COVID-19 vaccines: what do we know so far?

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When the novel coronavirus was described in late 2019, it could not have been imagined that within a year, more than 100 vaccine candidates would be in preclinical development and several would be in clinical trials and even approved for use. The scale of the COVID-19 outbreak pushed the scientific community, working in collaboration with pharmaceutical companies, public health bodies, policymakers, funders and governments, to develop vaccines against SARS-CoV-2 at record-breaking speed. As well as driving major amendments to the usual timeframe for bringing a vaccine to fruition, the pandemic has accelerated the development of next-generation technologies for vaccinology, giving rise to two frontrunner RNA vaccines. Although none of the critical safety and efficacy steps have been skipped within the compressed schedules, and the technologies underpinning the novel vaccines have been refined by scientists over many years, a significant proportion of the global population is sceptical of the benefits of COVID-19 vaccines and wary of potential risks. In this interview-based article, we give an overview of how the vaccines were developed and how they work to generate a robust immune response against COVID-19, as well as addressing common questions relating to safety and efficacy.

Introduction

At the time of writing, 22% of the global population has received at least one dose of a COVID-19 vaccine [1]. Here in the UK, over 43 million individuals have received their first dose and over 31 million – over half of the adult population – are double-vaccinated [1]. Public reactions to the unprecedentedly rapid development, authorisation and delivery of COVID-19 vaccines have been mixed even in countries with a relatively high vaccination rate, such as the UK. While some people eagerly awaited their turn and celebrated receiving a dose, others reacted with trepidation, mistrust and anger. The number of people who consider COVID-19 vaccines to be our way out of a pandemic that has wreaked havoc worldwide over the past ~ 18 months seems to be matched by those who are sceptical of the benefits, fearful of the side effects or simply don't consider COVID-19 to be a significant threat. In the UK, it is estimated (based on data collated by Imperial College London YouGov Covid-19 Behaviour Tracker Data Hub) that up to 15% of over-18s are unwilling or hesitant to be vaccinated, and vaccine hesitancy is considerably higher in other countries including Italy, Germany, France and the United States [1]. An earlier study conducted by Kantar also highlighted a particularly high level of vaccine hesitancy in the latter two countries [2]. Women, younger age groups and communities with a low level of trust in central government are less likely to accept COVID-19 vaccines [3]. In the UK and the United States, the pandemic has also had a disproportionately high impact on ethnic minorities, in part due to firmly embedded racial inequalities and a lack of trust in health services that have translated to particularly high rates of vaccine hesitancy amongst these groups [4–6].

It is understandable that many people are apprehensive about vaccines that have been developed at an accelerated pace for a disease that we don't yet fully understand, but much of the uncertainty has been fuelled by misinformation and the distortion of scientific findings. This is a consequence of the explosion in unverified information relating to SARS-CoV-2 that we have witnessed over the past year, spread via social media, preprint servers, journals, news sites and other platforms [7–9].

Here, we aim to explain the science and lessen some of the concerns surrounding COVID-19 vaccines by addressing several key questions relating to the development and effects of the vaccines. An expert view is offered by two immunologists from Imperial College London: Professor Daniel (Danny) Altmann, who heads an immunology and infectious disease-focused laboratory at the Hammersmith Hospital Campus, and Dr Victoria (Viki) Male, a Sir Henry Dale Fellow and Lecturer in Reproductive Immunology based in the Department of Metabolism, Digestion and Reproduction. As well as investigating aspects of the biology of SARS-CoV-2 since the onset of the pandemic, Danny and Viki have been involved in a variety of public engagement and outreach activities aiming at providing accurate, expert information about COVID-19 to members of the public.

To start with, can you give an overview of your research group's major focus and goals?

Danny:

We've spent many decades working in immunology, focusing on infectious diseases in a UK and global health setting, autoimmune disease and tumours. When COVID-19 came along, we applied our laboratory's skillset to key questions as they arose – such as the possibility of reinfection, mapping of immunity after vaccination and the immunological basis of long COVID [10–12] – and have pretty well worked on it 7 days a week for the past year.

Viki:

My group works on defining immunological processes in the lining of the uterus and how these affect the success of pregnancy. Our goal is to find ways to improve outcomes of pregnancy for mothers and babies, for example by finding new ways we can prevent preterm birth. My interest in preventing preterm birth led me to looking at COVID-19 vaccination in

pregnancy, since we know that catching COVID-19 late in pregnancy is associated with an increased risk of preterm birth, and vaccination is one way we can reduce this risk [13,14].

When you first heard reports of a novel coronavirus, did you anticipate that it would trigger a pandemic? What was your initial reaction to the news emerging from China?

Danny:

I'm not sure it would be honest to claim we'd foreseen a pandemic as such. I'd previously sat through international 'pandemic preparedness' meetings that considered precisely this event, though most of the attention was on flu. I do remember seeing the data coming out of Wuhan in December and January and feeling that we were watching a car crash in slow motion as cases zigzagged across the world.

