



## RNA vaccine

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**Abstract:** An RNA vaccine or mRNA (messenger RNA) vaccine is a type of [vaccine](#) that uses a copy of a natural chemical called [messenger RNA](#) (mRNA) to produce an immune response. The vaccine [transfects](#) molecules of [synthetic RNA](#) into [immunity cells](#). Once inside the immune cells, the vaccine's RNA functions as mRNA, causing the cells to build the foreign [protein](#) that would normally be produced by a [pathogen](#) or by a cancer cell. These protein molecules stimulate an [adaptive immune response](#) which teaches the body how to identify and destroy the corresponding pathogen or cancer cells. The [delivery](#) of mRNA is achieved by a co-formulation of the molecule into [lipid nanoparticles](#) which protect the RNA strands and helps their absorption into the cells.

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An **RNA vaccine** or **mRNA (messenger RNA) vaccine** is a type of [vaccine](#) that uses a copy of a natural chemical called [messenger RNA](#) (mRNA) to produce an immune response.<sup>[1]</sup> The vaccine [transfects](#) molecules of [synthetic RNA](#) into [immunity cells](#). Once inside the immune cells, the vaccine's RNA functions as mRNA, causing the cells to build the foreign [protein](#) that would normally be produced by a [pathogen](#) (such as a virus) or by a cancer cell. These protein molecules stimulate an [adaptive immune response](#) which teaches the body how to identify and destroy the corresponding pathogen or cancer cells.<sup>[1]</sup> The [delivery](#) of mRNA is achieved by a co-formulation of the molecule into [lipid nanoparticles](#) which protect the RNA strands and helps their absorption into the cells.<sup>[2][3]</sup>

[Reactogenicity](#), the property of a vaccine of being able to produce common adverse reactions, is similar to that of conventional, non-RNA, vaccines.<sup>[4]</sup> People susceptible to an [autoimmune response](#) may have an adverse reaction to RNA vaccines.<sup>[4]</sup> The advantages of RNA vaccines over traditional protein vaccines are superior design and production speed, lower cost of production,<sup>[5][4]</sup> and the induction of both [cellular](#) as well as [humoral immunity](#).<sup>[6]</sup> A disadvantage in the Pfizer-BioNTech mRNA vaccine for [COVID-19](#) is that it requires [ultracold storage](#) before distribution.<sup>[1]</sup>

In [RNA therapeutics](#), [mRNA](#) vaccines have attracted considerable interest as [COVID-19 vaccines](#). By December 2020, there were two novel mRNA vaccines for COVID-19 that had completed the

required eight-week period post-final human trials and were awaiting [emergency use authorization](#) (EUA): the [Moderna COVID-19 vaccine](#) (mRNA-1273) and the [Pfizer–BioNTech COVID-19 vaccine](#) (BNT162b2).<sup>[1]</sup> On 2 December 2020, the UK's [Medicines and Healthcare products Regulatory Agency](#) (MHRA) became the [first medicines regulator](#) to approve an mRNA vaccine, authorizing the Pfizer–BioNTech COVID-19 vaccine (Comirnaty) for widespread use.<sup>[7][8][9]</sup> On 11 December 2020, the US [Food and Drug Administration](#) (FDA) issued an EUA for the Pfizer-BioNTech COVID-19 vaccine and the US [Centers for Disease Control and Prevention](#) (CDC) recommended its use in those aged 16 and older on 12 December 2020.<sup>[10][11]</sup> On 19 December 2020, the CDC recommended the use of the Moderna COVID-19 vaccine in adults after the FDA granted an EUA.<sup>[12][13]</sup>

The use of [RNA](#) in a vaccine has been the basis of substantial [misinformation](#) circulated via social media, wrongly claiming that the use of RNA alters a person's [DNA](#), or emphasizing the technology's previously unknown safety record, while ignoring the more recent accumulation of evidence from trials involving tens of thousands of people.<sup>[14]</sup>

