

Long-term Side Effects of COVID-19 Vaccine? What We Know.

Since COVID-19 vaccines are new, some people have asked about their effects on those who take them. Short-term side effects (i.e., those that happen in the days after a vaccine has been given) are readily apparent because of clinical trial reports and personal experiences, but people also wonder about possible long-term effects of these vaccines. To answer this question, scientists study the available evidence, and while the rules of science do not allow scientists to say that long-term effects can never happen, the evidence is strong that these vaccines will not cause long-term harm.

The evidence

Vaccine history

The history of vaccines shows that severe effects following vaccination can occur. But when they do, these effects tend to happen within two months of vaccination:

- **Oral polio vaccine** — About 1 in 2.4 million recipients of the oral polio vaccine, which is no longer used in the U.S., were paralyzed following vaccination when the vaccine virus reverted to “wild type” poliovirus. This happened when genetic changes to weaken the virus in the lab were lost during viral replication in the vaccine recipient. Paralysis occurred about seven to 30 days (one to four weeks) after vaccination. Because vaccine recipients “shed” the virus in their stools, on occasion, contacts of these people would be paralyzed when they were infected, and the genetic reversion occurred in them. This secondary event could happen up to 60 days (eight to nine weeks) after the first person was vaccinated (because it took time for the virus to spread to the next person).
- **Yellow fever vaccine** — The yellow fever vaccine is not routinely recommended in the U.S., but it is required for travel to certain countries. Two delayed negative effects have been detected after receipt of this vaccine:
 - Nervous system involvement — This effect causes swelling of the brain or spinal cord. It occurred most often when infants younger than 6 months of age received this vaccine, which is why this group is not recommended to get the vaccine. It can also happen, albeit less frequently, in those older than 6 months of age who receive the vaccine. When this happens, the average time between receipt of the vaccine and symptom onset is two weeks, with the range up to three weeks.
 - Viscerotropic disease — This condition is characterized by multisystem organ failure. Yellow fever infection can also cause multisystem organ failure. This adverse event happened so infrequently that it was not described until the early 2000s. In this situation, vaccine virus replicates and spreads throughout the body; onset occurs less than one week after vaccination, most often, occurring about three days after receipt of the vaccine.
- **Influenza vaccine** — Two severe adverse events associated with influenza vaccine are also instructive:
 - A 1976 swine influenza vaccine was identified as a rare cause of Guillain-Barré syndrome (GBS), an ascending paralysis that can involve the muscles of breathing. Subsequent studies have found flu vaccines to be a cause of GBS in about 1 person per 1 million doses of vaccine. In contrast, influenza infection, which is also a cause of GBS, causes this condition in about 17 people per 1 million infections — 17 times more frequently than following vaccination. Almost all cases following vaccination occurred in the eight weeks after receipt of the vaccine.
 - In 2009, during the H1N1 pandemic, one influenza vaccine used in Europe was found to cause narcolepsy in about 1 in 55,000 vaccine recipients. Narcolepsy is a sleep disorder characterized by excessive fatigue and periods of sleep throughout the day. Despite various influenza vaccines used during the pandemic, only one caused this issue, which was believed to have resulted from a confluence of conditions presented by that vaccine compared with all other vaccines used. The average onset of symptoms occurred within seven weeks of vaccination.
- **MMR vaccine** — About 1 of 30,000 recipients of measles, mumps and rubella (MMR) vaccine can experience a temporary decrease in platelets; a condition called thrombocytopenia. Platelets are the cells responsible for clotting of blood. Both measles and mumps infections can cause thrombocytopenia. This condition is most often found between one and three weeks after vaccination, but in a few cases, it occurred up to eight weeks after vaccination.

These experiences demonstrate two important findings. First, when these events occurred, the onset was within eight weeks of receipt of the vaccine. Second, in all of these cases, except narcolepsy following H1N1 vaccine, the side effect of the vaccine was something that could be caused by the infection, meaning that getting infected with the virus also carried a risk of experiencing these outcomes. In the narcolepsy experience, the cause was determined to be related to the adjuvant used in that preparation of vaccine.

Regardless, this history humbles vaccine scientists. They know that they hold people’s lives in their hands. As stated by Dr. Maurice Hilleman, perhaps the most prolific vaccine scientist in history, “I never breathe a sigh of relief until the first few million doses are out there.” (Personal communication, Paul Offit, 2004). For this reason, scientists and public health officials carefully analyze and continually monitor the data related to every vaccine before, during and after it becomes available.

COVID-19 vaccines

Even with this history in mind, some reasonably wonder about the COVID-19 vaccines because they have not previously been approved for use in people. Now that millions of doses have been administered, we have learned about a few rare but severe side effects. They all occur shortly after vaccination:

- **Thrombosis with thrombocytopenia syndrome (TTS)** — TTS is a condition in which a person experiences blood clotting as well as low platelet count, called thrombocytopenia. The clots can occur in vessels in various organs or in the legs. TTS occurs in about 1-2 of every 1 million people who receive an adenovirus-based COVID-19 vaccine, like the J&J/Janssen vaccine. TTS develops up to three weeks after getting vaccinated. While anyone between 18 and 64 years of age can experience this side effect, it occurs most commonly among women between 30 and 49 years of age.
- **Guillain-Barré syndrome (GBS)** — GBS is a condition in which the immune system attacks the peripheral nervous system, meaning the nerves that are not part of the brain or spinal cord, but which are located throughout the rest of the body. GBS has been found to occur in about 1 of every 100,000 people who receive an adenovirus-based vaccine (e.g., J&J/Janssen). It typically occurs during the first three weeks after getting vaccinated. The condition has most often been identified in males between 50 and 64 years of age, but it can occur in females and those 65 years and older on occasion.