Viki:

To begin with, I didn't think it would cause a pandemic – after all, both SARS-CoV-1 and MERS-CoV outbreaks remained relatively contained. Clearly, I was wrong! But there was a 2- to 3-week period during which it was clear to me that this was serious, but the government (in the UK) was taking no action and I shut down my laboratory ahead of official guidance to do so. It was only a week later that the national lockdown was declared, but that was a very uncomfortable week for me.

Scientists and the global pharmaceutical industry stepped up to the mark and produced vaccines for COVID-19 at an accelerated pace. How were the vaccines developed in less than a year when it usually takes a decade or longer?

Danny:

Development of COVID-19 vaccines was informed by previous vaccine activities, particularly for other coronaviruses and related viruses. Decades of work have gone into nucleic acid vaccines, with huge advances being made in RNA technology in recent years [15]. This meant that we were able to adapt platforms and apply lessons from 10 to 20 years of hard graft investment in

Table 1. Key features of leading COVID-19 vaccines.

Name of vaccine and developer(s)	Vaccine platform/ technology	No. of doses required	Storage temperature	Efficacy against symptomatic infection (based on phase 3 clinical trial results)[a]	Status in early 2021[b]
Pfizer-BioNTech – BNT162b2 *Pfizer (Germany) BioNTech (USA)*	Modified mRNA in lipid nanoparticle	2	−70 °C	52% after first dose, 95% after second dose [35]	Full authorisation for use in 5 countries; 109 countries have approved the vaccine for emergency use. Authorised for use in 12- to 15-year-olds in some jurisdictions.
Moderna – mRNA-1273 *Moderna (USA) NIAID (USA BARDA (USA)*	Modified mRNA in lipid nanoparticle	2	−20 °C	Trial not designed to evaluate efficacy after one dose, 94.1% after second dose [36]	Full authorisation for use in UK and Switzerland; 73 countries have approved the vaccine for emergency use. Moderna's second mRNA-based COVID-19 vaccine moved into phase I clinical trials.
Oxford-AstraZeneca – AZD1222 *University of Oxford (UK) AstraZeneca (Sweden)*	Nonreplicating adenovirus vector (ChAdOx1) carrying DNA	2	2–8 °C	76% after a single dose, 81.3% after second dose [21]	Full authorisation for use in Brazil and Australia; 170 countries have approved the vaccine for emergency use. Use suspended in some countries due to concerns about a rare clotting syndrome. Now being modified to improve efficacy towards variants.
Janssen – Ad26.COV2 *Janssen Vaccines (Netherlands), subsidiary of Johnson & Johnson (USA) Beth Israel Deaconess Medical Center (USA)*	Nonreplicating adenovirus vector (Ad26) carrying DNA	1	2–8 °C	66.1% after 28 days in one-dose regimen [52]	Full authorisation for use in Switzerland; 77 countries have approved the vaccine for emergency use. Use suspended in some countries due to concerns about a rare clotting syndrome. Single-dose and low cost of vaccine make it a good choice for low- and middle-income countries.
Sputnik V *Gamaleya Research Institute of Epidemiology and Microbiology (Russia)*	Nonreplicating adenovirus vector (Ad5 and Ad26) carrying DNA	2	−18 °C	91.6% 21 days after first dose, which was when the second dose was administered [61]	Full authorisation for use in Turkmenistan and Uzbekistan; 71 countries have approved the vaccine for emergency use. Full phase 3 trial results awaited. The interim analysis of trial results has come under scrutiny.
CoronaVac *Sinovac Biotech (China) Dynavax Technologies (USA)*	Inactivated SARS-CoV-2	2	2–8 °C	Between 50% and 84% depending on trial location [62]	Full authorisation for use in China; 47 countries have approved the vaccine for emergency use. Trust in the vaccine is low in some countries is low due to early lack of transparency.
BBIBP-CorV *Sinopharm (China)*	Inactivated SARS-CoV-2	2	2–8 °C	78.1%, based on interim analysis of randomised clinical trials [63]	Full authorisation for use in 4 countries; 71 countries have approved the vaccine for emergency use. Full phase 3 trial results awaited. Approved for use in WHO-supported COVAX.
Covaxin – BBV152	Inactivated SARS-CoV-2	2	2–8 °C		Has received emergency authorisation in 19 countries. Full

Table 1. (Continued).

Name of vaccine and developer(s)	Vaccine platform/ technology	No. of doses required	Storage temperature	Efficacy against symptomatic infection (based on phase 3 clinical trial results)[a]	Status in early 2021[b]
Bharat Biotech (India), Indian Council of Medical Research (India)				78% reported by Bharat Biotech in April 2021, full trial results awaited [64]	phase 3 trial results awaited. Clinical trials on minors have been approved.
Novovax – NVX-CoV2373 *Novovax (USA)*	Protein-based: recombinant spike protein + adjuvant	2	2–8 °C	89.7% overall in UK trial results (higher against the original virus strain compared to the B.1.1.7 variant) [65], 90.4% in USA & Mexico trial [66]	Pending authorisation in the United States, Europe, and elsewhere. Novovax plans to produce 100 million doses a month by September 2021. Phase 3 trials are ongoing, and a paediatric arm was recently added.