## History

In 1989, researchers at the [Salk Institute](#), the [University of California, San Diego](#), and Vical published work demonstrating that mRNA, using a

liposomal nanoparticle for drug delivery, could transfect mRNA into a variety of eukaryotic cells.<sup>[15]</sup> In 1990, the University of Wisconsin reported positive results where naked mRNA was injected into the muscle of mice.<sup>[3]</sup> These studies were the first evidence that in vitro transcribed (IVT) mRNA could deliver the genetic information to produce proteins within living cell tissue.<sup>[3]</sup>

The use of RNA vaccines goes back to the 1990s. The *in vitro* demonstration of mRNA in animals was first reported in 1990,<sup>[16]</sup> and the use of mRNA for immunization was proposed shortly thereafter.<sup>[17][18]</sup> In 1993, Martinon demonstrated that liposome-encapsulated RNA could stimulate T-cells *in vivo*, and in 1994, Zhou & Berglund published the first evidence that RNA could be used as a vaccine to elicit both humoral and cellular immune response against a pathogen.<sup>[3][19][20]</sup>

In 2000, German biologist Ingmar Hoerl published an article on the efficiency of RNA-based vaccines, which he studied as part of his doctoral degree.<sup>[21][22]</sup> After completing his PhD, he founded CureVac together with his PhD supervisor Günther Jung, Steve Pascolo, Florian von der Muelbe, and Hans-Georg Rammensee.

Hungarian biochemist Katalin Kariko attempted to solve some of the main technical barriers to introducing mRNA into cells in the 1990s. Kariko partnered with American immunologist Drew Weissman, and by 2005 they published a joint paper that solved one of the key technical barriers by using modified nucleosides to get mRNA inside cells without setting off the body's defense system.<sup>[3][23]</sup> Harvard stem cell biologist Derrick Rossi (then at Stanford) read Kariko and Weissman's paper and recognized that their work was "groundbreaking",<sup>[23]</sup> and in 2010 founded the mRNA-focused biotech Moderna along with Robert Langer, who also saw its potential in vaccine development.<sup>[23][3]</sup> Like Moderna, BioNTech also licensed Kariko and Weissman's work.<sup>[23]</sup>

Up until 2020, these mRNA biotech companies had poor results testing mRNA drugs for cardiovascular, metabolic and renal diseases; selected targets for cancer; and rare diseases like Crigler–Najjar syndrome, with most finding that the side-effects of the mRNA delivery methods were too serious.<sup>[24][25]</sup> mRNA vaccines for human use have been developed and tested for the diseases rabies, Zika, cytomegalovirus, and influenza, although these mRNA vaccines have not been licensed.<sup>[26]</sup> Many large pharmaceutical companies abandoned the technology,<sup>[24]</sup> while some biotechs re-focused on the less profitable area of vaccines, where the doses would be at lower levels and side-effects reduced.<sup>[24][27]</sup>

At the onset of the COVID-19 pandemic, no mRNA drug or vaccine had been licensed for use in

humans. In December 2020, both Moderna and Pfizer–BioNTech obtained emergency use authorization for their mRNA-based COVID-19 vaccines, which had been funded by Operation Warp Speed (directly in the case of Moderna and indirectly for Pfizer–BioNTech).<sup>[23]</sup> On 2 December 2020, seven days after its final eight-week trial, the UK's Medicines and Healthcare products Regulatory Agency (MHRA), became the first global medicines regulator in history to approve an mRNA vaccine, granting "emergency authorization" for Pfizer–BioNTech's BNT162b2 COVID-19 vaccine for widespread use.<sup>[7][8][28]</sup> MHRA CEO June Raine said "no corners have been cut in approving it",<sup>[29]</sup> and that, "the benefits outweigh any risk".<sup>[30][31]</sup> On 11 December 2020 the FDA gave emergency use authorization for the Pfizer–BioNTech COVID-19 vaccine.<sup>[32]</sup>

### Mechanism

The goal of a vaccine is to stimulate the adaptive immune system to create antibodies that precisely target that particular pathogen. The markers on the pathogen that the antibodies target are called antigens.<sup>[33]</sup>

mRNA vaccines operate in a very different manner from a traditional vaccine.<sup>[1]</sup> Traditional vaccines stimulate an antibody response by injecting antigens, an attenuated virus (weakened or harmless virus), or a recombinant antigen-encoding viral vector (carrier virus engineered to have antigens into muscles). These antigen-containing ingredients are prepared and grown outside the body.

