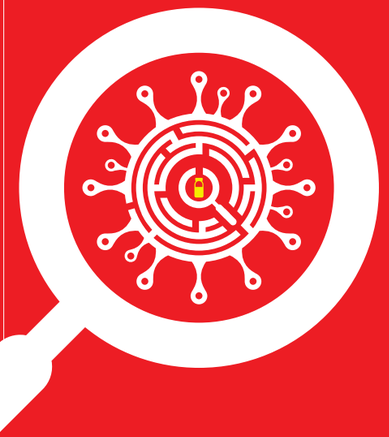
# IN SEARCH OF A VACCINE

**We look at the frontline of vaccine development and how and when immunity to COVID-19 may be a possibility.**

On 10 April this year, a month after the World Health Organization announced that the COVID-19 outbreak could be considered a pandemic, the global death toll reached more than 100,000 people. Nearly two million cases of the disease have been confirmed worldwide. With nearly all regions of the world affected by the virus SARS-CoV-2, a novel type of coronavirus that first emerged in central China at the end of 2019, this can be considered the worst pandemic in the world's recent history.

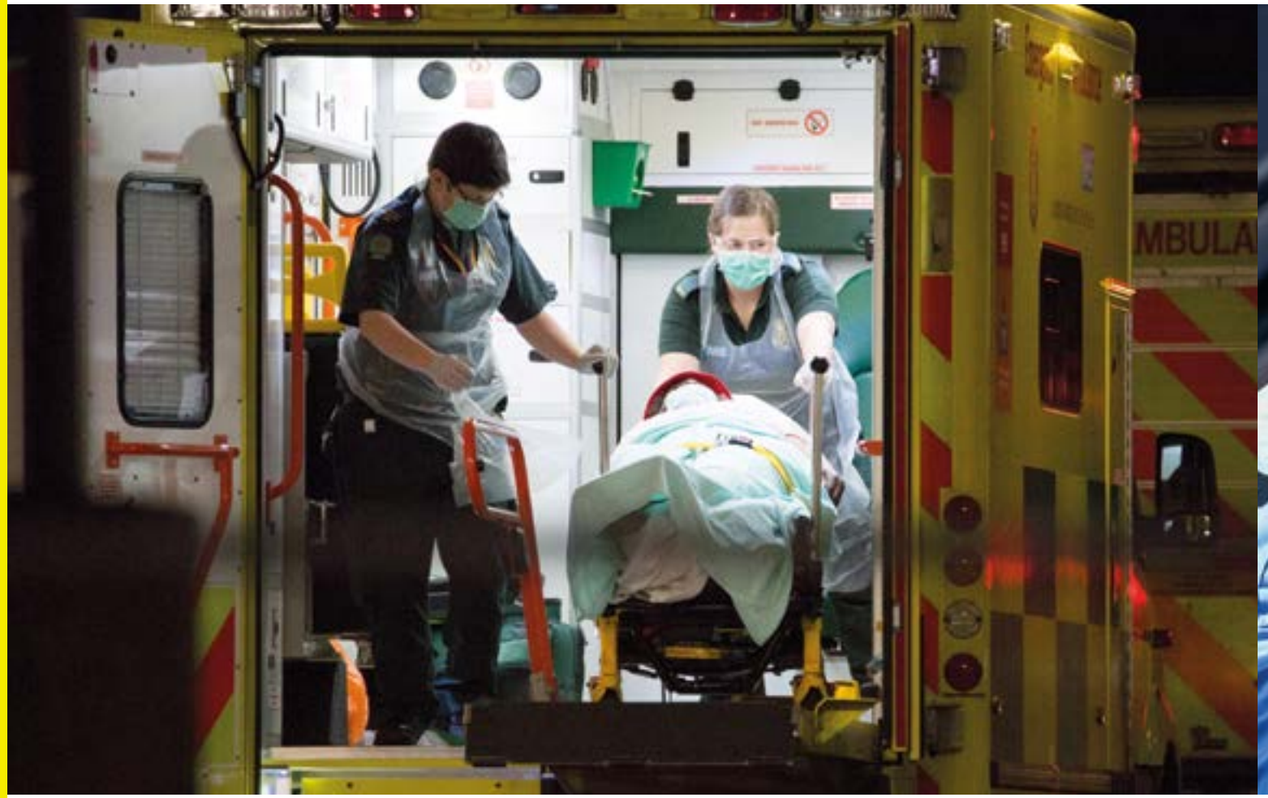
## Responding to the crisis

Research teams worldwide have been on the frontline since January 2020, supporting healthcare workers by working to design diagnostic tests, experiment treatment options and gather crucial information about the virus itself. Yet, despite the growth of the anti-vaccination movement in many countries around the world in recent years, it's the perspective of developing a safe and effective vaccine against the deadly disease that is crystallising all the hope. "Getting a safe and effective vaccine for COVID-19 would be a game-changer in this pandemic, protecting people against the disease, cutting down the number of deaths, and making measures, such as quarantine, unnecessary. Experts expect a vaccine to be ready in 12 to 18 months", says Gary Kobinger, Director of the Infectious Disease Research Centre at the Université Laval (Canada) and member of the Strategic and Technical Advisory Group for Infectious Hazards at the World Health Organization.



Although the timeline remains uncertain, vaccine development in response to COVID-19 is going at an unprecedented pace. On 11 January 2020, the genetic sequence of SARS-CoV-2, was published and shared with scientists worldwide. This marked the beginning of intense global R&D efforts to develop a vaccine against COVID-19, paving the way for the start of many vaccine trials in 2020. As of 8 April 2020, 115 vaccine candidates were being studied as part of the global COVID-19 vaccine R&D landscape. In total, 78 of these were confirmed as active, with 73 at exploratory or preclinical stages.

The most advanced vaccine candidate, the mRNA-1273 vaccine from US-based company Moderna Therapeutics, entered