[a]Efficacy evaluations should not be compared for different vaccines because clinical trials use different protocols, involve different pools of people across different geographic locations and were carried out at different time points during the pandemic, with varying levels of infection.
[b]Status as of June 2021.

molecular immunology and vaccinology, preparing for just such a moment. And that investment has paid off better than we ever dared dream, with hundreds of vaccine candidates being developed and ready to test simultaneously followed by the rapid progress through clinical trials of promising candidates (Table 1).
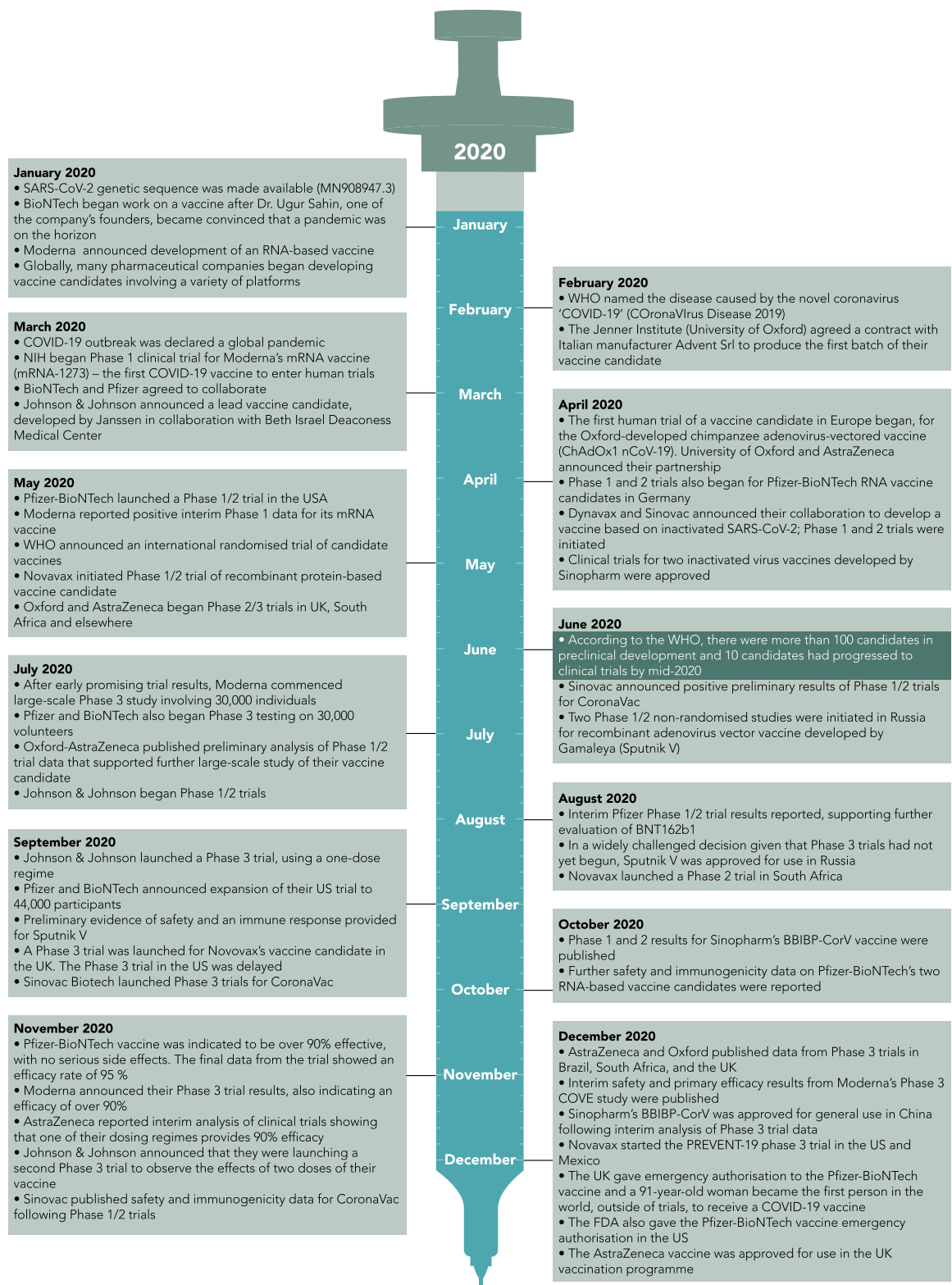
Viki:

Yes, a lot of groundwork had been laid down ahead of the pandemic and we had two mature platforms (mRNA and adenovirus vectors) that were ready to take on any antigen to produce an emergency vaccine. Then, the fact that we were in a pandemic meant that two of the main barriers to testing were reduced. First, trials were run with overlapping phases, which is not usually done because this is very expensive if the vaccine fails – but money was no object here. Second, when a pathogen is not very common, it might take years for enough people in the placebo arm of a vaccine trial to become infected so that we can know whether the vaccine works – in the context of a pandemic, infection rates were so high that we could collect these data in only a couple of months [16,17]. There were some regulatory allowances, such as doing rolling reviews of the trial data, rather than unblinding at the end of the trial, which also speeded things up. But it's important to emphasise that these vaccines were in no way 'rushed'. The safety and efficacy standards that we are holding these to are the same as for any other vaccine (Fig. 1).