In contrast, mRNA vaccines introduce a short-lived<sup>[34]</sup> synthetically created fragment of the RNA sequence of a virus into the vaccinated individual. These mRNA fragments are taken up by dendritic cells—a type of immune system cell — by phagocytosis.<sup>[35]</sup> The dendritic cells use their own internal machinery (ribosomes) to read the mRNA and produce the viral antigens that the mRNA encodes before destroying the mRNA.<sup>[4]</sup> Although non-immune cells can potentially absorb vaccine mRNA, manufacture spikes, and display spikes on their surfaces, dendritic cells absorb the mRNA globules much more readily.<sup>[36]</sup>

Once the viral antigens are produced by the host cell, the normal adaptive immune system processes are followed. Antigens are broken down by proteasomes, then class I and class II MHC molecules attach to the antigen and transport it to the cellular membrane, activating the dendritic cell.<sup>[37]</sup> Once the dendritic cells are activated, they migrate to lymph nodes, where the antigen is presented to T cells and B cells.<sup>[38]</sup> This eventually leads to the production of antibodies that are specifically targeted to the antigen, resulting in immunity.<sup>[33]</sup>

The benefit of using mRNA to have host cells produce the antigen is that mRNA is far easier for vaccine creators to produce than antigen proteins or attenuated virus.<sup>[37][1][4]</sup> Another benefit is speed of design and production. Moderna designed their [mRNA-1273](#) vaccine for COVID-19 in 2 days.<sup>[39]</sup> Another advantage of RNA vaccines is that since the antigens are produced inside the cell, they stimulate [cellular immunity](#), as well as [humoral immunity](#).<sup>[6][40]</sup>

mRNA vaccines do not affect or reprogram DNA inside the cell. The synthetic mRNA fragment is a copy of the specific part of the viral RNA that carries the instructions to build the antigen of the virus (a protein spike, in the case of the main coronavirus mRNA vaccines), and is not related to human DNA. This misconception was circulated as the COVID-19 mRNA vaccines came to public prominence, and is a debunked [conspiracy theory](#).<sup>[41][42]</sup>

The mRNA should [degrade](#) in the cells after producing the foreign protein. However, because the specific formulation (including the exact composition of the lipid nanoparticle drug delivery coating) is kept confidential by the manufacturers of the candidate mRNA vaccines, details and timings have not been researched yet by third parties.<sup>[43]</sup>

### **Delivery**

The method of vaccine delivery can be broadly classified by whether the RNA transfer to cells happens within (*in vivo*) or outside (*ex vivo*) the organism.<sup>[3]</sup>

#### **Ex vivo**

[Dendritic cells](#) are a type of immune cells that display antigens on their [surfaces](#), leading to interactions with [T cells](#) to initiate an immune response. Dendritic cells can be collected from patients and programmed with the desired mRNA. Then, they can be re-administered back into patients to create an immune response.<sup>[44]</sup>

#### **In vivo**

Since the discovery that introducing *in vitro* transcribed mRNA leads to expression *in vivo* following direct administration, *in vivo* approaches have become more and more attractive.<sup>[45]</sup> They offer some advantages over *ex vivo* methods, particularly by avoiding the cost of harvesting and adapting dendritic cells from patients, and by imitating a regular infection. There are still obstacles for these methods to overcome for RNA vaccination to be a potent procedure. [Evolutionary mechanisms](#) that prevent the infiltration of unknown [nucleic material](#) and promote degradation by [RNases](#) need to be circumvented in order to initiate translation. In addition, RNA is too heavy to move around on its own inside the cell via [diffusion](#), making

it vulnerable to being discovered and eliminated by the host cell.

