNA (mRNA) to produce viral proteins in the body but have yet to bring one to the market. In January, they began developing a vaccine for coronavirus. The vaccine contains genetic instructions for building a coronavirus protein, known as spike. When injected into cells, the vaccine causes them to make spike proteins, which then get released into the body and provoke a response from the immune system.



Genetic vaccines

Vaccines that deliver one or more of the corona virus' own genes into our cells to provoke an immune response



The US government provided nearly $1 billion in support. In partnership with National Institutes of Health, they found that the vaccine protects monkeys from the coronavirus. In March, they were the first to put a COVID -19 vaccine into human trials. After those studies yielded promising results, Phase 3 testing on 30,000 volunteers began on July 27.

On Nov 16, Moderna announced that a preliminary analysis of the trial indicated that the vaccine was 94.5% effective. Out of 95 participants who got COVID-19, 90 had the placebo and only 5 had the vaccine. The results came just a week after Pfizer made a similar announcement about their own vaccine, which is also based on an mRNA molecule encoding the spike protein. Another promising result from Moderna's trial was the finding that the vaccine appears to protect people from severe disease. Of the 11 volunteers who developed severe disease, none were vaccinated. The trial will continue to gather more results; Moderna plans to submit an application for an emergency use authorisation within a few weeks.

Moderna lost a patent dispute in July over some of their vaccine technology; stating it could not be certain it was the first to make the inventions claimed in their patents, including its coronavirus vaccine. Meanwhile, the company has entered deals with several countries to

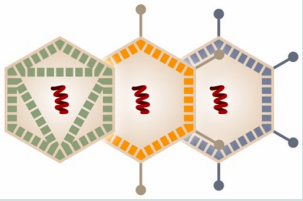
supply the vaccine if approved. On Aug 11, the US government awarded the company an additional $1.5 billion in exchange for 100 million doses if the vaccine proves safe and effective. Moderna has made similar deals with Canada, Japan, and Qatar.

A week before the Moderna announcement, New York based Pfizer and the German company BioNTech presented preliminary data indicating that their coronavirus vaccine was over 90% effective. In May, Pfizer and BioNTech launched a Phase 1/2 trial on two versions of a mRNA vaccine. They found that both versions produced antibodies against SARS-CoV-2, as well as immune T cells. One version, called **BNT162b2**, produced significantly fewer side effects, such as fevers and fatigue. On July 27, the companies announced a Phase 2/3 trial with 30,000 volunteers in the US and other countries including Argentina, Brazil, and Germany. In an interim study, they reported that after getting the first dose, volunteers experience mostly mild to moderate side effects. On Sept 12, they announced that they would seek to expand their U.S. trial to 43,000 participants. The following month, they gained permission to start testing the vaccine on children as young as 12y.

In September, the CEO of Pfizer, said the Phase 3 trial would deliver enough results as soon as October to show if the vaccine worked or not, but it was not until Nov 8 that Pfizer released preliminary analysis of the first 94 cases. Ten days later, they followed up with the final results, based on 164 cases. concluding that the vaccine is about 95% effective including amongst people over 65y, who often have weak responses to vaccine. Additionally, the trial detected no serious side effects.

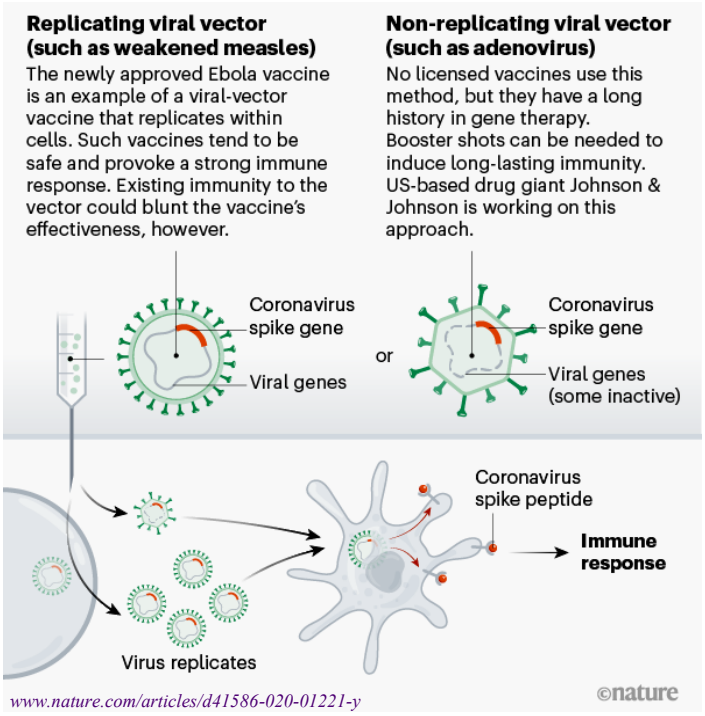
On Nov 20, the company submitted a request for an emergency use authorisation. The FDA is expected to take several weeks to review the application. In the summer, the companies began inking deals to deliver large orders to countries around the world. The US Administration awarded a $1.9 billion contract in July for 100 million doses to be delivered by December and the option to acquire 500 million more doses. Japan made a deal for 120 million doses, and the European Union for 200 million doses. If their vaccine is authorised, Pfizer and BioNTech expect to manufacture over 1.3 billion doses of their vaccine worldwide by the end of 2021.

Getting the vaccine from the factory to people's arms could pose major challenges. Like Moderna's vaccine, Pfizer and BioNTech's preparation is based on mRNA, which is unstable unless it's kept in a deep freeze. This vaccine will have to be chilled to -70^{0}C until it's ready to be injected. Pfizer is building boxes that will keep the vaccines cold as they're being transported. In addition, like most vaccines currently in trials, it requires two doses. Ensuring that people return after three weeks for their second injection will add an extra layer of complexity to the vaccine's distribution.



Viral vector vaccines

About 25 groups say they are working on viral-vector vaccines. A virus such as measles or adenovirus is genetically engineered so that it can produce coronavirus proteins in the body. These viruses are weakened so they cannot cause disease. There are two types: those that can still replicate within cells and those that cannot because key genes have been disabled.



The Chinese company **CanSino Biologics** developed a vaccine based on an adenovirus called Ad5, in partnership with the Institute of Biology at the country's Academy of Military Medical Sciences**.** In May, they published promising results from a Phase 1 safety trial, and in July they reported that their Phase 2 trials demonstrated the vaccine produced a strong immune response. In an unprecedented move, the Chinese military approved the vaccine on June 25 for a year as a

"specially needed drug." Starting in August, CanSino began Phase 3 trials in Saudi Arabia, Pakistan and Russia (updated Sept 24)

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

The Gamaleya Research Institute, part of Russia's Ministry of Health, launched clinical trials in June of a vaccine called Gam-Covid-Vac a combination of two adenoviruses, Ad5 and Ad26, both engineered with coronavirus gene.

On Aug 11, President Putin announced that a Russian health care regulator had approved the vaccine, renamed Sputnik V, before Phase 3 trials had even begun. Vaccine experts decried the move as risky, and Russia later announced that the approval was a "conditional registration certificate," which would depend on positive results from Phase 3 trials. Those trials, initially planned for just 2,000 volunteers, were expanded to 40,000.

In addition to Russia, volunteers were recruited in Belarus, the UAE and Venezuela. On Oct 17, a Phase 2/3 trial was launched in India.

On Sept 4, Gamaleya published the results of their Phase 1/2 trial. In a small study, they found that Sputnik yielded antibodies to the coronavirus and mild side effects. Meanwhile, Russia negotiated agreements to supply the vaccine to countries including Argentina, Brazil, Mexico and India.

On Nov. 11, the Russian Direct Investment Fund announced preliminary evidence from their Phase 3 trial indicating that the vaccine is effective. Based on 20 cases of COVID-19 among the trial participants, Russian scientists estimated that the vaccine demonstrated 92% efficacy. Outside experts said that was possible, but that data from more cases would be needed to see if estimates held up. In their press release, the fund said that the results of the trial would be eventually published in a peer-reviewed scientific journal. The announcement came two days after Pfizer announced similar results on 94 volunteers in its own Phase 3 trial.

Johnson & Johnson Beth Israel Lahey Health Beth Israel Deaconess Medical Center

A decade ago, researchers at Beth Israel Deaconess Medical Center in Boston developed a method for making vaccines out of a virus called Adenovirus 26. Johnson & Johnson developed vaccines for Ebola and other diseases with Ad26 and have now made one for the coronavirus. In March they received $456 million from the US government to support production. The vaccine has provided protection in experiments on monkeys. J&J began Phase 1/2 trials in July and launched a Phase 3 trial with up to 60,000 participants in September. Unlike other Phase 3 trials, Johnson & Johnson administered just a single dose instead of two.

In August, the federal government agreed to pay $1 billion for 100 million doses if the vaccine is approved. The European Union reached a similar deal on Oct. 8 for 200 million doses. The company is aiming for production of at least a billion doses in 2021.

On Oct. 12, Johnson & Johnson announced it put its trial on pause to investigate an adverse reaction in a volunteer. The trial resumed eleven days later. Despite the delay, the company expects to get results by the end of the year. On Nov 16, Johnson & Johnson announced they were launching a second Phase 3 trial to observe the effects of two doses of their vaccine.

AstraZeneca UNIVERSITY OF OXFORD

The British-Swedish company AstraZeneca and University of Oxford developed a vaccine based on a chimpanzee adenovirus ChAdOx1. A study on monkeys found that the vaccine protected them from the disease. In a Phase 1/2 trial, severe side effects were reported. The vaccine raised antibodies against the coronavirus as well as other immune defenses. It began Phase 2/3 trials in England and India (where it's known as *Covishield*). In addition, AstraZeneca launched Phase 3 trials in Brazil, South Africa and the US.