In the UK, two vaccines have been primarily used in the vaccination programme so far – Oxford-AstraZeneca and Pfizer-BioNTech – and two other vaccines, Moderna and Janssen (Johnson & Johnson), have recently been approved for use. How do these vaccines work to promote an immune response to SARS-CoV-2?

Danny:

To cut a long story short, while the pathophysiology is complex, the vaccinology proved to be relatively simple: any vaccine that could generate really high levels of neutralising antibodies to the SARS-CoV-2 spike protein (known to bind the host cell receptor ACE2 [18]) would prevent infection. This was appreciated pretty much from day one. So, the mRNA vaccines, Pfizer and Moderna, do this by delivering the mRNA that encodes the spike protein into cells to stimulate an antibody response, and the viral vector vaccines, including the one produced by Oxford and AstraZeneca, do this by delivering the spike-encoding gene into cells via a modified cold virus (adenovirus) (Fig. 2). For any interested in the detail, our laboratory recently published a paper in npj Vaccines that presents a scholarly comparison of every aspect of all currently available COVID-19 vaccines [11].

2020

January

January 2020
• SARS-CoV-2 genetic sequence was made available (MN908947.3)
• BioNTech began work on a vaccine after Dr. Ugur Sahin, one of the company's founders, became convinced that a pandemic was on the horizon
• Moderna announced development of an RNA-based vaccine
• Globally, many pharmaceutical companies began developing vaccine candidates involving a variety of platforms

February

February 2020
• WHO named the disease caused by the novel coronavirus 'COVID-19' (COronaVIrus Disease 2019)
• The Jenner Institute (University of Oxford) agreed a contract with Italian manufacturer Advent Srl to produce the first batch of their vaccine candidate

March

March 2020
• COVID-19 outbreak was declared a global pandemic
• NIH began Phase 1 clinical trial for Moderna's mRNA vaccine (mRNA-1273) – the first COVID-19 vaccine to enter human trials
• BioNTech and Pfizer agreed to collaborate
• Johnson & Johnson announced a lead vaccine candidate, developed by Janssen in collaboration with Beth Israel Deaconess Medical Center

April

April 2020
• The first human trial of a vaccine candidate in Europe began, for the Oxford-developed chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19). University of Oxford and AstraZeneca announced their partnership
• Phase 1 and 2 trials also began for Pfizer-BioNTech RNA vaccine candidates in Germany
• Dynavax and Sinovac announced their collaboration to develop a vaccine based on inactivated SARS-CoV-2; Phase 1 and 2 trials were initiated
• Clinical trials for two inactivated virus vaccines developed by Sinopharm were approved

May

May 2020
• Pfizer-BioNTech launched a Phase 1/2 trial in the USA
• Moderna reported positive interim Phase 1 data for its mRNA vaccine
• WHO announced an international randomised trial of candidate vaccines
• Novavax initiated Phase 1/2 trial of recombinant protein-based vaccine candidate
• Oxford and AstraZeneca began Phase 2/3 trials in UK, South Africa and elsewhere

June

June 2020
• According to the WHO, there were more than 100 candidates in preclinical development and 10 candidates had progressed to clinical trials by mid-2020
• Sinovac announced positive preliminary results of Phase 1/2 trials for CoronaVac
• Two Phase 1/2 non-randomised studies were initiated in Russia for recombinant adenovirus vector vaccine developed by Gamaleya (Sputnik V)

July

July 2020
• After early promising trial results, Moderna commenced large-scale Phase 3 study involving 30,000 individuals
• Pfizer and BioNTech also began Phase 3 testing on 30,000 volunteers
• Oxford-AstraZeneca published preliminary analysis of Phase 1/2 trial data that supported further large-scale study of their vaccine candidate
• Johnson & Johnson began Phase 1/2 trials

August

August 2020
• Interim Pfizer Phase 1/2 trial results reported, supporting further evaluation of BNT162b1
• In a widely challenged decision given that Phase 3 trials had not yet begun, Sputnik V was approved for use in Russia
• Novavax launched a Phase 2 trial in South Africa

September

September 2020
• Johnson & Johnson launched a Phase 3 trial, using a one-dose regime
• Pfizer and BioNTech announced expansion of their US trial to 44,000 participants
• Preliminary evidence of safety and an immune response provided for Sputnik V
• A Phase 3 trial was launched for Novovax's vaccine candidate in the UK. The Phase 3 trial in the US was delayed
• Sinovac Biotech launched Phase 3 trials for CoronaVac

October

October 2020
• Phase 1 and 2 results for Sinopharm's BBIBP-CorV vaccine were published
• Further safety and immunogenicity data on Pfizer-BioNTech's two RNA-based vaccine candidates were reported