### **Naked mRNA injection**

A naked injection means that the [delivery](#) of the vaccine is simply held in a [buffer](#).<sup>[46]</sup> This mode of mRNA uptake has been known for since the 2000s. The first worldwide clinical studies (Tübingen, Germany) used [intradermal injections](#) of naked mRNA for vaccination.<sup>[47][48]</sup>

The use of RNA as a vaccine tool was discovered in the 1990s in the form of self-amplifying mRNA.<sup>[49][50]</sup> The two main categories of mRNA vaccines are non-amplifying (conventional, viral delivery), and molecular self-amplifying mRNA (non-viral delivery). When mRNA is delivered non-virally it enters the cell's cytoplasm and can amplify and express the antigenic protein.<sup>[51][52]</sup>

It has also emerged that the different routes of [injection](#), such as [into the skin](#), [blood](#) or to [muscles](#), resulted in varying levels of mRNA uptake, making the choice of administration route a critical aspect of delivery. One study showed, in comparing different routes, that [lymph node](#) injection leads to the largest T cell response.<sup>[53]</sup>

The mechanisms and consequently the evaluation of self-amplifying mRNA may be different, as self-amplifying mRNA is fundamentally different by being a much bigger molecule in size.<sup>[3]</sup>

### **Polyplex vector**

[Cationic polymers](#) can be mixed with mRNA to generate protective coatings called [polyplexes](#). These protect the recombinant mRNA from [ribonucleases](#) and assist its penetration in cells. [Protamine](#) is a natural cationic [peptide](#) and has been used to encapsulate mRNA for vaccination.<sup>[54]</sup>

### **Lipid nanoparticle vector**

The first time the FDA approved the use of [lipid nanoparticles](#) as a drug delivery system was in 2018, when the agency approved the first [siRNA](#) drug, [Onpattro](#).<sup>[55]</sup> Encapsulating the mRNA molecule in lipid nanoparticles was a critical breakthrough for producing viable mRNA vaccines, solving a number of key technical barriers in delivering the mRNA molecule into the host cell.<sup>[55][56]</sup> Research into using lipids to deliver siRNA to cells became a foundation for similar research into using lipids to deliver mRNA.<sup>[57]</sup> However, new lipids had to be invented to encapsulate mRNA strands, which are much longer than siRNA strands.<sup>[57]</sup>

Principally, the [lipid](#) provides a layer of protection against degradation, allowing more robust translational output. In addition, the customization of the lipid's outer layer allows the targeting of desired

cell types through [ligand](#) interactions. However, many studies have also highlighted the difficulty of studying this type of delivery, demonstrating that there is an inconsistency between *in vivo* and *in vitro* applications of nanoparticles in terms of cellular intake.<sup>[58]</sup> The nanoparticles can be administered to the body and transported via multiple routes, such as [intravenously](#) or through the [lymphatic system](#).<sup>[55]</sup>

One issue with lipid nanoparticles is that several of the breakthroughs leading to the practical use of that technology involved the use of [microfluidics](#). Microfluidic reaction chambers are difficult to scale up, since the entire point of microfluidics is to exploit microscale behaviors of liquids. The only way around this obstacle, as of 2021, is to conduct the process in a massively parallel fashion by building a great many microfluidic reaction chambers to run in parallel, a novel task requiring custom-built equipment. As of February 2021, this was thought to be the primary bottleneck in the manufacturing of mRNA vaccines.<sup>[59][60]</sup> Pfizer has since revealed that it used this approach to solve this problem. After verifying that impingement jet mixers could not be directly scaled up,<sup>[61]</sup> Pfizer made about 100 of the little mixers (each about the size of a [U.S. half-dollar coin](#)), connected them together with pumps and filters with a "maze of piping,"<sup>[62][63]</sup> and set up a computer system to regulate flow and pressure through the mixers.<sup>[61]</sup>

Another issue is the availability of the novel lipids used to create lipid nanoparticles, especially ionizable cationic lipids. Before 2020, such lipids were manufactured in small quantities measured in grams or kilograms, and they were used for medical research and for a handful of drugs for rare conditions. As the safety and efficacy of RNA vaccines became clear by late 2020, the few companies able to manufacture the requisite lipids were confronted with the challenge of scaling up production to respond to orders for several tons of lipids.<sup>[60][64]</sup>