On Sept 6, AstraZeneca halted global trials to investigate one volunteer, who developed a form of inflammation called transverse myelitis. Within a week, the trials began in all countries except the US. A newspaper in Brazil reported on Oct 21 that a volunteer in the trial there died of COVID-19. While AstraZeneca did not comment, the Brazil trial was not paused, suggesting that the volunteer received a placebo. On Oct 23, the FDA authorised the restart of the US trial.

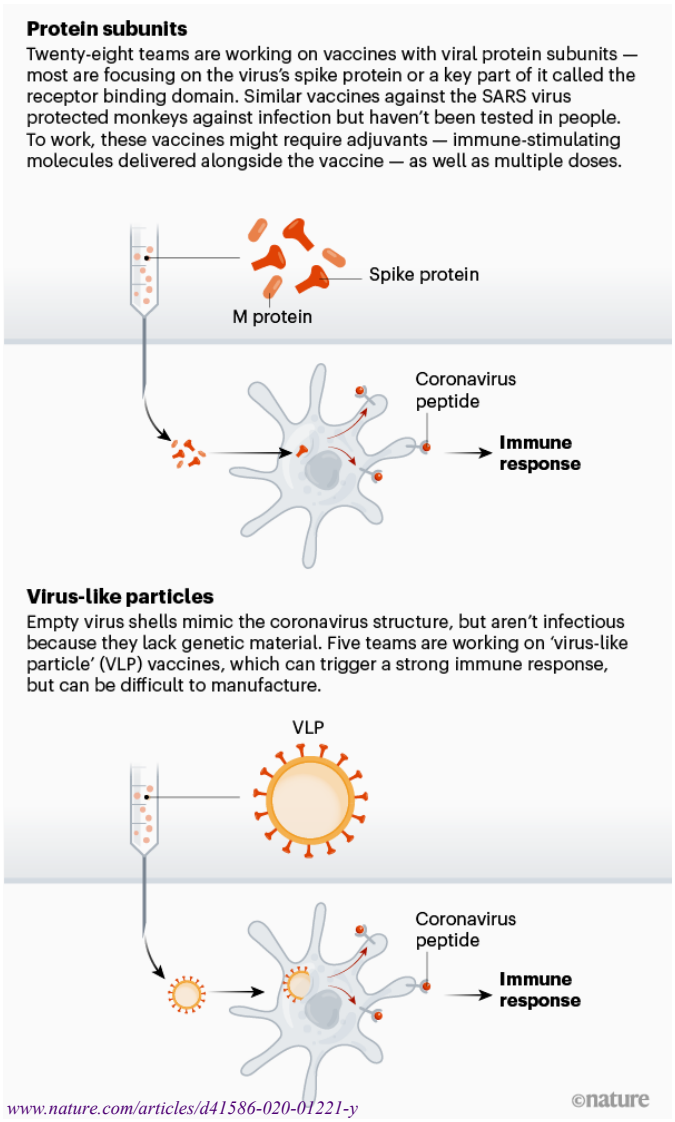
On Nov 19, researchers published findings from the Phase 2/3 trials in England. Studying 160 people aged 18 to 55 y, 160 between 56 and 69, and 240 of 70 y or older, they didn't observe any serious side effects at any age. Older volunteers produced about as many antibodies against the coronavirus as the younger ones. The CEO of AstraZeneca said in a Nov 5 interview with Bloomberg that the company expected results from their trial by end of December.

Starting in May, AstraZeneca secured a series of agreements to provide vaccines to governments should they prove effective. The US awarded the project $1.2 billion in support for 300 million doses. In August the European Union reached an agreement for 400 million

doses if the trials yield positive results. The company has said their total annual manufacturing capacity for the vaccine, if approved, stands at two billion doses.

Protein-based vaccines

Vaccines that contain coronavirus proteins but no genetic material. Some vaccines contain whole proteins and some contain fragments. Some pack many of these molecules on nanoparticles



NOVAVAX
Creating Tomorrow's Vaccines Today

Maryland-based Novavax makes vaccines by sticking proteins onto microscopic particles. Their flu vaccine finished Phase 3 trials in March. The company launched trials for a COVID-19 vaccine in May, and the Coalition for Epidemic Preparedness Innovations invested $384 million in the vaccine. In July the US government awarded $1.6 billion to support the vaccine's clinical trials and manufacturing.

After promising results from preliminary studies in monkeys and humans, Novavax launched a Phase 2 trial in South Africa in August. The blinded, placebo-controlled trial on 2,900 people will measure not just the safety of the vaccine but its efficacy. The following month, Novavax launched a Phase 3 trial enrolling up to 15,000 volunteers in the UK. It could potentially deliver results by the start of 2021. A larger Phase 3 trial is in development to launch in the US by the end of November.

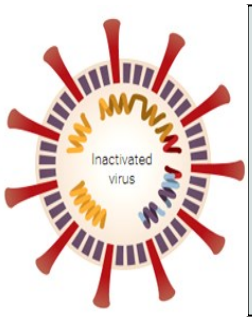
In September Novavax reached an agreement with the Serum Institute of India, a major vaccine manufacturer, that they said would enable them to produce as many as 2 billion doses a year. If the trials succeed, Novavax expects to deliver 100 million doses for use in US by the first quarter of 2021. On Nov 4 they announced another agreement to deliver 40 million doses to Australia.

medicago gsk

Canada-based Medicago, partly funded by Philip Morris, uses a species of tobacco to make vaccines. They deliver virus genes into leaves, and the plant cells then create protein shells that mimic viruses. In July, Medicago launched Phase 1 trials on a plant-based COVID-19 vaccine in combination with adjuvants to boost the immune system's response to the viral proteins. In that study, they found that an adjuvant made by GSK produced promising levels of antibodies in volunteers. On Oct 23, the company announced it had reached an agreement with the government of Canada to supply 76 million doses. A Phase 2/3 trial of the vaccine began on Nov 12.

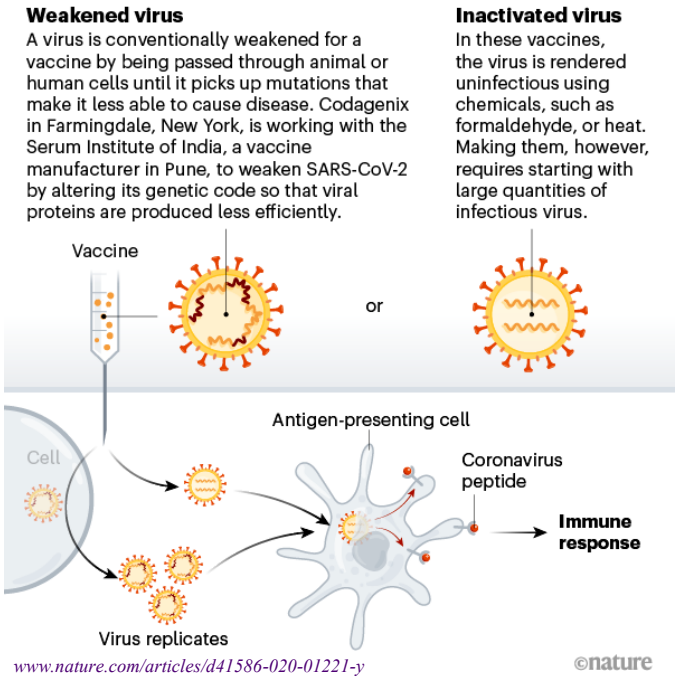
ZFSW The Biologics Company
INSTITUTE OF MEDICAL BIOLOGY
CHINESE ACADEMY OF MEDICAL SCIENCES

The Chinese company Anhui Zhifei Longcom and the Chinese Academy of Medical Sciences partnered to make a vaccine. Their candidate is composed of the RBD section of the spike protein of the coronavirus, along with an adjuvant. They launched Phase 2 trials in July, and on Nov 20 China Daily reported that they launched a Phase 3 trial starting in China. They plan to recruit 29,000 volunteers, expanding their trials to Ecuador, Indonesia, Pakistan, and Uzbekistan.



Inactivated or Attenuated Coronavirus Vaccines

At least seven teams are developing vaccines using the virus itself, in a weakened or inactivated form. Many existing vaccines are made in this way, such as those against measles and polio, but they require extensive safety testing.



武汉生物制品研究所有限责任公司
WUHAN INSTITUTE OF BIOLOGICAL PRODUCTS CO.,LTD.

Approved for limited use in UAE

The Wuhan Institute of Biological Products developed an inactivated virus vaccine, which the state-owned Chinese company Sinopharm put into clinical tests. The Phase 1/2 trial showed that the vaccine produced antibodies in volunteers, some of whom experienced fevers and other side effects.

They launched Phase 3 trials in the UAE in July, and in Morocco and Peru the following month. Over the summer, the company later said, the Chinese government gave it approval to inject the Wuhan vaccine as well as a second candidate from the Beijing Institute of Biological Products into government officials, health care workers, and other select groups. By November, the chairman of Sinopharm said, almost a million people in China had received the vaccines.

On Sept 14, the UAE gave emergency approval for Sinopharm's vaccine to use on health care workers, and soon government officials and others were also receiving it. Yet Sinopharm has yet to publish Phase 3 data on either vaccine to demonstrate that they are safe and effective.

In addition to their Wuhan vaccine, Sinopharm also began testing an inactivated virus vaccine developed by the Beijing Institute of Biological Products. After running early clinical trials in China, they launched Phase 3 trials in the UAE and Argentina. In October, the chairman of said the company was gearing up manufacturing for their two vaccines, with plans for producing a billion doses a year.

sinovac **Approved for limited use in China**

Sinovac Biotech, a private Chinese company, developed an inactivated vaccine called CoronaVac. In June the company announced that Phase 1/2 trials on 743 volunteers found no severe adverse effects and produced an immune response. Sinovac published the details of the trial in November in a medical journal, showing a comparatively modest production of antibodies. Only a Phase 3 trial would demonstrate if that was enough to protect people from COVID-19.

