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Two years of the coronavirus

How has our understanding of the virus changed since it went global in 2020 and where does that leave us? Helen Thomson reports

ON 31 December 2019, Chinese authorities informed the World Health Organization (WHO) about a cluster of “viral pneumonia” cases of unknown cause in the city of Wuhan. Two years later, the coronavirus now known as SARS-CoV-2 has resulted in at least 5.4 million deaths. As the world awaits the full impact of the new variant omicron, New Scientist looks back at the phenomenal scientific endeavour across the pandemic, and at how much we now know about the virus and how to fight it.

Where did covid-19 come from?

In March 2021, a group tasked by the WHO to investigate covid-19’s origins concluded that SARS-CoV-2 is most likely to be an animal virus that moved into humans through contact with an animal host, either at the Huanan Seafood Wholesale Market, a live animal market in Wuhan, or at another step in the trade of wildlife.

“From early on in the pandemic, experts disagreed about how covid-19 was spread”

The WHO group hedged its bets because the first person reported to have become ill with covid-19 on 8 December 2019 had no link with the market. A more recent analysis, however, suggests that this individual actually developed symptoms on 16 December, and only visited a hospital on 8 December for dental problems.

This means the earliest known case may indeed have had ties to the market: a seafood vendor who became sick on 11 December. A third of the 168 people later identified as having had the virus in December 2019 had connections to the market.

The mounting evidence for a market origin weakens the case for a lab leak, a premise that couldn’t be ruled out by an investigation commissioned by US president Joe Biden in 2021. Since these investigations, coronaviruses that are the closest match yet found to SARS-CoV-2 have been discovered in bats in Laos, says Marion Koopmans at Erasmus University Medical Centre in the Netherlands, who was part of the WHO’s investigation team. Certain features of these wild viruses were the same as those that some researchers claimed could only have arisen during “gain of function” tests in a lab, in which an organism is genetically altered to enhance certain characteristics.

A June 2021 paper in Scientific Reports adds further support to the market origins story. The authors were serendipitously surveying markets in the Wuhan area that were selling wild animals for food or pets between May 2017 and November 2019. They discovered many animal welfare and exploitation issues with “considerable implications for food hygiene”. The animals traded are capable of hosting a wide range of infectious diseases, they say.

Some early covid-19 cases were linked to an area of Huanan market where wild animals such as raccoon dogs were kept. These animals can be infected and display few symptoms, boosting the idea that animals in the market acted as an intermediate reservoir for the virus, says Koopmans.

In response to covid-19, China temporarily prohibited all wildlife trade until the pandemic concludes and permanently banned the eating and trading of non-livestock animals for food.

How does the coronavirus spread?

Back in January 2020, researchers urgently needed to understand the nature of the virus and how it was spreading. On 3 January, Yong-Zhen Zhang at Fudan University in Shanghai, China, was given a box containing swabs from people with the mysterious pneumonia sweeping Wuhan.

By 5 January, having worked two nights straight, Zhang’s team had sequenced the virus and identified it as a coronavirus. That same day, Zhang uploaded the genome to the US National Center for Biotechnology Information. By comparison, in 2003, scientists took two months to identify the cause of an international outbreak of a new disease, SARS, as a coronavirus.

It soon became clear that SARS-CoV-2 spread easily and could cause severe disease, particularly in older age groups or in those with underlying health issues. By the end of February, its death count had surpassed those caused by the coronaviruses responsible for the SARS outbreak and MERS, a disease that emerged in 2012.

The WHO declared the covid-19 outbreak a pandemic on 11 March 2020. Working out how to minimise transmission was key, but from early on, there was...
disagreement among experts. At first, the focus was on surface transmission – infected people contaminating surfaces that were then touched by others. Swabs from hospitals found the virus lurking everywhere, from stethoscopes to reading glasses. Sales of hand sanitiser soared.

Other researchers concentrated on transmission via large droplets spread as an infected person coughs or sneezes near others. Droplets are heavy and fall from the air within seconds, rarely travelling more than 2 metres.

Social distancing and face coverings were widely implemented as a way to help prevent this type of spread. But rigorous evidence on the effectiveness of face coverings was slow to appear and often contested. The WHO initially only recommended them for people who were actively coughing or caring for those with covid-19.

Today, we know that all face coverings help cut the risk of catching and transmitting the virus to a certain extent. Then, there is the issue of aerosols. These tiny particles hang in the air and so can travel further than 2 metres, but many researchers initially disregarded this route of spread. The WHO stated at a press conference on 27 March 2020 that “transmission of covid-19 is through droplets, it is not airborne”.