### Viral vector

In addition to non-viral delivery methods, [RNA viruses](#) have been [engineered](#) to achieve similar immunological responses. Typical RNA viruses used as vectors include [retroviruses](#), [lentiviruses](#), [alphaviruses](#) and [rhabdoviruses](#), each of which can differ in structure and function.<sup>[65]</sup> Clinical studies have utilized such viruses on a range of diseases in [model animals](#) such as [mice](#), [chicken](#) and [primates](#).<sup>[66][67][68]</sup>

### Side effects and risks

[Reactogenicity](#) is similar to that of conventional, non-RNA vaccines. However, those susceptible to an [autoimmune response](#) may have an adverse reaction to RNA vaccines.<sup>[4]</sup> The mRNA strands in the vaccine may elicit an unintended immune

reaction. To minimize this, mRNA sequences in mRNA vaccines are designed to mimic those produced by host cells.<sup>[5]</sup>

Strong but transient reactogenic effects were reported in trials of novel COVID-19 RNA vaccines; most people will not experience severe side effects which include fever and fatigue. Severe side effects are defined as those that prevent daily activity.<sup>[69]</sup>

### General

Before 2020, no mRNA technology platform (drug or vaccine) had been authorized for use in humans, so there was a risk of unknown effects.<sup>[40]</sup> The 2020 coronavirus pandemic required faster production capability of mRNA vaccines, made them attractive to national health organizations, and led to debate about the type of initial authorization mRNA vaccines should get (including [emergency use authorization](#) or [expanded access authorization](#)) after the eight-week period of post-final human trials.<sup>[70][71]</sup>

### Storage

Because mRNA is fragile, the vaccine must be kept at very low temperatures to avoid degrading and thus giving little effective immunity to the recipient. Pfizer–BioNTech's [BNT162b2](#) mRNA vaccine has to be kept between  $-80$  and  $-60$  C ( $-112$  and  $-76$  F).<sup>[72][73]</sup> Moderna says their [mRNA-1273](#) vaccine can be stored between  $-25$  and  $-15$  C ( $-13$  and  $5$  F),<sup>[74]</sup> which is comparable to a home freezer,<sup>[73]</sup> and that it remains stable between  $2$  and  $8$  C ( $36$  and  $46$  F) for up to 30 days.<sup>[74][75]</sup> In November 2020, [Nature](#) reported, "While it's possible that differences in LNP formulations or mRNA secondary structures could account for the thermostability differences [between Moderna and BioNtech], many experts suspect both vaccine products will ultimately prove to have similar storage requirements and shelf lives under various temperature conditions."<sup>[40]</sup>

### Advantages

#### Traditional vaccines

RNA vaccines offer specific advantages over traditional [protein vaccines](#).<sup>[5][4]</sup> Because RNA vaccines are not constructed from an active pathogen (or even an inactivated pathogen), they are non-infectious. In contrast, traditional vaccines require the production of pathogens, which, if done at high volumes, could increase the risks of localized outbreaks of the virus at the production facility.<sup>[5]</sup> RNA vaccines can be produced faster, cheaper, and in a more standardized fashion (with fewer error rates in production), which can improve responsiveness to serious outbreaks.<sup>[4][5]</sup> For example, the Pfizer-BioNtech vaccine originally required 110 days to produce (before Pfizer began to optimize the manufacturing process to only 60 days),



but this was still far faster than traditional flu and polio vaccines.<sup>[62]</sup> Within that larger timeframe, the actual production time is only about 22 days: two weeks for molecular cloning of DNA plasmids and purification of DNA, four days for DNA-to-RNA [transcription](#) and purification of mRNA, and four days to encapsulate mRNA in lipid nanoparticles followed by [fill and finish](#).<sup>[76]</sup> The majority of the days needed for each production run are allocated to rigorous quality control at each stage.<sup>[62]</sup>