In July, Sinovac launched a Phase 3 trial in Brazil; this was followed by others in Indonesia and Turkey. While Sinovac has yet to release late-stage trial data, on Oct 19 officials in Brazil said that it was the safest of five vaccines they were testing in Phase 3 trials.

Reuters reported that the Chinese government gave the Sinovac vaccine an emergency approval for limited use in July. In October, authorities in the eastern Chinese city of Jiaxing announced they were giving CoronVac to people in relatively high-risk jobs, including medical workers, port inspectors and public service personnel.

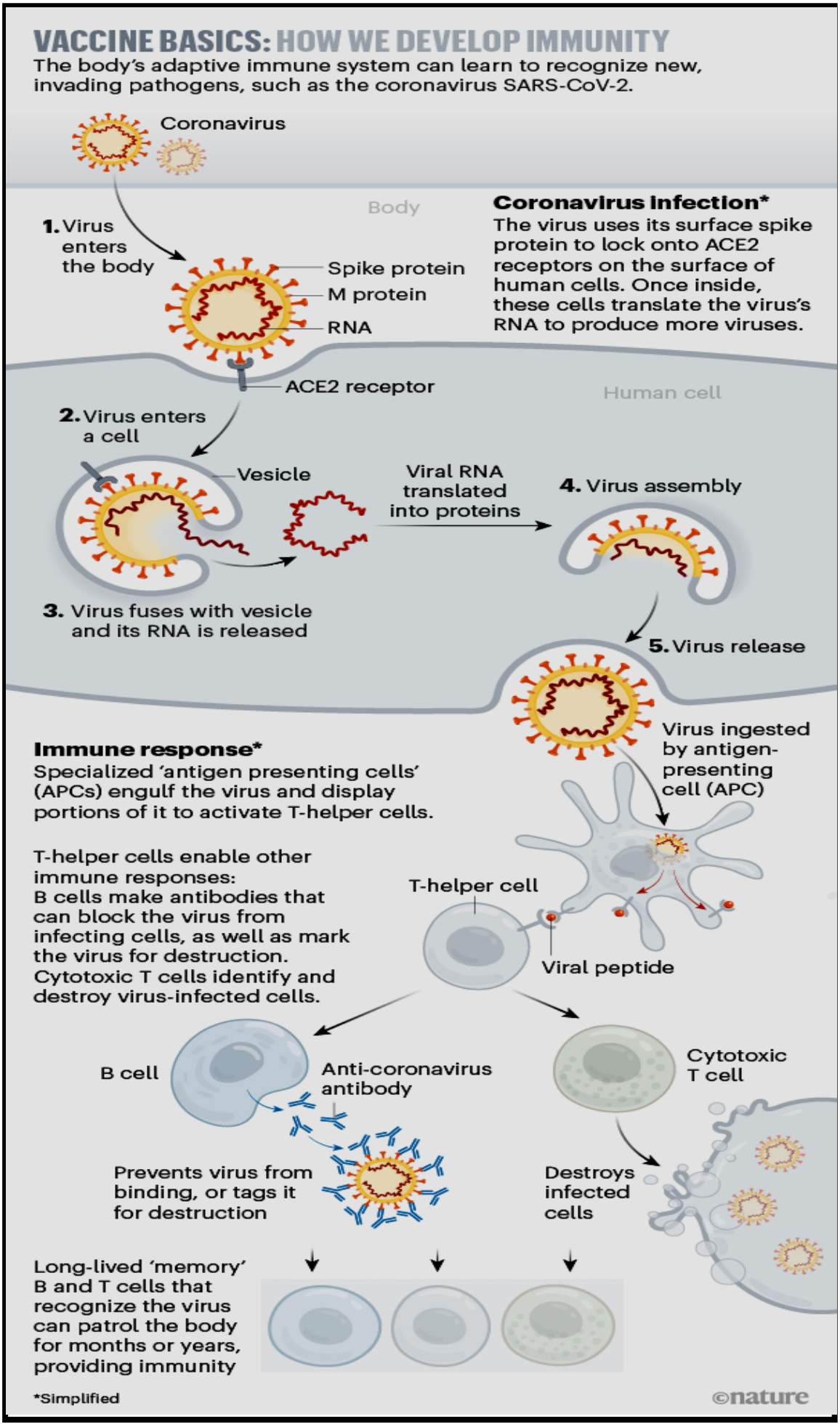
Meanwhile, Sinovac has been preparing to manufacture the vaccine for global distribution, reaching an agreement to supply Indonesia with at least 40 million doses by March 2021. In September, the CEO of Sinovac, said the company planned on worldwide distribution of the vaccine in early 2021- including the US.

On Nov 9, the Brazilian government announced they had paused the country's Sinovac trial the previous month because of an adverse event. The details of the pause were murky, raising suspicions that politics were involved. Two days after the announcement, the trial was allowed to resume.

BHARAT BIOTECH icmr INDIAN COUNCIL OF MEDICAL RESEARCH NATIONAL INSTITUTE OF VIROLOGY PUNE

In collaboration with the Indian Council of Medical Research and the National Institute of Virology, Bharat Biotech designed a vaccine called Covaxin based on an inactivated form of the coronavirus. Studies on monkeys and hamsters found that it provided protection against infection. When the company launched clinical trials in July, reports circulated that the vaccine would be ready by Aug 15. But the CEO of Bharat told reporters it would be available no sooner than early 2021. On Oct 23, the company announced they were initiating a Phase 3 trial.

In addition to the trials summarised above, there are many other ongoing trials which are in phase 1 and 2 stages that are quite likely to produce their own vaccines, that could turn out to be just as useful but will take longer to show successful outcomes.


VACCINE BASICS: HOW WE DEVELOP IMMUNITY
The body's adaptive immune system can learn to recognize new, invading pathogens, such as the coronavirus SARS-CoV-2.
Coronavirus
Body
1. Virus enters the body
Spike protein
M protein
RNA
ACE2 receptor
Coronavirus Infection*
The virus uses its surface spike protein to lock onto ACE2 receptors on the surface of human cells. Once inside, these cells translate the virus's RNA to produce more viruses.
Human cell
2. Virus enters a cell
Vesicle
Viral RNA translated into proteins
4. Virus assembly
3. Virus fuses with vesicle and its RNA is released
5. Virus release
Virus ingested by antigen-presenting cell (APC)
Immune response*
Specialized 'antigen presenting cells' (APCs) engulf the virus and display portions of it to activate T-helper cells.
T-helper cells enable other immune responses:
B cells make antibodies that can block the virus from infecting cells, as well as mark the virus for destruction.
Cytotoxic T cells identify and destroy virus-infected cells.
T-helper cell
Viral peptide
B cell
Anti-coronavirus antibody
Cytotoxic T cell
Prevents virus from binding, or tags it for destruction
Destroys infected cells
Long-lived 'memory' B and T cells that recognize the virus can patrol the body for months or years, providing immunity
*Simplified
©nature

TEST YOUR KNOWLEDGE

Answers on back page

1. Which of the following is an unusual feature of the replication cycle in coronaviruses?

a) *The RNAs all terminate in a common 3´ and produce nested set transcripts*
b) They take advantage of recombination with the long RNA genome
c) They are not highly mutable
d) They use capped cellular mRNA's

2. Which of the following coronaviruses has caused thousands of deaths around the world as an 'emergent' virus?

a) MERS
b) SARS
c) OC43
d) HKU1

3. Describe the coronavirus structure

a) Club shaped glycoprotein spikes protrude through a lipid bilayer
b) An icosahedral structure with an envelope
c) An icosahedral large pleomorphic virus
d) Large regimented barrel shaped virus

4. SARS is described as a zoonotic virus - what does this mean?

a) Such viruses are confined to animals
b) They do not cause disease in humans
c) They emerge from animals to cross the species barrier infrequently
d) They cause pandemic

5. MERS has four special characteristics and here we have one exception - which is it?

a) Reservoir in bats
b) Aerosol droplet transmission
c) Spread by faecal oral route
d) A conduit to humans via camels

6. The COVID-19 mRNA vaccines instruct human cells to produce

a) Spectrin
b) Protein C
c) Spike protein
d) Protein S

7. The study that helps to know if a vaccine works by intentionally exposing the volunteer to a pathogen is

a) Retrospective study
b) Re-challenge study
c) Ecological study
d) Challenge study

8. Which of the following is an antigen-presenting cell?

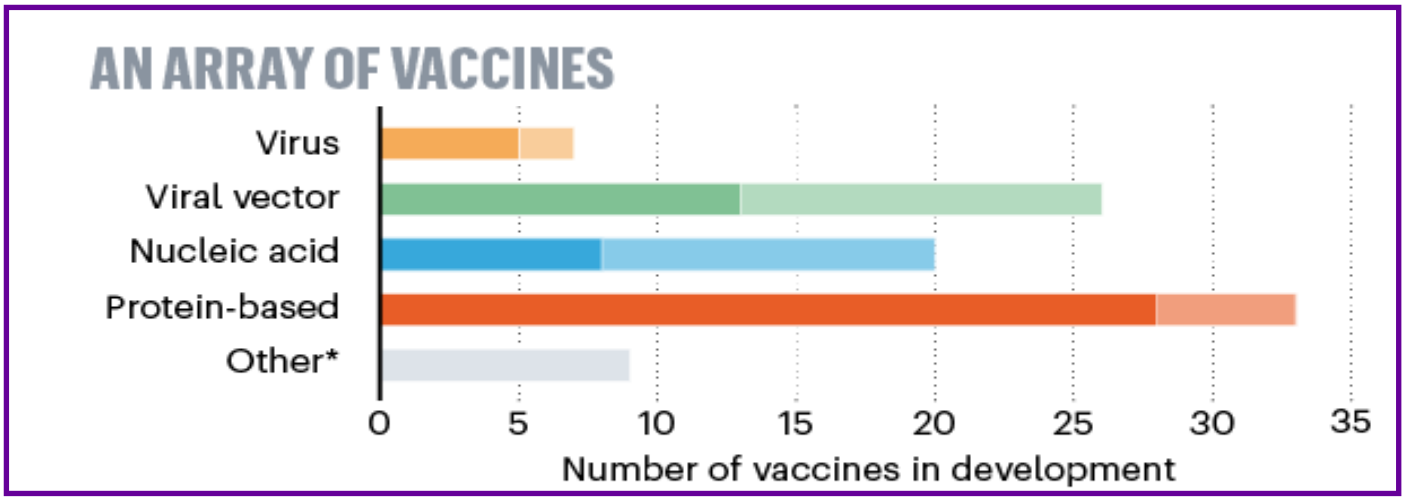
a) Macrophages
b) B lymphocytes
c) Dendritic cells
d) All of the above