November

November 2020
• Pfizer-BioNTech vaccine was indicated to be over 90% effective, with no serious side effects. The final data from the trial showed an efficacy rate of 95 %
• Moderna announced their Phase 3 trial results, also indicating an efficacy of over 90%
• AstraZeneca reported interim analysis of clinical trials showing that one of their dosing regimes provides 90% efficacy
• Johnson & Johnson announced that they were launching a second Phase 3 trial to observe the effects of two doses of their vaccine
• Sinovac published safety and immunogenicity data for CoronaVac following Phase 1/2 trials

December

December 2020
• AstraZeneca and Oxford published data from Phase 3 trials in Brazil, South Africa, and the UK
• Interim safety and primary efficacy results from Moderna's Phase 3 COVE study were published
• Sinopharm's BBIBP-CorV was approved for general use in China following interim analysis of Phase 3 trial data
• Novavax started the PREVENT-19 phase 3 trial in the US and Mexico
• The UK gave emergency authorisation to the Pfizer-BioNTech vaccine and a 91-year-old woman became the first person in the world, outside of trials, to receive a COVID-19 vaccine
• The FDA also gave the Pfizer-BioNTech vaccine emergency authorisation in the US
• The AstraZeneca vaccine was approved for use in the UK vaccination programme

Why are two doses required for most of the vaccines and why are the second doses being administered so many weeks after the first, in some countries?

Viki:

Almost all vaccines require a booster to be fully effective, and the clinical trial data for those COVID-19 vaccines that use two doses show that protection does increase after the second dose [19]. Indeed, I suspect that a booster would also improve the efficacy of the 1-dose Janssen vaccine (phase 3 trial data are awaited), but the aim there was to produce something that worked well enough with a single dose – which makes the logistics of administering it much easier.

The question of the interdose interval is an interesting one. Pfizer and Moderna both chose the shortest interval they thought would work [19], essentially to accelerate the trials. Most countries are continuing to use the same intervals for these vaccines, because we know exactly how well those work from the trials. Meanwhile, AstraZeneca used a variety of interdose intervals in their trial and found slightly better efficacy with a 12-week interval [20,21]. The UK decided to use a 12-week interdose interval for both the AstraZeneca and the Pfizer vaccine, largely because it was thought that it would be better to rapidly get more people partially vaccinated than fewer people fully vaccinated. This was a gamble, and I was against it at the time, but it seems to have paid off so far in terms of reducing the incidence of severe infection and hospitalisation [22,23]. That said, the situation has recently changed, in that the recently emerged Delta variant (lineage B.1.617) has become increasingly prevalent. We know that a two-dose regime is reasonably good at protecting against the variant, but one dose is pretty poor [24]. For this reason, I think there is an argument to be made for reducing the interdose interval, and the Joint Committee on Vaccination and Immunisation recently issued guidance to bring forward second doses for at-risk priority groups [25].
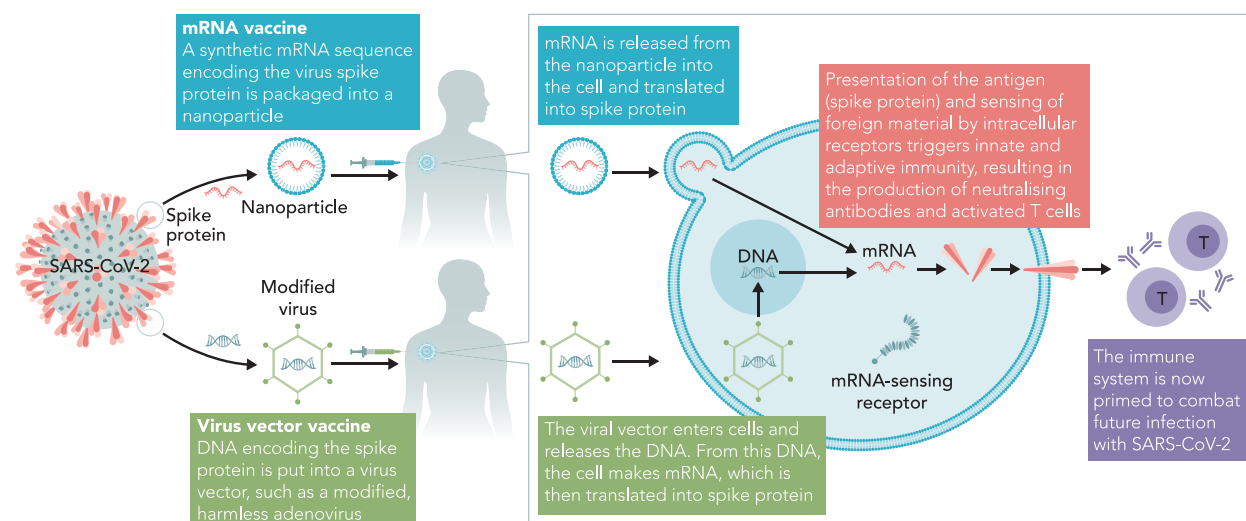
Fig. 2. Mechanism of action of mRNA and viral vector vaccines for SARS-CoV-2. The basic mechanisms through which COVID-19 vaccines that use the mRNA platform (shown in blue, top) and the adenoviral vector platform (shown in green, bottom) elicit a robust and long-lasting immune response against SARS-CoV-2 infection are demonstrated. Both platforms involve the delivery of synthetic nucleic acid (mRNA or DNA) that leads to production of the viral antigen, spike protein, inside cells. A key advantage over vaccines involving inactivated virus or recombinant proteins is that cell-mediated immunity is triggered as well as humoral (antibody-mediated) immunity, providing high efficacy (Table 1).