This is because doctors have traditionally assumed that respiratory diseases, like tuberculosis and influenza, are spread mainly by droplets – “coughs and sneezes spread diseases”, says Trisha Greenhalgh at the University of Oxford. “It’s a mindset that’s deeply ingrained in the infectious disease community.” But more recent research has shown that both TB and flu can be spread via aerosols, upending conventional wisdom.

The tide began to turn in July 2020, when 239 scientists from 32 countries published evidence that SARS-CoV-2 was airborne, appealing to the WHO and others to acknowledge its impact. However, it wasn’t until May 2021 that the WHO and the US Centers for Disease Control and Prevention changed their guidance, stating that aerosols are the primary route for transmitting the virus, mainly between people in close proximity with each other, and typically 1 to 2 metres apart, or in poorly ventilated or crowded indoor environments.

An electron micrograph of the SARS-CoV-2 virus that causes covid-19

Subsequent research has shown that surface transmission is likely to be a factor in the spread of the virus, but not a primary means. Good ventilation is now seen as a vital control measure. All of this has left some scientists urging a paradigm shift in how we combat respiratory infection. In a call for action published in Science in May 2021, a group of more than 30 scientists and doctors pointed to the great disparity in the way in which we address different sources of environmental infection. While governments have long invested in food safety, sanitation and clean drinking water, the group argued that airborne infections haven’t been targeted strongly enough through changes to regulations, standards and building design that could help prevent their transmission.

How has the virus evolved?

As soon as the coronavirus started spreading, it also began to mutate, leading to new variants. “Omicron should not surprise anyone, it is what viruses do,” said Tedros Adhanom Ghebreyesus, director general of the WHO, at a press conference in December 2021. “It’s what this virus will continue to do as long as we allow it to continue to spread.”

Each time a virus replicates, it has a chance of mutating. Some mutations make it better at moving through a population. The first new variant to spread widely was alpha, which was sequenced in September 2020 and is about 50 per cent more transmissible than earlier variants. It was first identified in the UK and research suggests that it may have evolved in someone with a weakened immune system. This meant they couldn’t wipe out the virus, encouraging it to evolve and mutate.

Next came beta, which was first spotted in South Africa and was first sequenced in October 2020. Among its mutations is one that alters the shape of a key protein, helping it to evade antibodies that are effective against other variants. Recent work suggests it spread quickly because it is 20 per cent better than previous variants at evading the immune response in previously infected people.

In late 2020, another variant, gamma, emerged and caused a surge of cases in Manaus, Brazil. Here, it was estimated that 75 per cent of the population had already been infected with SARS-CoV-2. The new variant had a mutation allowing the virus’s spike protein to bind more easily to cells, making it more infectious. This protein is the part of the virus that recognises host cells, and is the main target of our immune
response. Another mutation helped it evade antibodies from past infections.

Then delta swept the world. The variant was sequenced in October 2020 and first detected in India, where it caused a huge wave of infections. At least 50 per cent more transmissible than alpha, delta outcompeted all other variants over the course of 2021, becoming the most common one in the world. Vaccines are still effective against it, but are around 15 per cent worse at preventing infection by delta than by alpha.

Omicron, which emerged in November 2021, has the highest number of mutations so far seen in the spike protein, and we don’t yet know their full impact. You can eyeball the mutations in order to work out what effect they might have, says Danny Altmann at Imperial College London, “but many are new”.

Omicron spread rapidly in South Africa, where a large majority of the population has previously been infected but only about 25 per cent are fully vaccinated.

By 18 December 2021, a total of 89 countries had detected the presence of omicron. The variant appears to spread much faster than others. A December study of data from South Africa suggested that omicron is 4.2 times more transmissible in its early stages than delta, and there is some evidence that it may multiply in our airways 70 times faster.

The variant also seems to exhibit “immune escape”, to some extent evading the immune responses of people who have already had covid-19 or been vaccinated. Lab studies by Pfizer suggest that three doses of the vaccine it developed with BioNTech offer significant protection against infection from omicron, but two doses don’t.

Uğur Şahin, CEO of BioNTech, said in a press statement that a component of our immune system, called memory T-cells, generated by the vaccine, may prevent severe disease in those who haven’t had three shots.

The variant’s ability to infect the double-vaccinated prompted the UK to open its booster programme to all adults in December. Infection numbers in the UK have since hit record highs, but there has been some good news, as preliminary analyses of data from England suggested that infection with omicron may be around 20 to 70 per cent less likely to result in a hospital visit. In people who haven’t yet caught covid-19 or been vaccinated, hospitalisation with omicron appears to be about 11 per cent less likely than with delta. However, this is unlikely to be enough to counteract the variant’s extreme transmissibility, and health systems worldwide are bracing for surges in hospital admissions.