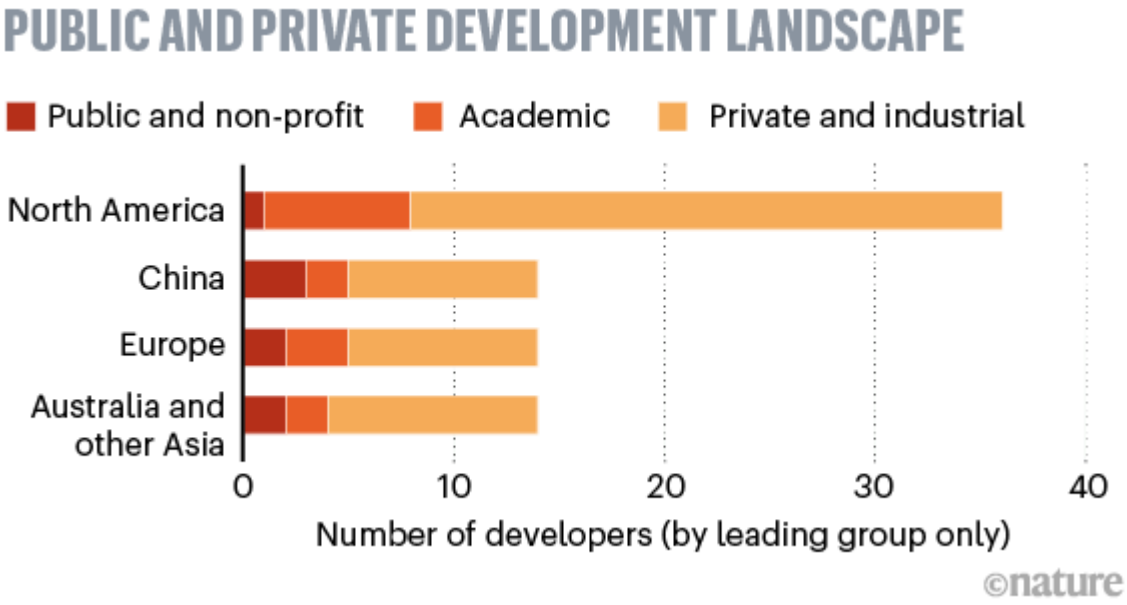
9. Which of the following is <u>not</u> a function of helper T cells?

a) Macrophage activation
b) Cytokine secretion
c) Killing of virus-infected cells
d) Help CD8 T cells

10. In vaccination, booster doses are often required especially when inactivated organisms are used as immunogens.

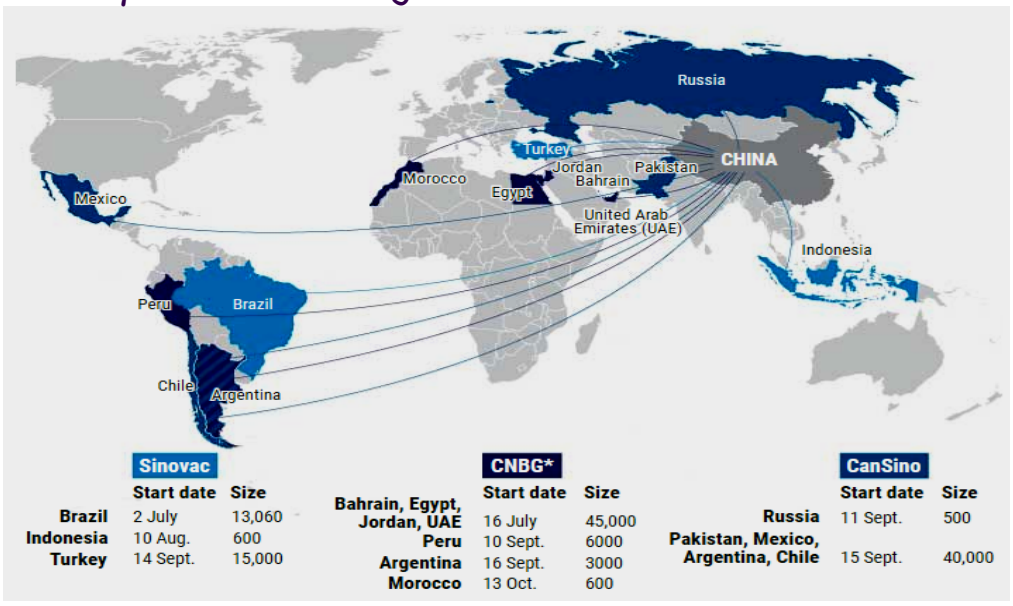
a) True
b) False





Sources: *Nature* analysis based on: WHO COVID-19 Vaccine Landscape/Milken Institute COVID-19 Treatment and Vaccine Tracker/Le *et al. Nature Rev. Drug. Disc*. http://doi.org/ggrnbr (2020)/F. Amanat & Krammer *Immunity* **52**, 583–589 (2020)/Shang *et al. npj Vaccines* **5**, 18 (2020).

China spreads its coverage worldwide in the frantic vaccine race



Sinovac	Start date	Size
Brazil	2 July	13,060
Indonesia	10 Aug.	600
Turkey	14 Sept.	15,000

CNBG*	Start date	Size
Bahrain, Egypt, Jordan, UAE	16 July	45,000
Peru	10 Sept.	6000
Argentina	16 Sept.	3000
Morocco	13 Oct.	600

CanSino	Start date	Size
Russia	11 Sept.	500
Pakistan, Mexico, Argentina, Chile	15 Sept.	40,000

While the 'western media' remains largely focused on the efforts of four or five enterprises in the USA and Western Europe, China has also been busy with its own vaccine programmes that have been less publicised. Ironically, since it seems to have controlled Covid spread more effectively than many of the other large industrialised nations, it has had to conduct its trials outside its own borders, collaboratively in other countries.

https://www.sciencemag.org/news/2020/11/global-push-COVID-19-vaccines-china-aims-win-friends-and-cut-

Editorial

In the absence of any generally effective treatment against the corona virus infection that has spread across the globe, all hopes have been pinned on the earliest development of a vaccine to control the pandemic. That several have appeared in record time should, one would have thought, be greeted with the loudest of cheers, but ironically the relief, hope and enthusiasm for these has been tempered with anxiety and uncertainty, trepidation and even suspicion. *Why?*

Probably the three main reasons are
i), the record speed of getting them arouses concern about side effects and long term effects
ii), distrust of big Pharma (ie profit motive)
iii), not seeing need for a medication if one is not ill

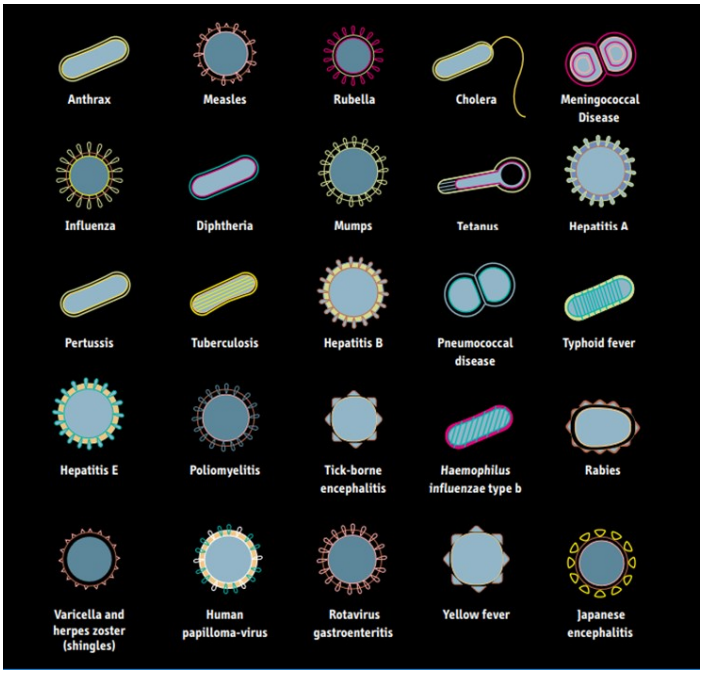
The advent of social media and instant access to information is a double-edged sword; while educating, it also has the capacity to deliver incorrect, fake and often damaging information whether intentionally or otherwise.

In the current situation, mixed with sound scientific information and advice there is a deluge of often confusing and contradictory messages regarding the emergence and application of the new vaccines. Unfortunately, much of this emanates not only from uninformed or malicious sources but worryingly often from apparently bonafide 'medical experts' with alternative opinions, sometimes further manipulated by influential world leaders for political or monetary gain.

To be clear, a vaccine is the same as any other drug and will be associated with a variable degree of failure and side effects due to biological variation in humans, particularly in ethnicity, age, sex and general state of health.

We already have more than 20-30 routinely administered vaccines that have helped to virtually eradicate or restrict previously devastating infectious diseases (see fig). So why the controversy with Covid vaccines?