Danny:

The real-life data have been very reassuring in demonstrating that one dose appears to be broadly protective, even though in terms of immune parameters, one dose provides a relatively feeble antibody response, especially in the elderly [26]. But, by the 2nd dose, levels of neutralising antibodies are enormous, generally high enough even to deal with the variants [11,27].

Can a person still get COVID-19 after being vaccinated? If so, can they transmit the virus?

Viki:

Some people do get COVID-19 after being vaccinated, and most of these infections will happen in the immediate post-vaccine period, before the recipient's immune system has fully kicked into gear to protect them [28–32]. But even in people who have had enough time to get fully protected, we still see some infections. In clinical trials, the AstraZeneca vaccine prevented between 62% and 90% of infections [33,34] and the mRNA vaccines prevented about 95% [35,36]. Differences in trial approaches mean that you can't directly compare these figures, but they were both 100% effective at preventing severe disease. We also now have real-world data from the UK showing that two doses of the AstraZeneca vaccine prevents 89% and the Pfizer vaccine prevents 90% of symptomatic infections [37]. That the vaccines should perform so well in real-world conditions is really very encouraging and better than many people would have predicted or dared to hope.

The question of whether people who get COVID-19 following vaccination can transmit the virus onwards is still very much under investigation, but we do know that when people who have received one dose of the vaccine become infected, they are about 40–50% less likely to transmit the virus to other members of their household than those who are unvaccinated [38]. This is supported by other preliminary data indicating that the viral burden of vaccinated people may be lower, which suggests that they are less likely to transmit the virus [39].

Danny:

I'd only add to Viki's point that, while public health decisions have necessarily been based on the typical response, individual variation in immunity is huge. There will be some double-vaccinees with very poor immunity and thus *are* potentially likely to transmit.

How long is immunity to COVID-19 likely to last following vaccination? Do unvaccinated individuals who have been infected with the virus show the same degree of immunity?

Danny:

I think people (including policymakers) have gotten a little confused: somehow the fact that natural serum antibodies wane rather quickly after infection with other coronaviruses and that seasonal flu vaccines are given annually has been conflated to suggest that COVID-19 vaccines won't provide a lasting antibody response and will need frequent boosting. The current answer is we don't know until we have more data, but I'd be surprised if immunity following vaccination didn't last a good few years. Until we have a little more data on actual durability of protection, we have a conundrum of how much faith to put in our knowledge of the basic immunology: serum antibodies have a relatively short half-life, yet decades of immunology research tells us that B-cell memory should be established, with high-affinity clones ready to kick into action and protect. The data are starting to come through to support that much higher levels of virus-neutralising antibodies are generated by the vaccines compared to natural infection with SARS-CoV-2, indicating that a more durable, robust immune response is produced through vaccination [40–43].

Viki:

There is a lot of heterogeneity in immune responses following natural infection, so there is no guarantee that a person will be protected from reinfection [44,45]. This is the basis for the advice that even if you have already had COVID-19, you should get vaccinated. As Danny mentions, it's difficult to know exactly how long vaccine-induced immunity will last, but the trial participants continued to display a high level of protection six months after they had been vaccinated [46], which is a good sign.

What risk do you feel that emerging variants of the virus pose on management of the pandemic? Are the vaccines likely to still be effective?

Danny:

Emerging variants are our biggest threat. It's all very well to track the emergence of variants in countries with the sequencing capacity to do this, such as the

UK, but the vast majority of affected countries aren't able to do this. This suggests that we may not spot them till they're on our doorstep.

On the other hand, I look at the convergent evolution among the mutations we've spotted around the globe and suspect that the virus doesn't have an infinite number of tricks up its sleeve that don't come with an unacceptable fitness cost. We've previously commented on this point by analogy to the evolution of escape variants in HIV – they're shown to be finite and constrained by the fact that there's a tipping point where further mutations just create new epitopes recognised by protective immunity [47].

Like other vaccinations, the COVID-19 vaccines can cause mild but short-lived side effects. However, a rare and potentially severe clotting syndrome has been linked to the Oxford-AstraZeneca and Janssen vaccines, attracting significant media attention. Is there strong evidence that these vaccines can cause blood clotting and if so, what's going on, from the immunological point of view?