phase 1 human clinical trials on 16 March 2020. Phase 2 clinical trials are expected to start in May. Most of the other advanced candidates are based in the US and in China and include Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio, LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Geno-Immune Medical Institute. In other countries, research groups – such as the Jenner Institute at the University of Oxford – have announced that they would also go through the first phases of human testing before the end of the year.

## The challenges of developing a vaccine

Designing a vaccine in under 18 months represents a considerable feat, considering that most vaccines take between five and 10 years to be developed. A number of challenges need to be addressed before a vaccine candidate is deemed safe and effective. Perhaps one of the biggest difficulties is the fact that SARS-CoV-2 remains elusive to researchers. In order to develop a safe and effective vaccine, interrogations surrounding the way the immune system responds not only to the virus, but to any potential vaccine too, first need to be addressed.

"We need to better understand the immune response before we can progress to successful vaccine development.

Studies looking at the type of coronavirus that can cause the common cold suggest that antibodies built against this virus don't last long in the body. This tells you that the immune response differs to what can be seen with other viruses. This is one of the reasons why a vaccine against SARS-CoV-2 may be difficult – it might be hard to elicit long-term immunity against this novel coronavirus," Sarah Pitt, microbiologist and professor at the School of Pharmacy and Biomolecular Science at the University of Brighton, points out.

Research from the 2002-04 SARS outbreak suggests immunity against the virus may not last long after a first exposure. A study published in *Annual Reviews of Immunology* showed that 10% of people who had been infected by the virus had lost the immunity they had built within 12 months. Understanding how long people who have been infected by SARS-CoV-2 are immune to it, and how long a vaccine candidate can elicit protection, are key questions researchers are trying to solve in order to improve vaccine development. The yellow fever vaccine is considered one of the best vaccines in the world, because only one dose is needed to confer lifelong immunity, with few sideeffects. It is unclear whether sustaining a robust immune response in the long term with a COVID-19 vaccine will be possible.