One of the issues that has been raised regarding the use of these novel RNA vaccines is that the viral RNA will become integrated into our genetic makeup and then cannot be reversed or removed if necessary. This is an incorrect notion based on a lack of understanding of the biology of viral infection. Several viral elements are need for viral RNA (which must first be copied into DNA by viral reverse transcriptase enzyme) to be integrated into host chromosomes, including terminal repeat elements. None of these are present in the viral vaccine, which is composed of only a very small part of the total viral RNA genome.



Drug (and vaccine) development is traditionally a long expensive process with high failure rate, resulting in economic consequences for the pharmaceutical developer. The majority of the cost comes *after* a drug has passed initial laboratory and animal screening and goes into clinical human trials. The latter involves a series of processes with typical timelines of several years depending on the prevalence of the target disease and its etiology. *It may surprise some, however, that often the shortest parts are the actual testing* (and this would be particularly true for vaccines where an end point can be achieved in a matter of weeks). Aside from consideration of the long term effects of having *any* drug in your body, what takes the longest times are the recruitment of volunteers and patients, the analysis of often complex data, and the regulatory approvals from government bodies that are required at every stage of the operation- which involves wide consultation with expert reviewers and other stakeholders. And you can imagine, with the large number of pending applications, it can be months before a particular filing is even discussed, let alone processed for review. Normally a sizeable pharmaceutical company would have tens of drugs in their pipeline, waiting in this queue, and their resources and attention would also be divided between these.

In complete contrast to the above, with the Covid, vast resources (both private and governmental) have been specifically dedicated to this single task, resulting in rapid progress through the initial laboratory construction and animal testing of different types of vaccines. This has been followed by equally rapid human testing made possible by *facilitated* recruitment and *immediate prioritised* attention and processing of applications by the regulatory authorities (eg FDA in the US and EMA in Europe). Approval can be given as a *"temporary*

authorisation for emergency use" but detailed analyses of the submissions will continue to be scrutinised.

This is 'cutting red tape' *not* 'cutting corners'

The trials for the main contender vaccines are large enough to be reliable. But of course, as vaccines are administered to several millions, as opposed to 20,000 trialists, adverse reactions are to be expected as happens even with the safest of our drugs such as antibiotics. Indeed, with the current roll out of the Pfizer/BioNTech vaccine in the UK, just a few bad reactions in specific individuals prone to allergies, has caused a totally disproportionate reaction in the social media, due to lack of proper understanding.

So the speed of development of these vaccines, as explained, is not a good reason against taking them, given the circumstances.

In terms of trust, similar consideration should apply here as with any other drug or indeed any product, as everything has a profit motive attached. Nutritional supplements (often highly priced) for example are widely and readily consumed – entirely on trust, with little or no real medical evidence of benefit.

Taking this medication as a healthy person (prophylaxis) is possibly the most difficult issue to reconcile and there is no right answer. There are many things we can take or do as preventive measures to maintain our health status, and our choice in this is often an arbitrary one, and again may well be based upon scant evidence.

In the end, the choice may be made for us one way or the other, either by government mandate or by requirement for certain activities such as boarding a plane.

Stop Press- Recent press announcements (19th December), regarding mutations arising in the viral genome (and appearing at a high rate in infected individuals in the UK) have just raised further concerns about the efficacy of all current vaccines.

Mutations in viruses are actually common and are due to either selective adaptation or random replication errors; either way it can result in small changes in the amino acid sequence of its proteins. The concern is that the antibodies formed against the 'old components' being used in the (preventive) vaccine may not work against a future infecting virus whose spike protein has changed- *a kind of moving target*.

Indeed, this has been a major factor in the failure to produce effective vaccines against HIV (and also SARS and MERS), resulting in over 42 million infected people, with 1.7m fatalities this year alone (approximately the same as the number of recorded COVID-19 deaths).

However, in this context it should also be noted that an advantage of using vaccines based on mRNA is that they can be quickly adapted to include any new sequences that are found in the virus- and this may only require minimal additional Regulatory compliance.

Until vaccinated individuals have been tested for the presence of antibodies against corona virus and *shown* to be protected against the virus, we will not know whether the vaccine has been effective or protective.

How this will be done has not been made clear. There are two obvious ways. We can wait to see if there is a significant decline in the infection rate over the next few months following mass vaccination (indirect method)- OR -volunteers receiving vaccinations will have to be deliberately exposed to the virus in meaningful numbers.

Thus, the arrival of the vaccines should not make us complacent and public health vigilance, preparedness, and control measures will continue for the forseeable future.

Yunus Luqmani (ed.)

Q &As specifically for the Pfizer/BioNTech vaccine

Emergency authorisation has recently made a vaccine from Pfizer and BioNTech available in the UK where it has already being widely administered.

How effective is the vaccine?

The phase 3 trials involved 42,000 people, about half of whom got the vaccine and the rest a placebo. In total, 170 people fell ill with COVID-19. Only eight of them were in the vaccine group; 162 had received the placebo. So 5% of cases were in the vaccine group, which is where the 95% effectiveness figure comes from: WHO has said it would be happy with 50%

What is in the vaccine?

The active ingredient is messenger RNA that carries instructions for making the virus's spike protein, which it uses to gain entry to cells. The mRNA is synthetic, not extracted from actual viruses. It is delivered inside a tiny lipid nanoparticle suspended in saline solution and injected into muscle tissue in the upper arm. The mRNA is hopefully taken up by immune cells, which use it to make the spike protein, just as they would do if they had become infected with the actual virus.

The spike protein is recognised as foreign by the immune system, which then mounts an attack against it with antibodies produced by B cells and T cells are

activated, An immune memory is also laid down, which means the immune system has learned how to defeat the pathogen and is primed to mount a swift response if it encounters the coronavirus again.

How long does the immune memory last?
WHO says that a minimum of six months would be acceptable. BioNTech expect protection to last months or even years. As with some other common vaccines annual boosters may be needed.

How long does it take for immunity to develop fully after vaccination?
The trial began assessing immunity 7 days after the second shot; BioNTech say protective immunity builds up within four weeks or earlier of the first dose

What happens to the mRNA in the body?
It is active for a few days then degrades rapidly.

It's a two-shot vaccine, so what happens if people miss their 2nd shot? Is a single shot still protective?
Two shots are needed; the second shot is required to attain immunity. The gap between doses in the trial ranged between 19-42 days. Only 2% of people in the trial missed their second dose so it isn't entirely clear what happens under those circumstances.

Are there any side effects?
Sometimes, but they are mild. In the trial, the vaccine was generally well-tolerated, and an independent data monitoring committee reported no serious safety concerns. Worst side effects were fatigue and headaches after the second dose; pain at the injection site and muscle pain -common reactions you would have with vaccination

Does it work in older people and vulnerable groups?
Yes. Trial participants were aged up to 85y, and the efficacy in people over 65 was 94%
The vaccine appears to be equally effective regardless of recipients' age, sex and ethnicity, according to BioNTech. It has been tested extensively in people who have already had the virus and doesn't cause any ill effects. It has also been tested in people with "stable" pre-existing conditions – also known as comorbidities – including diabetes, cancer, hepatitis B, hepatitis C and well-managed HIV. Their response was as good as anyone else's.

Does it stop people from catching and transmitting the virus?
The trial was designed to test for symptomatic COVID-

19 and confirmed infection with the virus. Assessing whether the vaccine prevents transmission- which is probably a prerequisite for attaining vaccine-induced herd immunity -is under investigation.

Some vaccines can paradoxically make a disease worse through a process called antibody-enhanced disease. Is that a risk?
Yes, theoretically. But it hasn't been seen with this vaccine or any other against COVID-19, and hasn't occurred naturally, as sometimes happens with other viruses.

Has the full data from the trial been published yet?
No, it hasn't, but there is nothing sinister about that. Companies can release news to the market as soon as they have it but publishing it in a top-ranking peer-reviewed scientific journal can take some time.

Regulatory Process- What does "temporary authorisation for emergency use" mean?
The UK's Medicines and Healthcare products Regulatory Agency (MHRA) has expedited the approval process in recognition of a public health emergency, and could rescind the approval just as quickly. But that is highly unlikely as it says it has done a thorough assessment of the safety and efficacy data and has seen nothing to give it reason not to approve.

It all happened very quickly, can we be confident corners weren't cut?
Yes. The MHRA is an independent body and so is the Commission on Human Medicines, which also had a say in the decision to approve the vaccine in the UK. Even though the MHRA only received the full clinical trial data just over a week ago, the vaccine developers have been submitting information since October, which has been subject to ongoing review.

The European Medicines Agency, has said that its process for assuring the safety and efficacy of the vaccine is based on more evidence and more checks than the emergency authorisation used in the UK. According to the vaccine developers, the MHRA asked for exactly the same amount of information as any other regulatory agency.

Are other countries likely to approve the vaccine soon as well?

Yes. Pfizer/BioNTech have also applied for approval in the US (just granted), EU, Australia, Canada, Japan and New Zealand, and say they are preparing to submit applications to other regulatory agencies around the world. Decisions are expected from the EU this month.

Logistics- How many doses is the UK getting?

In total, the UK government has pre-ordered 40 million single doses, which is enough for 18 million people assuming double dosing and about 10% wastage. But it won't get all 40 million at once. The full order will be delivered in batches over the course of 2020 and 2021.

The first batches currently being packaged at Pfizer's vaccine factory in Puurs, Belgium, are already being dispatched to the UK and vaccination has started.

Doesn't the vaccine require complicated cold storage?

Yes and no. For long-term storage- meaning for six months or so-the vaccine has to be kept at -70°C, which requires specialist cooling equipment. But Pfizer has invented a distribution container that keeps the vaccine at that temperature for 10 days if unopened. These containers can also be used for temporary storage in a vaccination facility for up to 30 days as long as they are replenished with dry ice every five days. Once thawed, the vaccine can be stored in a regular fridge at 2-8°C for up to five days.

Where will people be vaccinated?

The usual places: GP surgeries, health centres and hospitals. People will be invited by the NHS. The entire supply is going to the various NHS bodies in the UK and nobody will be able to jump the queue by buying a vaccine privately, according to Pfizer.