Viki:

I think it's clear now that this is a real, but rare, side effect of the adenovirus-vectored vaccines, which occurs at a rate of between 1 in 26 500 and 1 in 127 300, depending on the country that is reporting [48]. Although we say 'clotting' as a shorthand, I think it's crucial to be clear that this effect encompasses a whole set of symptoms, which include clotting, but also include a lack of platelets and the presence of antibodies that recognise the platelet protein known as PF4 (platelet factor 4) [49]. This is important to realise because lots of people who are already at higher risk of clotting, such as individuals who are pregnant or using oral contraceptives, might worry that they are at higher risk of this rare side effect of certain COVID-19 vaccines. Actually, because it's a different kind of clotting, they are not. It's also important for doctors to realise this, because the way in which we treat this side effect is quite different to how we would usually treat clots – one of the commonly used treatments, heparin, may very well make things worse.

The exact pathway is still very much under investigation, but it seems that in some people, rarely, the vaccine raises an antibody response to PF4. These antibodies bind and activate platelets, causing the clotting effect [50]. Widespread clotting also uses up the

platelets, which is why the hallmark features are both the presence of clots and a lack of platelets. One important question is what exactly triggers the production of these antibodies. Since we see this rare side effect in both adenovirus-vectored vaccines but not the mRNA vaccines, we think it is a reaction to something in the vector, rather than SARS-CoV-2 spike protein, which is in all the vaccines.

Danny:

Many speedy studies have come out implicating autoantibodies to PF4 in the causality of this [51]. But the rarity of the effect has to be emphasised; vaccines are much less risky than natural infection, and the clots are generally treatable once you know what to be on the lookout for.

Amongst the rumours that have been circulating about COVID-19, there are suggestions that the vaccine could also impact on fertility. Is there any basis to this?

Danny:

I'm sure that Viki has lots to say about this! This was based on some really spurious misinformation from someone who had got excited about a sequence of a few amino acids they'd spotted in common between spike and a placenta protein – there is no scientific basis to this.

Viki:

None whatsoever. This rumour was started by a prominent vaccine sceptic last December and has become very widely believed, despite a lack of evidence to support it. In fact, we have lots of evidence that the vaccines do *not* impact fertility. Participants in the clinical trials were asked not to become pregnant, but nonetheless, across the Moderna, Pfizer, AstraZeneca [reviewed in Ref. 14] and Janssen trials [52], 65 people became pregnant unintentionally. The pregnancies occurred equally across the vaccinated and unvaccinated groups, showing that vaccination does not reduce the chance of becoming pregnant. People are also now becoming pregnant following vaccination in the general rollout – in the United States, nearly 5000 such pregnancies had been reported to the CDC by 31 March 2021 [53], although this is likely to be an underestimate since not everyone will report their pregnancy, and we also have data showing that IVF patients who have received the vaccine are just as likely to become pregnant as those who have not [54].

In the UK, we are also vaccinating individuals who are already pregnant to protect them and their babies from the known dangers of COVID-19 in late pregnancy, which includes increased risk of preterm birth and stillbirth [13]. The United States and Israel have been vaccinating pregnant people since last December so we now have extensive real-world safety data from the United States showing that there is no increased risk of miscarriage, preterm birth or stillbirth associated with COVID-19 vaccination during pregnancy [53].

What about a genetic effect: can the vaccines alter our DNA in any way?

Danny:

Not in any way whatsoever. The vaccines simply turn on brief production of the spike protein to stimulate immunity. No mechanism exists to convert the mRNA into DNA or to integrate the spike-encoding gene into our own DNA.

How likely is it that there will be other long-term adverse effects of any of the vaccines?

Viki:

It's understandable that people worry about this, especially with the mRNA vaccines, since they seem to have arrived on the scene out of nowhere. But it's worth remembering that the first people to receive an mRNA vaccine did so in 2006 [15], so we actually have 15 years of follow-up data on those first recipients. And the first vaccines on an adenovirus-vectored background were given in 2012 [55], so again we have nearly a decade of follow-up for this platform.

If we think about how vaccines work, they induce an immune response in a couple of weeks, so any adverse event tends to happen in the same timeframe. In the past, we have detected all the adverse effects of new vaccines quite quickly after their rollout – in the order of about half a year, and we have been giving the COVID-19 vaccines for 6 months now. From all of this, we can say the likelihood of adverse effects emerging later on is very low.

Danny:

On the very rare occasions that there have been adverse events linked to COVID-19 vaccines, these tend to be rapid and short-term [28]. I've heard the hypothetical speculation that there might be some

uncharted consequence of vaccination, years down the line: I've never seen any evidence in support of this view, and it's hard to envisage a mechanism.

As a parent, I have to ask whether vaccination will be necessary in children and adolescents to keep COVID-19 in check? What evidence do we have to support efficacy and safety in younger age groups?

Viki:

We already have clinical trial data to show that the Pfizer vaccine is safe and effective in 12- to 15-year-olds [56], and Moderna will shortly publish their own results in this age group. The Pfizer vaccine has now been approved for use in 12- to 15-year-olds in the United States, UK and Europe and trials are being conducted in younger age groups.