Another source of concern for the teams working on vaccine development is how to avoid a phenomenon that seems to contradict our conventional understanding of vaccine science, and which has been observed since the 1960s, during vaccine trials for diseases such as dengue or SARS. Indeed, in some animal models or even in some human trials, those who had received a vaccine candidate and were later re-exposed to the virus paradoxically developed a more severe form of the disease. In other words, the vaccine-primed immune system, in some cases, malfunctions when the body is exposed to natural infection. Known as antibody-dependent enhancement (ADE), this reaction involves the virus leveraging antibodies to aid infection. Making sure that ADE is not happening in the context of the COVID-19 pandemic, and that none of the vaccine candidates currently tested against the disease trigger such a reaction, is a priority for research teams.

*It is unclear if a robust, long-term immune response with a COVID-19 vaccine will be possible*

For some experts, setting up human challenge models, which involves testing vaccine candidates in healthy human volunteers and then intentionally infecting them with an attenuated form of the virus under controlled conditions could provide useful information about the immune system's interaction with the virus. In the case of malaria vaccine research, for example, these models have allowed for more thorough vaccine efficacy testing and are informing rational vaccine development. Without knowing more about SARS-CoV-2 though, and without properly addressing safety concerns that participants may have

*In 1955, the inactivated poliovirus vaccine was introduced with massive support from the federal government*

before taking part in this kind of research, these models may be difficult to set up. Animal models to start testing candidates will remain the norm.

## Funding research

Financial concerns are also still on the table. Developing successful vaccines and using them for large-scale immunisation not only requires robust research but also support from the industry and appropriate funding. "Different factors can influence whether a vaccine will be developed or not, such as how many people are dying and whether it is a high-profile disease. There are financial considerations that are taken into account by pharmaceutical companies. Take polio for example – in the 1950s there was a lot of interest in getting a vaccine, and the US government secured funding for it, because the disease was affecting teenagers in the US and in Europe," Sarah Pitt says.

The virus that caused polio was identified in the early 20th century, but it took more than 40 years for vaccine trials to start. However, from the 1950s, the US government's financial involvement was crucial in the fight against the disease. In 1955, the inactivated poliovirus vaccine was introduced with massive support from the federal government. Federal funds were allocated to states in 1955 and 1956 to help them buy and administer the vaccine and, in 1960, Congress made an appropriation for a stockpile of the vaccine to be used in combating future polio epidemics.

The scale of the current pandemic means that massive funding has already been allocated to vaccine research. However, it is crucial that this research be allowed to go on and that some vaccine candidates be allowed to go through different stages of clinical testing. When SARS appeared in China, about 20 years ago, investigations of potential vaccine candidates were conducted. However, before clinical trials could start, funding was cut short as SARS was no longer spreading, and there was reduced interest in developing a vaccine. Many researchers now believe that if candidate vaccines for SARS, or even for Middle East Respiratory Syndrome (MERS), had received clinical trial funding years ago, current research to develop a vaccine against COVID-19 would have been facilitated, with a lot of lessons learnt for the current pandemic.

## Identifying the right vaccine technology

Despite the magnitude of the crisis, the vaccine development landscape for COVID-19 is particularly dynamic, with many different technology platforms being evaluated. This dynamism, and the innovation displayed by different research teams around the world, enables different approaches to be tested quickly, comparing their efficacy, in the hope of finding a successful vaccine candidate among them. Furthermore, developing and testing different technologies gives scientists more opportunities to test and identify vaccine platforms that may be better suited for specific population subtypes (such as the elderly, immunocompromised patients and healthcare workers).