Could something still go wrong?

Yes, but that is highly unlikely. Vaccine effectiveness in the real world is almost always lower than efficacy in trials, but the drop-off would have to be spectacular to dip below the 50% threshold accepted by the WHO.

There could still be rare severe adverse effects down the road, especially as mRNA vaccines are a new technology and have never been rolled out on a massive scale before.

Vaccine clinical trials aren't big or long enough to rule out rare but serious side effects, which sometimes appear months or even years after vaccination. People who have been vaccinated will be followed up for two years.

Source:
https://www.newscientist.com/article/2261805-everything-you-need-to-know-about-the-pfizer-biontech-COVID-19-vaccine/#ixzz6g0jq6juW

Why does Pfizer/BioNTech's COVID-19 vaccine need to be kept colder than Antarctica?

Pfizer and Moderna have announced promising interim results for their vaccine candidates, raising hopes that the end of the pandemic may be in sight. Although these two vaccines have now been authorised by UK and US authorities, distributing them presents a no less daunting challenge.

Why? Because the Pfizer COVID-19 vaccine needs to be stored at -70^{0}C. Health care providers will need to store it either in dry ice for shorter stints or in specialised freezers.

Moderna has said that its vaccine needs to be frozen too, but only at -20^{0}C, more like a regular freezer, so can be distributed in more of a standard fashion.

Presumably to boost its position, Pfizer has tried to calm concerns about the challenges presented by these cold temperatures. It has designed its own packaging (nicknamed "the pizza box") to keep doses super cold with dry ice, so that they can be stored for a few weeks without specialised freezers.

Why the deep freeze?

Both vaccine candidates use a new approach to stimulate the body's immune defenses. This uses mRNA, which is introduced into the body and taken up by cells which, thinking its their own genetic material, use this instruction to make one particular coronavirus protein.

That protein, however, if it enters the bloodstream

elicits an immune response as if there was a real coronavirus infection. To be clear, since it's only one single viral protein that is made, there's no way the vaccine could actually infect someone or make them sick with COVID-19. Then, if someone who was immunised gets exposed to the coronavirus later on, their body's immune system will be able to fight it off more easily and they're more likely to avoid serious illness since now they will have a reservoir of primed T and B lymphocytes

It's a vaccine technology that's so new, no mRNA vaccines have ever been approved by the FDA. Vaccines made from mRNA can be made much faster. The problem is that mRNA is really easily destroyed by a very active enzyme called ribonuclease, which is the cell's protective mechanism to destroy RNA that has inadvertently escaped from inside cells where it belongs.

The first step was to modify the mRNA nucleosides-the "building blocks" of the RNA vaccine, into more stable versions. The next step was to use lipid nanoparticles. But even with the stabilised building blocks and lipid coating, the mRNA could still be easily degraded, which is why the vaccine is frozen to reduce ribonuclease activity. Because the specific formulations are secret, it's not clear exactly why these two mRNA vaccines have different temperature requirements.

A Moderna spokesperson explained that its vaccine doesn't need to be kept so cold because of its particular "lipid nanoparticle properties and structure" .

Temperature requirements call for different distribution plans

A Pfizer scientist told a CDC advisory council that it's special container is not supposed to be opened more than twice a day and needs to be closed within one minute of opening. That's a tremendous logistical issue not only in the US. but more especially outside the Western world. Once it's thawed, the vaccine can be refrigerated for five days.

Moderna says its vaccine candidate is stable at regular freezer temperature -20^{0}C up to six months, and after thawing it can last in the refrigerator for 30 days. It can also be kept at room temperature for up to 12h. This is useful for health care workers in the field, because now the vaccine doesn't need to go in and out of the refrigerator each time it's administered.

The Centres for Disease Control and Prevention, the US federal agency in charge of vaccine distribution and decisions about which groups receive the first shots, has tried to discourage health departments and hospitals from buying expensive freezers to accommodate the Pfizer vaccine. But according to a recent report in Stat, wealthier hospitals are buying up specialised freezers, raising concerns that hospitals with fewer resources or in rural areas will be left behind.

Moderna's announcement may temper those fears, although since Pfizer's vaccine doses will be urgently needed as well, it doesn't mean that ultra-cold storage is no longer an issue.

Maintaining the cold chain for coronavirus vaccines won't be easy in most parts of the world including most of Central Asia, much of India and southeast Asia, Latin America except for the largest countries, and all but a tiny corner of Africa where Investment in infrastructure and cooling technology lags behind the high-speed leap that vaccine development has taken this year due to the virus.

To uphold the cold chain in developing nations, international organisations have overseen the installation of tens of thousands of solar-powered vaccine refrigerators. Keeping vaccines at stable temperatures from the time they are made until they are given to patients also requires mobile refrigeration, reliable electricity, sound roads and advance planning.

For poor countries, the best chance of receiving a coronavirus vaccine is through the Covax initiative, led by WHO and the Gavi vaccine alliance. Their goal is to place orders for multiple promising vaccine candidates and to allocate the successful ones equitably.

UNICEF began laying the global distribution groundwork months ago, in Copenhagen. At the world's largest humanitarian aid warehouse, logistics staff are trying to foresee shortages by learning from the past, especially the spring chaos surrounding global shortages of masks and other protective gear that were commandeered off airport tarmacs or stolen and traded on the black market.

Opportunities for vaccines to be lost expand the farther a vaccine travels. DHL estimated that 15,000 cargo flights would be required to vaccinate the entire planet against COVID-19, stretching global capacity for aircraft and potentially supplies of dry ice.

Gavi and UNICEF worked before the pandemic to supply much of Africa and Asia with refrigeration for vaccines, fitting out 40,000 facilities since 2017. UNICEF is now offering governments a checklist of what they will need to maintain a vaccine supply chain and asking them to develop a plan.

Cracks in the global cold chain start once vaccines leave the factory. Container ships are not equipped to refrigerate pharmaceutical products with a limited shelf life. Shipping vaccines by air costs a lot more, and air cargo traffic is only now rebounding from pandemic-related border closures.

Even when flights are cold and frequent enough, air freight carries other potential hazards. WHO estimates that as much as half of vaccines globally are lost to wastage, sometimes due to heat exposure or vials breaking while in transit. With coronavirus vaccines, which will be one of the world's most sought-after products, theft is also a danger.

Temperature-sensitive labels that change colour when a vaccine is exposed to heat too long and no longer safe to use, and live delivery tracking to ensure vaccines reach their destinations as intended also have allowed for progress in delivering safe shots.

By the end of the year, UNICEF expects to have 520 million syringes pre-positioned for coronavirus vaccines in the developing world and maps of where the refrigeration needs are greatest to ensure that these supplies arrive in countries by the time the vaccines do.

Reference:
www.npr.org/sections/health-shots/2020/11/17/ 935563377/

Could alternative vaccines become available soon?

As mentioned in the first article, there are many other vaccines under development worldwide. Aside from the Moderna and BioNTech ones, one from AstraZeneca and Oxford University has attracted particular attention, especially in the UK.

'Encouraging' results for older people from Oxford COVID-19 Vaccine (Nov 19, 2020)

The Oxford ChAdOx1 nCoV-19 vaccine, was greeted with initial excitement after encouraging immune responses in older adults were published in *The Lancet,* but doubts have crept in since, over some discrepancies in the data, and further investigations are underway

In phase 2 trials, evaluated in 560 healthy adult volunteers, similar safety and immunogenicity results were seen in participants aged 56y and older to those seen in adults aged 18-55y, and was also better tolerated in older people compared to younger adults. Those aged over 55y were also split into groups and either given a single dose of vaccine, or two doses 28 days apart. The vaccine induces neutralising antibodies and T-cell responses in all age groups from 18-70+ irrespective of whether participants received one or two doses. A T-cell response peaked at 14 days after the first dose of vaccination, and an antibody response within 28 days of the booster dose of vaccination.

According to the investigators side effects were those normally seen after a flu vaccine, or any other vaccines- so, tiredness, headaches, muscle aches. The data clearly showed that as you got older, the symptoms were less troublesome. The early findings are likely to boost hopes that prioritising older people for vaccination could be justified. However, doubts remain whether older people in care homes would respond as well as the healthy older adults in the trial.

At one month after giving two doses of the vaccine, all age groups showed a similar level of antibody response. Some age-related differences in the cellular immune response were recorded which require further investigation. However, if the immune measures recorded in the phase 2 part of this study correlate with protection from SARS-CoV-2, then positive outcomes may be expected from the larger phase 3 trials; interim results expected in the coming weeks.

It is reported that the UK Government has ordered 100 million doses of the Oxford vaccine. That is more than the 40 million doses of the Pfizer-BioNTech and the five million of the Moderna vaccine.

Source: *Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): single-blind, randomised, controlled, phase 2/3 trial. Lancet November 18, 2020 doi.org/10.1016/S0140-6736(20)32466-1*

Race to find 'warm' Covid vaccine to solve issue of cold storage

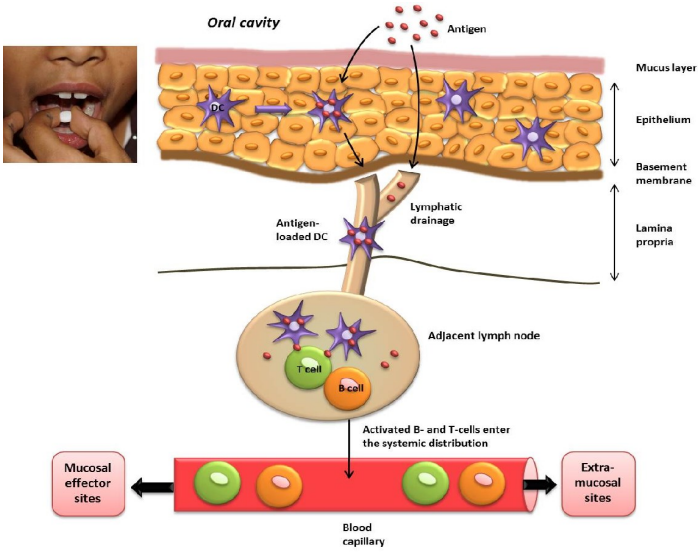
With the cold storage logistics, current vaccines could be out of reach for two-thirds of the world's population.