I think it's important to emphasise that, so long as the evidence continues to show that the vaccines are safe and effective in children, there is a benefit to vaccination to the children themselves – not just that vaccinating them reduces the spread of the virus to more vulnerable people. Although severe COVID-19 disease is less common in children than older people, it does happen, and there have been cases of a rare Kawasaki-like syndrome linked to COVID-19 [57] as well as reports of adolescents suffering from long COVID [58,59]. My own children have missed out on a lot of school during the pandemic and I see the ability to keep schools open as another major benefit of vaccination in this age group. So, if the policy in the UK was to offer children the vaccine, I would like my children to be vaccinated. However, I do also see this as somewhat of a moral dilemma: is it fair that children in wealthy countries should receive the vaccine before adults who are at higher risk in poorer ones?

Danny:

As many have commented, it becomes an ethically challenging question if younger age groups are less likely to suffer severe or lethal infection. However, we've seen with each of the variants that they can have very different clinical phenotypes through the life course. With the Delta variant, we're seeing that, overwhelmingly, infections are peaking in younger age groups [60]. So, one reason to extend vaccines down into younger age groups is that some will get severely unwell and many, perhaps 10-20%, will face the long-term consequences of long COVID. Also, there's the

public health argument that, if we allow the virus to percolate in perpetuity in the young, we inevitably face a more protracted relationship with this virus and serious illness from it, including new mutations leading to new waves of variants.

Have the Pfizer-BioNTech and Moderna breakthroughs with mRNA-based vaccines opened up a whole new world of potential therapeutics for other pathogens, as well as potential treatments for other conditions?

Danny:

Yes – these are very exciting times. Modern molecular immunology has produced this incredible arsenal for use against infectious disease and other diseases, but before COVID-19 there was too much inertia and risk aversion in the system to spot and utilise it.

Viki:

Having this platform means that we will be able to rapidly respond to emerging pathogens in the future. And certainly, now that it has been proven as a technology, scientists are seeing if it can be used against diseases that have been intractable to vaccination in the past, such as malaria. But before this can be really useful as a global vaccine technology, we need to find ways to transport and store it at temperatures higher than -70 °C – that is something that is actively being worked on.

Despite a huge amount of scientific evidence in support of the safety and efficacy of the vaccines, there are many vaccine sceptics. Why do you think this is?

Viki:

I think it's important to make a distinction between people who are 'anti-vax' and those that we might call 'vaccine hesitant', or 'vaccine-deliberating'. People with a strong anti-vax stance often won't believe evidence presented to them, which makes it very difficult to engage with them. Those people who are deliberating about whether to get vaccinated are very different. They have a variety of reasonable concerns, which we should take seriously. For example, they may have been treated badly by the medical establishment in the past and are unwilling to trust health professionals now.

They may have heard a rumour about an effect of vaccination and are unaware of the evidence that shows the rumour is not true. Or they may just want to wait for more evidence to emerge before they get vaccinated themselves. We can get a long way with these people by asking: 'What information would you need to have before you would feel comfortable getting the vaccine?'

Danny:

I've spent an enormous amount of time speaking with various groups about this. Often the people I speak with are highly intelligent, but also anxious and scared by bad experiences they've had or heard accounts of from others. Addressing these concerns requires dialogue, empathy and lots of talking and listening.

What role can scientists play in engaging the public to understand how the vaccines work and to address common questions and concerns?

Viki:

Anyone can be a resource for their own community; for example, by answering questions asked by friends and family or on social media. You may think that you won't make much of a difference by doing this, but it does spread. Think of how many times you have heard someone say something like 'My friend's daughter, who is a GP, says that...' in support of their side of an argument.

Danny and I are both members of the British Society of Immunology (BSI), who have put together lots of resources to help researchers engage with members of the public in discussions relating to COVID-19 vaccines.

Danny:

The pandemic has transformed so many aspects of how we do and report science. One of these is science communication. We were to some extent trained to keep our heads down in our own academic bubble and debates, but at a time when the debates really matter (and everyone including policymakers is instantly an immunology expert), you need to be prepared to stick your head above the parapet if clarifications are needed. There's an understandable appetite for comment and answers in real time. I've taken a fair amount of time on this on a daily basis, from speaking to community groups where there are vaccine concerns, to engagement with various groups in government, as well as radio, TV and newspapers.

Finally, do you think that the COVID-19 pandemic will have a long-lasting impact on science and the public's perception of it, or even the way that we interact socially? What will be the most striking legacy of the pandemic, in your view?

Danny:

I maybe feel too battle-scarred to imagine that there'll be a new rapprochement with science. But I do think the way we do science has changed for the better in many ways, not least, getting data out and shared in real time...

Viki:

The pandemic has fast-tracked a lot of changes that were already underway, both in science and in society. In science, it has certainly given an enormous boost to the mRNA vaccine platform. It has also accelerated the acceptance of preprints, which I think is generally a good thing. But probably the biggest change will be more broadly, in how we live. Having worked remotely for a year, many people will want to continue doing so and this may change the nature of our cities. As a city person myself, I am not sure how I feel about this!

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Conflict of interest

Danny Altmann receives remuneration as a Consultant to Oxford Immunotec Ltd. The authors have no other conflicts of interest to declare.

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