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- Myocarditis — Myocarditis is an inflammation of the heart. About 1 of every 50,000 mRNA-vaccine recipients experience this condition, but it is most likely in adults 29 years and younger, and more often occurs in males. This condition typically occurs within four days of vaccination. It is more likely after receipt of the second dose but can occur following any dose.

In each of these cases, the side effect occurred within a few days up to a few weeks of vaccination, but all occurred well before two months after vaccination. Likewise, COVID-19 infection also causes myocarditis and GBS and is associated with a variety of blood clotting issues, and the risk of experiencing them is greater following infection than following vaccination.

Some still wonder what might happen months or years after receipt of these vaccines, but we can also be reassured by what we know about how these vaccines are processed:

mRNA vaccine

- Although COVID-19 mRNA vaccines are new, this type of vaccine has been studied in people before. mRNA vaccines against HIV, rabies, Zika and flu have been tested in phase 1 and phase 2 trials in people. The technology has also been used in clinical trials as a way to treat some cancers. Even though these products have not been licensed for use in people, the reasons have not related to safety. In fact, these efforts allowed us to accumulate important preliminary information about mRNA technology and its safety, which was useful when considering it for COVID-19 vaccines.
- mRNA is made and used in protein production in all cells of our bodies every day. As such, cells have mechanisms in place to ensure that no protein is made in quantities greater than needed. One way this happens is that mRNA has a “poly(A) tail.” In the cytoplasm, this tail ensures mRNA decay. As the mRNA is used to make proteins in the cell, the length of the poly(A) tail decreases, until it is too short for the mRNA to continue being used as a protein blueprint. Once this happens, the mRNA breaks down and is removed as cellular debris. This process limits how long mRNA remains in the cytoplasm — and, therefore, how much protein is produced.

As such, poly(A) tails ensure that the cell breaks down the vaccine mRNA in a timely manner. Likewise, this understanding allows scientists to design vaccine-delivered mRNA in a way that ensures it does not stay in the cell longer than needed to generate immunity.

Adenovirus-based vaccine

- Although COVID-19 adenovirus vaccines are new, this type of vaccine has been studied in people before, and another adenovirus-based vaccine was approved for use in Europe in those 1 year of age and older starting in the summer of 2020. That vaccine is one of two doses of an Ebola vaccine, and it uses the same type of adenovirus as the Johnson & Johnson vaccine.
- Adenovirus-based vaccines deliver DNA to the nucleus of the cell, which is used to make mRNA that serves as a blueprint for making the protein. DNA is more stable and lasts longer than mRNA, which is evidenced by strengthening of the immune response for one to two months after vaccination. However, studies of the AstraZeneca COVID-19 vaccine have shown that if people get a second dose six weeks after the first dose, they have lower immune responses than if they get the second dose 12 weeks after the first dose. Because the second dose generates memory responses, it is better to administer after the primary immune response is fully developed. As such, the improved responses after 12 weeks instead of six weeks suggests that the vaccine is done being processed between six and 12 weeks after a dose is given.
- This timing agrees with studies in mice, which suggested that protein was no longer being produced three weeks after inoculation, but that specialized cells of the immune system, called antigen-presenting cells, containing pieces of protein from the antigen, could be found in lymph nodes for about four to six weeks after inoculation.

Because of the knowledge gained with other vaccines, the FDA required companies making COVID-19 vaccines to follow trial participants for a minimum of eight weeks before they could submit their data for approval. Likewise, the participants in the vaccine trials continue to be followed even though the vaccines have been approved for use.

The misinformation

While concerns about long-term effects of vaccines are legitimate, it is important to be aware that the organized anti-vaccine industry has targeted this issue as a way to sow doubt and confusion about COVID-19 vaccines. According to the Center for Countering Digital Hate, professional anti-vaccine activists organized a meeting in the fall of 2020 to create messaging that would decrease acceptance of COVID-19 vaccines once available. These organized efforts aim to move people to extreme positions about vaccines — that is to say, from having legitimate questions about vaccines to becoming “anti-vaccine,” refusing all vaccines and believing conspiracy theories and false narratives. In some cases, individuals in these groups do not believe the science, and in other cases, they are seeking to profit from this hesitancy by encouraging the use of other products to “protect” against COVID-19.

With this in mind, we recommend carefully vetting sources of information, and the statements they are making, to ensure that you are getting answers from reliable sources. Find out more about evaluating information and recognizing false narratives using these tools; links can be found in the online version of this article (chop.edu/news/long-term-side-effects-covid-19-vaccine):

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