Scientists are exploring whether future COVID-19 vaccines could be in the form of inhaled vapours, powders, tablets, oral drops or intranasal sprays that could virtually eliminate the need both for complex transportation as well as the need for medical staff to administer it.

Apart from a few exceptions (including the polio vaccine) almost every vaccine in use comes with a needle for injection. But a few researchers are hoping to harness the immune arsenal of the mucous membranes lining the nose, mouth, lungs and digestive tract, regions typically colonised by respiratory viruses- including COVID-19.

Over the last decade, it's been more recognised that protective mechanisms exist at the mucosal surface. They are specialised to protect those tissues against infection more quickly, and perhaps more completely, than waiting for the antibodies to come from the blood.

Exploiting mucosal immunity has potential advantages. Using oral or nasal passages could help people with



Taken from A Borde Materials Science 2012 Corpus ID: 54170674

needle phobia, and also allow people to vaccinate themselves and be easily and comfortably administered to babies and young children. It cannot be overstated how much impact that would have on rolling out vaccines to low- and middle-income settings.

Crucially, some of these alternatives may be able to be stored at room temperature.

Researchers at the Indian Institute of Science in Bengaluru believe their *"warm" vaccine* against COVID-19 could survive in both powder form, and in solution-withstanding hot summer temperatures across India.

Their formulation is still being tested on guinea pigs and may take more than a year to be approved, but if it comes through, they may have a heat-stable vaccine that can be turned into a powder and easily transported across the country.

Vaxart, a San Francisco-based biotechnology company, is testing a tablet-form COVID-19 vaccine that would be easily transportable.

Targeting mucosal tissues has the potential to produce so-called "sterilising immunity", the complete elimination of infection in the body, thereby reducing transmission.

Altimmune, is another company developing an intranasal COVID-19 vaccine, but warn that "it is quite likely masks will be here to stay even after the first crop of vaccines hit the market because you may be protected [from the disease], but you're not protected from spreading the virus". Neither of these companies expect to have their formulations ready for regulatory review before the end of 2021.

There have been hiccups in the quest for non-injectable vaccines. For example, an existing nasal spray flu vaccine has been shown to outperform flu shots in young children, but is less effective in adults.

Another German biotech group, *Curevac,* plans to test its mRNA vaccine on 35,000 participants across Europe and Latin America. Its phase 2b portion of the clinical trial will generate safety, reactogenicity and immunogenicity data to inform the start of the phase 3. It will randomise 4,000 subjects across two age cohorts; 18-60y and 61+ y to take two doses of CVnCoV or placebo four weeks apart.

Once 1,000 subjects have at least one week of follow-up after the first vaccination, the Data and Safety Monitoring Board will review the data and make a decision on the phase 3 if it supports the larger study. The phase 3 study will recruit 32,500 subjects and pool data from the phase 2b and 3 portions.

The co-primary endpoints of the trial cover prevention of all COVID-19 cases and just severe cases. The first interim review is set to take place when 56 people have developed COVID-19, with later reviews scheduled for 111 and 185 cases; estimated for around five months after the first vaccination. If seven cases or fewer are in the CVnCoV arm at that point, CureVac will be able to claim success and likely start preparing for regulatory filings.

Given the phase 3 results from other mRNA vaccines, it would be surprising if CureVac's candidate is completely ineffective. However, as AstraZeneca has found, BioNTech, Pfizer and Moderna have reset expectations for COVID-19 vaccines. CureVac will need 90%-plus efficacy and a good safety profile to join the top tier of COVID-19 vaccines.

Based on the available data, and with the caveat that cross-trial comparisons can be unreliable, the CureVac candidate appears to trigger roughly comparable immune responses to other vaccines but have a somewhat worse tolerability profile. A higher proportion of subjects who received 12 µg of CVnCoV had moderate to severe fever, headache and fatigue than was seen in the BioNTech-Pfizer phase 3, although the CureVac results come from a small cohort presented last month.

Source: *https://www.fiercebiotech.com/biotech/curevac-starts-late-phase-clinical-trial-COVID-19-vaccine*

How to ensure COVID-19 vaccines actually work?

After the US FDA approves a vaccine or authorises a vaccine, following clinical trials, for emergency use, CDC and other federal partners continue to study how well it works under real-world conditions. Many of these assessments build on existing CDC programmes, such as the Emerging Infections Programme and Coronavirus Disease 2019-Associated Hospitalisation Surveillance Network (COVID-NET)

Do clinical trial results show whether vaccines are effective?

Yes. Clinical trials provide data about how well a vaccine prevents an infectious disease and about how safe it is. FDA evaluates these data, as well as manufacturing information, to assess the safety and effectiveness of vaccines. FDA then decides whether to approve or authorise it for emergency use in the US.

Why is vaccine effectiveness continued to be assessed in real-world conditions?

There are many factors that can affect a vaccine's effectiveness in real-world situations. These factors include vaccine transportation, storage or even how patients are vaccinated, differences in the underlying medical conditions of people vaccinated in the real-world compared to those in the clinical trials, etc.

How will the effectiveness of COVID-19 vaccines be evaluated in real-world conditions?

Experts are working on many different types of real-world vaccine effectiveness assessments, and each uses a different method as described below.

Case-control studies: These assessments will include cases (people who have the virus that causes COVID-19) and controls (who do not have the virus that causes COVID-19). Experts will look to see if the cases were less likely to have received the vaccine than controls, which would show the vaccine is working.

Test-negative design: This is a special type of case-control study. These assessments will enroll people who are seeking medical care for symptoms that could be due to COVID-19. Experts will then compare the COVID-19 vaccination status of those who test positive (meaning they have COVID-19) to those who test negative (meaning they do not have COVID-19).

Cohort studies: These assessments will follow people who have and haven't had a COVID-19 vaccine for several months to see if getting vaccinated protects them from getting the disease. This can be done in prospectively retrospectively) using data that were already collected, such as information in participants' electronic health records (medical records).

Screening method: These assessments look at vaccination coverage among a group of cases (eg cases detected through ongoing COVID-19 surveillance) and compares it with vaccination coverage among the population where those cases come from (for example people from the same state). By comparing coverage among these two groups, researchers can get an early estimate of whether a vaccine is working as expected.

Ecologic analyses: These assessments look at groups of people – such as those in different geographic locations or at different times – and find out how many people were vaccinated and how many people were diagnosed with COVID-19. These analyses may be hard to interpret since the number of COVID-19 illnesses has changed rapidly over time and in different places.

Will assessments determine if the vaccines protect people from severe COVID-19 illness?

Yes. Severe illness from COVID-19 is defined as needing care in a hospital or intensive care unit (ICU), needing to be on a ventilator, or dying due to COVID-19. Experts will assess how well COVID-19 vaccines protect people against severe illness using case-control studies among hospitalized patients. Experts will also use electronic health record cohort studies to see if people hospitalised with COVID-19 received the vaccine or not.

Will assessments provide information about how well vaccines protect against less severe COVID-19 illness?

Yes. CDC will use case-control studies to assess how well COVID-19 vaccines protect people against less severe forms of COVID-19; eg. people with COVID-19 who need to visit a doctor but don't need hospitalisation

What groups of people will be included in the real-world vaccine assessments?

CDC is working to make sure real-world vaccine assessments include diverse groups of people, such as healthcare personnel, essential workers, older adults and those living in nursing homes, people with underlying medical conditions, racial and ethnic minority groups, and tribal nations.

Reference:
www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness.html

COVID-19 diagnostics: saliva tests compared to swabs

Since the early days of the pandemic, clinicians and researchers have been looking for alternatives to nasopharyngeal swabs. Although still considered the gold standard, these tests require more supplies, place health care workers in closer contact with potentially infected individuals, and are expensive for mass testing.

Saliva is a low-cost, easy alternative, but its efficacy and accuracy remain points of contention.

Even as large universities have begun rolling out ambitious, saliva-based initiatives on campuses across the US and other countries, private companies looking to develop rapid, in-home diagnostic tests have moved away from such tools. Trials of saliva based testing being deployed in the field have yielded mixed results, and it remains unknown under what conditions it can be rolled into the existing testing framework.

Epidemiologists at Yale have studied use of saliva as a source of genetic material for the last decade, and more recently investigated it in testing for COVID-19. They report that across the almost 30 studies analysed, it's almost half and half". Among 70 patients admitted to Yale-New Haven Hospital with suspected cases of CovidVID-19, saliva samples often contained more copies of SARS-CoV-2 than swab samples, and a higher percentage of saliva samples were positive up to 10 days after initial diagnosis. When applied to 495 health care workers, saliva tests identified two more asymptomatic cases than swabs, leading the team to conclude, "our findings provide support for the potential of saliva specimens in the diagnosis of SARS-CoV-2 infection". Thus in controlled health care settings, at least, it seems that saliva can perform comparably to nasopharyngeal swabs.

Saliva tests on college campuses

Used in the proper context, saliva may still be useful in tracking down even asymptomatic infections. College campuses across the US, for example, are using saliva-based tests to screen students and staff.

A pharmacologist at the University of South Carolina developed her school's saliva test and recently began testing as many as 1,200 student volunteers a day using Banister's saliva test, hoping to catch invisible infections. Rather than testing each person once, the university opened testing on a repeat basis, with results within 24 h. Through this mass testing, the university has identified clusters in campus fraternities and sororities, and by October 9 had 33 active cases.

Even if the tests are not as sensitive as swabs, the sheer number and repetition makes it possible to catch an infection that may have been missed the day before. Testing on this scale with saliva also requires fewer supplies, such as swabs and reagents that have become scarce during the pandemic, and people are more likely to do repeated tests if they only need to spit into a cup.

