Medical Xpress

Why we can't 'boost' our way out of the COVID-19 pandemic for the long term

April 18 2022, by Prakash Nagarkatti and Mitzi Nagarkatti

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With yet another COVID-19 booster available for vulnerable populations in the U.S., many people find themselves wondering what the end game will be.

The mRNA vaccines currently used in the U.S. against COVID-19 have been highly successful at preventing hospitalization and death. The Commonwealth Fund recently reported that in the U.S. alone, the vaccines have prevented over 2 million people from dying and over 17 million from hospitalization.

However, the vaccines have failed to provide long-term protective immunity to prevent breakthrough infections—cases of COVID-19 infection that occur in people who are fully vaccinated.

Because of this, the Centers for Disease Control and Prevention recently endorsed a second booster shot for individuals 50 years of age and older and people who are immunocompromised. Other countries including Israel, the U.K. and South Korea have also approved a second booster.

However, it has become increasingly clear that the second booster does not provide long-lasting protection against breakthrough infections. As a result, it will be necessary to retool the existing vaccines to increase the duration of protection in order to help bring the pandemic to an end.

As immunologists studying immune response to infections and other threats, we are trying to better understand the vaccine booster-induced immunity against COVID-19.

Activating longer-term immunity

It's a bit of a medical mystery: Why are mRNA vaccines so successful in preventing the serious form of COVID-19 but not so great at protecting against breakthrough infections? Understanding this concept is critical for stopping new infections and controlling the pandemic.

COVID-19 infection is unique in that the majority of people who get it recover with mild to moderate symptoms, while a small percentage get

the severe disease that can lead to hospitalization and death.

Understanding how our immune system works during the mild versus severe forms of COVID-19 is also important to the process of developing more targeted vaccines.

When people are first exposed to SARS-CoV-2—the virus that causes COVID-19—or to a vaccine against COVID-19, the immune system activates two key types of immune cells, called B and T cells. The B cells produce Y-shaped protein molecules called antibodies. The antibodies bind to the protruding spike protein on the surface of the virus. This blocks the virus from entering a cell and ultimately prevents it from causing an infection.

However, if not enough antibodies are produced, the virus can escape and infect the host cells. When this happens, the immune system activates what are known as killer T cells. These cells can recognize virus-infected cells immediately after infection and destroy them, thereby preventing the virus from replicating and causing widespread infection.

Thus, there is increasing evidence that antibodies may help prevent breakthrough infections while the killer T cells provide protection against the severe form of the disease.

Why booster shots?

The B cells and T cells are unique in that after they mount an initial immune response, they get converted into memory cells. Unlike antibodies, memory cells can stay in a person's body for several decades and can mount a rapid response when they encounter the same infectious agent. It is because of such memory cells that some vaccines against diseases such as smallpox provide protection for decades.

But with certain vaccines, such as hepatitis, it is necessary to give multiple doses of a vaccine to boost the immune response. This is because the first or second dose is not sufficient to induce robust antibodies or to sustain the memory B and T cell response.

This boosting, or amplifying of the immune response, helps to increase the number of B cells and T cells that can respond to the infectious agent. Boosting also triggers the memory response, thereby providing prolonged immunity against reinfection.

COVID vaccine boosters

While the third dose—or first booster—of COVID-19 vaccines was highly effective in preventing the severe form of COVID-19, the protection afforded against infection lasted for less than four to six months.

That diminished protection even after the third dose is what led the CDC to endorse the fourth shot of COVID-19 vaccine—called the second booster—for people who are immunocompromised and those aged 50 and older.

However, a recent preliminary study from Israel that has not yet been peer-reviewed showed that the second booster did not further boost the immune response but merely restored the waning immune response seen during the third dose. Also, the second booster provided little extra protection against COVID-19 when compared to the initial three doses.

So while the second booster certainly provides a small benefit to the most vulnerable people by extending immune protection by a few months, there has been considerable confusion over what the availability of the fourth shot means for the general population.

Frequent boosting and immune exhaustion

In addition to the inability of the current COVID-19 vaccines to provide long-term immunity, some researchers believe that frequent or constant exposure to foreign molecules found in an infectious agent may cause immune "exhaustion."

Such a phenomenon has been widely reported with HIV infection and cancer. In those cases, because the T cells "see" the foreign molecules all the time, they can get worn down and fail to rid the body of the cancer or HIV.

Evidence also suggests that in severe cases of COVID-19, the killer T cells may be exhibiting immune exhaustion and therefore be unable to mount a strong immune response. Whether repeated COVID-19 vaccine boosters can cause similar T cell exhaustion is a possibility that needs further study.

Role of adjuvants to boost vaccine-induced immunity

Another reason why the mRNA vaccines have failed to induce sustained antibody and memory response may be related to ingredients called adjuvants. Traditional vaccines such as those for diphtheria and tetanus use adjuvants to boost the immune response. These are compounds that activate the innate immunity that consists of cells known as macrophages. These are specialized cells that help the T cells and B cells, ultimately inducing a stronger antibody response.

Because mRNA-based vaccines are a relatively new class of vaccines, they do not include the traditional adjuvants. The current mRNA vaccines used in the U.S. rely on small balls of fat called lipid nanoparticles to deliver the mRNA. These lipid molecules can act as

adjuvants, but how precisely these molecules affect the long-term immune response remains to be seen. And whether the current COVID-19 vaccines' failure to trigger strong long-lived antibody response is related to the adjuvants in the existing formulations remains to be explored.

While the current vaccines are highly effective in preventing severe disease, the next phase of vaccine development will need to focus on how to trigger a long-lived antibody response that would last for at least a year, making it likely that COVID-19 vaccines will become an annual shot.

Provided by The Conversation

Citation: Why we can't 'boost' our way out of the COVID-19 pandemic for the long term (2022, April 18) retrieved 6 May 2024 from https://medicalxpress.com/news/2022-04-boost-covid-pandemic-term.html