How good are the vaccines?

The major success story of the pandemic has been how fast vaccines were created. Thanks to years of research following the SARS and MERS outbreaks, researchers had a good idea of what aspects of SARS-CoV-2 to target. The pandemic also coincided with the maturation of mRNA vaccine technology.

Traditional vaccines tend to contain weakened or inactivated virus that the body learns to recognise so it is ready to fight the virus when next encountered. The new Pfizer/BioNTech and Moderna vaccines introduce an mRNA sequence that tells the body to make a harmless part of the coronavirus’s spike protein, which triggers an immune response. These vaccines can be developed faster and more cheaply than traditional ones.

For vaccines of all types, money was pumped into trials so multiple studies could be run at the same time, and cash was given to manufacturers to increase production capacities.

We now have 23 covid-19 vaccines in use, and around 135 others in various stages of human trials. There have, of course, been hurdles. The Oxford/AstraZeneca

| What do we still not know? |
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| Two years on, several key questions about the virus are yet to be resolved, including the virus’s origins. Although evidence suggests it began in a market in China and that it derives from a bat coronavirus, it isn’t clear how it spread to humans. We don’t know the dose of SARS-CoV-2 needed to transmit infection. To work this out, several human challenge trials are under way, in which volunteers are given varying viral doses in controlled conditions. We also need to identify the level of antibodies needed to prevent infection, which is helpful for assessing how effective vaccines are and also for rapidly deciding whether they need to be changed. Researchers met in December 2021 to discuss data on antibodies for all the variants of concern, to reach an agreement on what antibody levels are required to protect people against severe disease. Results are forthcoming. We don’t know what future variants might be called, once we have run out of Greek letters. The World Health Organization is considering using lesser-known constellations next, says Maria Van Kerkhove at the WHO. And finally, we don’t know how dangerous future variants may be. |

The closed Huanan Seafood Wholesale Market in January 2020.
jab was linked to rare blood clotting events, which led to some countries restricting its use. Still, the vaccine programme has worked so well in high-income nations that covid-19 was referred to as a disease of the unvaccinated by Andrew Pollard, director of the Oxford Vaccine Group at the University of Oxford. He wrote in The Guardian in November 2021 that the “ongoing horror” of people with covid-19 fighting for breath in intensive care units across Britain “is now largely restricted to unvaccinated people”.

While we wait to see omicron’s impact on hospitalisations and deaths, the good news is that if it, or any other variant, undermines the current vaccine programme, scientists are prepared. Pfizer CEO Albert Bourla has said his company could make an updated vaccine in less than 100 days. Others are working on variant-specific and multi-variant vaccines.

What treatments do we have?

Vaccines aren’t our only tool against the virus. Steroids, including dexamethasone, the first drug proven to save lives from covid-19, have been used by medics from the beginning of the pandemic. Doctors reasoned that steroids would help reduce the impact of severe disease by preventing the immune system from going into overdrive and damaging organs. That turned out to be true – a discovery that was unprecedented in its speed, thanks to collaboration across seven clinical trials in 12 countries, coordinated by the WHO.

Three monoclonal antibodies, which are manufactured versions of antibodies that attach to the virus’s spike protein and make it harder for it to enter human cells, have been given emergency approval by the US Food and Drug Administration (FDA). The drugs showed promise in reducing hospitalisation in infected people at high risk of more severe disease. They also decreased the spread of disease to other people in the household when taken prophylactically. However, there are suggestions from recent data that some monoclonal antibody drugs may not be effective against omicron.

Monoclonal antibodies are also expensive and hard to give outside a hospital setting. Oral antivirals that can be taken at home may be a better option. One, a drug made by Pfizer called Paxlovid, has shown very promising results. When taken for five days shortly after symptoms start, the drug cut hospital admissions by 89 per cent in adults at high risk of severe illness. The drug appears to work well against omicron, and was given emergency approval by the FDA on 22 December. President Biden has already ordered enough pills to treat 10 million people.

Another antiviral, molnupiravir from Merck, appears to reduce the risk of hospitalisation or death by about 30 per cent in at-risk people with mild to moderate covid-19. The UK approved this drug in November 2021.

Other treatments are in human trials. For instance, the cheap oral antidepressant fluvoxamine has shown strong evidence of preventing covid-19 progressing from a mild case to a severe one in those at serious risk.