They also recruited two students living in the same house -one with a confirmed diagnosis and one at risk - to undergo pairwise, daily sampling for comparisons between swabs and saliva. Over the first two weeks of the infection, there was a "remarkable" concurrence between viral load detected in saliva and nasal swabs in the positive patient meaning that saliva is as sensitive as the nasopharyngeal swab.

After two weeks, the two samples diverged, with swabs continuing to detect virus for several more days. They attribute this finding not to a higher sensitivity of the swab test, but to the fact that saliva turns over much more quickly in the mouth, while the lungs and nasal cavity can hold the virus for longer, leading to positive results even when a person may no longer be infectious. How a positive diagnosis relates to infectiousness -and how one should use PCR numbers to decide if someone should remain quarantined isn't yet clear.

Scientists at Tulane University have developed a COVID -19 test that can be read using a smartphone to aid in widening testing capacity in community settings.

Using the gene-editing technology, CRISPR, the assay can identify very small amounts of SARS-CoV-2 virus RNA in saliva in just 15 min.

The PCR tests need a laboratory with sophisticated equipment and trained professionals whereas this saliva-based test alleviates the need for lab processing and can potentially increase testing capacity in outpatient clinics, community settings and other sites quickly.

Also, this latest test does not need an RNA isolation step; saliva is mixed with an assay solution on an assay chip and heated to amplify a small region of viral RNA. A modified CRISPR complex that has a guide RNA specific for this virus RNA region rapidly attaches and cleaves both the amplified RNA region and a tagged DNA probe to give a fluorescent signal that can be read using a a prototype smartphone-based fluorescent microscope device in 15-30 min

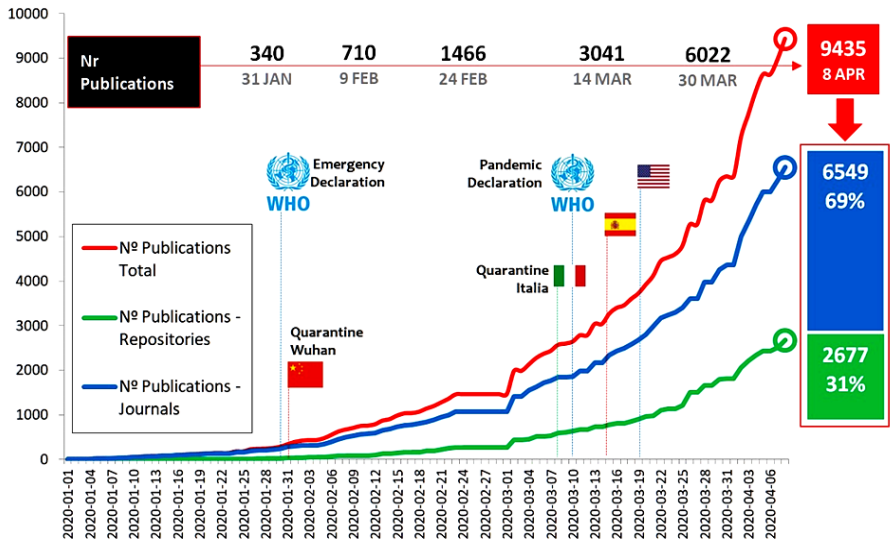
The researchers have sought emergency use authorisation (EUA) from FDA.

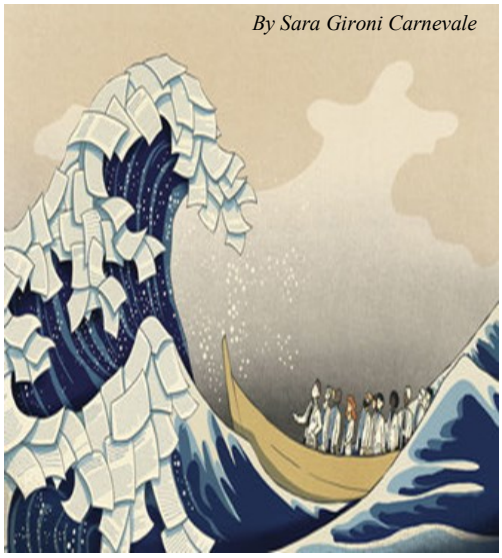
Reference: *www.the-scientist.com/news-opinion/COVID-19-diagnostics-how-do-saliva-tests-compare-to-swabs*

The other pandemic– a deluge of COVID-19 publications

Accumulated publications on COVID-19 in Dimensions classified by source

www.infodocket.com/2020/04/16/research-article-daily-growth-rate-of-scientific-production-on-COVID-19-analysis-in-databases-and-open-access-repositories/





The sudden explosion in research articles on COVID-19 has few parallels in the medical literature. Since start of 2020 till May, Dimensions has recorded an explosive growth of data on COVID-19. As of end April, this amounted to more than 19,250 publications, 250 datasets, 16 grants, 270 patents and 1,900 clinical trials-fed into more than 200 policy documents. By time of writing publication numbers will have ballooned to >100,000. However, crucial medical efforts are being drowned in an 'unholy scramble' by so-called researchers and authors who may not even have actually ever handled COVID-19 cases or themselves done any research! This may be exacerbated by mismanagement even by many reputable scientific journals who are sometimes being forced to retract articles published in haste. This creates a trust issue in the scientific and ultimately public arena and hampers release of genuine information.

It is imperative to enforce stricter controls and follow due diligence before allowing scientific articles into the public domain- so that genuine studies of first-hand experience of handling/management of COVID-19 patients, and authentic research is not submerged in a flood of unreliable, possibly dangerously misleading and even completely fake publications.

The world of scientific, technical, and medical publishing has become increasingly inundated with low quality and often highly questionable research submissions, often to be found in so-called 'predatory' journals that have sprung up in recent years to make 'quick' money by collecting article processing charges and by bypassing the process of careful scrutiny and genuine peer review by subject experts. Lamentably, in the wake of this pandemic there has been a 'relaxing' of publishing norms and controls even among some of the standard benchmark journals.

With online systems, initial publication of work which has not yet undergone a rigorous peer-review process can be placed by journals in the public domain for early dissemination, feedback, critique, designed to help improve their paper for later submission and formal publication. And, other investigators gain early access to work which may help them in their own research. Such preprints should not be circulated in the general public as established information nor used to formulate or modify public health policies. However, the insatiable demand to provide 'latest' information in hourly news bulletins has led reporters with none or very limited scientific training to translate preprint information hurriedly into 'breaking news'. This has led to much confusion among the public.

An army of data scientists, software developers and journal publishers (some backed by large technology firms and the US Administration) is racing to create digital collections holding thousands of freely available papers, and build data-mining and search tools that can help researchers quickly find the information they seek. Many teams are trying to clean things up with at least two basic strategies: creating easily accessible paper collections, including a few carefully curated collections designed to highlight strong papers; and building automated search tools that use artificial intelligence technologies to cut through the noise.

The CORD-19 data set and 2019 Novel Coronavirus Research Compendium are efforts to identify and collate quality papers as well as develop machine learning algorithms to trawl through them.

Covid myths

In the absence of an effective treatment, a pleithora of remedies has appeared on the internet, many of which are quite dangerous. Even some 'bonafide' medical practitioners have proposed several existing drugs (re-purposed), based on anecdotal and often flimsy evidence that has later proved to be ineffectual at best. Only advice from official, reputable medical sources should be followed.
Here are corrections to some common circulating misconceptions and false notions, in some order of seriousness:

- **The vast majority of people who get corona virus infection are either asymptomatic or quickly recover from it**
- Aside from new vaccines, there are ***no*** medicines that can prevent or treat COVID-19– may only provide relief
- COVID-19 is caused by a virus, not by bacteria
- There are currently *no* drugs licensed for the treatment or prevention of COVID-19
- **Spraying and introducing bleach or other disinfectant into your body will *not* protect you against COVID-19 and can be extremely dangerous**
- **Drinking alcohol like vodka does not protect you against COVID-19 and can be dangerous**
- **Drinking methanol, ethanol or bleach does not prevent or cure COVID-19 and can be extremely dangerous**
- Catching COVID-19 from surfaces is very low—mostly it is from direct contact with infected people through saliva or nasal secretions
- Prolonged use of medical masks *when properly worn*, does not cause CO_2 intoxication nor oxygen deficiency
- However, people should not wear masks while exercising/running
- Exposing yourself to the sun or temperatures higher than 25°C does not protect you from COVID-19
- Ultra-violet (UV) lamps should not be used to disinfect hands or other areas of your skin
- Studies show hydroxychloroquine does not have clinical benefits in treating COVID-19
- Thermal scanners measure body temperature to detect fever —they cannot detect COVID-19
- Rinsing your nose with saline does not prevent or cure COVID-19
- Vaccines against pneumonia do not protect against the COVID-19 virus
- COVID-19 is not transmitted through houseflies or other insects
- The COVID-19 virus cannot be spread through mosquito bites
- 5G mobile networks do not spread COVID-19
- People of all ages can be infected by the COVID-19 virus but catching it does not mean you will have it for life
- COVID-19 virus spreads in hot/humid climates as well as cold ones; cold weather cannot kill the COVID-19 virus
- Antibiotics are not effective against viruses and cannot prevent or treat COVID-19
- Vitamin/mineral supplements may have general health benefits and boost immunity but cannot cure COVID-19
- Eating garlic may have health benefits but it does not prevent COVID-19
- Adding pepper to your soup or other meals does not prevent or cure COVID-19
- Taking a hot bath or using hair dryers does not kill corona or other virus or prevent COVID-19
- The likelihood of shoes spreading COVID-19 is very low

Answers to: Test your knowledge

Correct answers: 1-a; 2-b; 3-a; 4-a; 5-c; 6-c; 7-d; 8-d; 9-c; 10-a

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