These different approaches include nucleic acid (such as the mRNA-1273 vaccine), peptide, viral vector recombinant protein, live attenuated virus and inactivated virus strategies. Some of the newest technologies are of particular interest to the scientific community. "Broadly speaking, we can divide these approaches into two groups – killed or live attenuated vaccines, and subunit vaccines that are designed using only specific parts of the virus, made with the newest technologies. These subunits have the clear advantage that they can't cause the disease, as opposed to attenuated vaccines, such as the polio vaccine that can cause an attenuated form of the disease," Gary Kobinger points out.

## Learning from a previous crisis

Recent large-scale epidemics, such as the 2013-2016 Ebola epidemic in West Africa, are providing researchers with valuable lessons for managing the current crisis and conducting research in an emergency context. Research teams worldwide hope a vaccine could be ready in 18 months because that's the time it took to get a vaccine against Ebola. Working quickly but ethically and with high standards of quality, coordinating international efforts and developing innovative technology platforms have all been important features of the research world during the Ebola crisis, and will be even more important in the current pandemic.

Gary Kobinger was a key scientist in the team working to create the Ebola vaccine and has conducted a lot of research work in the context of other epidemics, including the Zika outbreak. He believes some of the vaccine work done in these previous contexts can be useful in the fight against COVID-19. In fact, some teams are using some of the technology platforms investigated during Ebola to see if they could provide interesting clues to create a successful vaccine.

Working urgently to get a vaccine, and getting it done in less than 18 months, does not mean rushing through all the steps and forgetting safety and ethics rules, however. "A vaccine candidate needs to be tested not just for efficacy but also for safety; we don't want to rush the development of a vaccine just because there is panic caused by the epidemic, with the potential of worsening the situation with a poorly manufactured and poorly tested vaccine," Sarah Pitt warns.

There are ways to accelerate the pace of vaccine development without risking the safety of patients. Gary Kobinger explains: "The steps you need to follow in a clinical trial are always there, the question is how we can move through them faster. There are things that can be done, such as overlapping a phase 1 and a phase 2 trial, which means you start the phase 1 trial with the documentation for the phase 2 already in place, pending the results. Another way is to target specific subgroups, such as young adults, healthcare workers or the elderly. If you restrict the target population you may be able to go faster, because it makes the research easier to set up."

Many questions about the COVID-19 pandemic remain unanswered, and we still don't know exactly when a successful vaccine will be ready. Yet there's cause for optimism: all the research conducted today will prove useful in the future, not only to develop the future COVID-19 vaccine, but also to allow researchers to progress in their understanding of new technologies, advancing the development of subunit vaccines to protect us against future emerging viruses. BMS

## FAST FACTS: VACCINE DEVELOPMENT

**115**
**CANDIDATES**
**A total of 115 vaccine candidates were being studied as part of the global COVID-19 vaccine R&D landscape, as of 8 April.**

**5-10**
**YEARS**
**Most vaccines take between five and 10 years to be developed.**

**45**
**VOLUNTEERS**
**Initial human trials for mRNA-1273 featured 45 healthy adult volunteers aged 18 to 55 years, over approximately six weeks.**



## TIMELINE: DEVELOPMENT OF THE PANDEMIC

**31 DEC**
China reported a cluster of cases of pneumonia in Wuhan. A novel coronavirus was eventually identified.

**13 JAN**
Officials confirm a case of COVID-19 in Thailand – the first recorded case outside of China.

**31 JAN**
Two Chinese nationals staying in a hotel in York became the first confirmed cases of COVID-19 in the UK.

**28 FEB**
The earliest documented transmission within the UK appeared to take place.

**1 MAR**
COVID-19 was detected in England, Wales, Northern Ireland and Scotland.

**11 MAR**
The WHO declared the outbreak a pandemic.

**20 MAR**
UK restaurants, pubs, clubs, and indoor sport and leisure facilities were ordered to close.

**5 APR**
Boris Johnson was hospitalised after testing positive for COVID-19.

**12 APR**
Boris Johnson left hospital to recuperate at Chequers.

**16 APR**
Dominic Raab, deputising for Boris Johnson, announced the UK lockdown would stay in place until at least 7 May.