### DNA vaccines

In addition to sharing the advantages of theoretical [DNA vaccines](#) over established traditional [protein vaccines](#), RNA vaccination offers other benefits. The [mRNA](#) is [translated](#) in the [cytosol](#), so there is no need for the RNA to enter the [cell nucleus](#), and the risk of being integrated to the host [genome](#) is averted.<sup>[3]</sup> [Modified nucleosides](#) (for example, [pseudouridines](#), 2'-O-methylated nucleosides) can be incorporated to mRNA to suppress [immune response](#) stimulation to avoid immediate degradation and produce a more persistent effect through enhanced translation capacity.<sup>[77][78][79]</sup> The [open reading frame \(ORF\)](#) and [untranslated regions \(UTR\)](#) of mRNA can be optimized for different purposes (a process called sequence engineering of mRNA), for example through enriching the [guanine-cytosine content](#) or choosing specific UTRs known to increase translation.<sup>[80]</sup>

An additional ORF coding for a [replication](#) mechanism can be added to amplify antigen translation and therefore immune response, decreasing the amount of starting material needed.<sup>[50][81]</sup>

### Vaccine hesitancy

There is misinformation implying that mRNA vaccines could alter DNA in the nucleus.<sup>[14]</sup> mRNA in the [cytosol](#) is very rapidly degraded before it would have time to gain entry into the cell nucleus. (mRNA vaccines must be stored at very low temperature to prevent mRNA degradation.) [Retrovirus](#) can be single-stranded RNA (just as [SARS-CoV-2](#) vaccine is single-stranded RNA) which enters the cell nucleus and uses [reverse transcriptase](#) to make DNA from the RNA in the cell nucleus. A retrovirus has mechanisms to be imported into the nucleus, but other mRNA lack these mechanisms. Once inside the nucleus, creation of DNA from RNA cannot occur without a [primer](#), which accompanies a retrovirus, but which would not exist for other mRNA if placed in the nucleus.<sup>[82][83]</sup> Thus, mRNA vaccines cannot alter DNA because they cannot enter the nucleus, and because they have no primer to activate reverse transcriptase.

In November 2020, [The Washington Post](#) reported on novel mRNA vaccine hesitancy amongst healthcare professionals in the United States, citing

surveys that "some did not want to be in the first round, so they could wait and see if there are potential side effects".<sup>[84]</sup>

### Efficacy of mRNA vaccines for COVID-19

It is unclear why the novel mRNA COVID-19 vaccines from Moderna and Pfizer–BioNTech have shown potential efficacy rates of 90 to 95 percent, when the prior mRNA drug trials on pathogens other than COVID-19 were not so promising and had to be abandoned in the early phases of trials.<sup>[85]</sup> [Physician-scientist Margaret Liu](#) stated that it could be due to the "sheer volume of resources" that went into development, or that the vaccines might be "triggering a nonspecific inflammatory response to the mRNA that could be heightening its specific immune response, given that the [modified nucleoside technique](#) reduced inflammation but hasn't eliminated it completely", and that "this may also explain the intense reactions such as aches and fevers reported in some recipients of the mRNA SARS-CoV-2 vaccines". These reactions though severe were transient and another view is that they were believed to be a reaction to the lipid drug delivery molecules.<sup>[85]</sup>

Unlike DNA molecules, the mRNA molecule is a very fragile molecule that degrades within minutes in an exposed environment, and thus mRNA vaccines need to be transported and stored at very low temperatures.<sup>[86]</sup> Outside the cell, or its drug delivery system, the mRNA molecule is also quickly broken down by the host.<sup>[5]</sup> This fragility of the mRNA molecule is a hurdle to the [efficacy](#) of any mRNA vaccine due to bulk disintegration before it enters the cells, that could lead people to believe, and act, as if they are immune when they are not.<sup>[86][5]</sup>

### Self-amplifying RNA

Self-amplifying RNA (saRNA) is a technology similar to mRNA, except the saRNA produces multiple copies of itself in the cell before producing proteins like mRNA does. This allows smaller quantities to be used and has other potential advantages.<sup>[87][88]</sup> saRNA vaccines are being researched, including development of a [malaria vaccine](#).

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