As the days unfold with a seeming sameness in this odd summer of the pandemic, news of vaccine clinical trials begins to trickle in, and another buzzword from epidemiology is entering the everyday lexicon: **durability**.

To be successful, a vaccine’s protection must last or booster shots periodically restore it. Some vaccines lose efficacy over time, including those for yellow fever, pertussis, and of course influenza.

For some vaccines, antibodies and the B cells that make them persist and protect for a long time. For other infectious diseases, like TB and malaria, T cells are needed in vaccines too. B and T cells (lymphocytes) are types of white blood cells, which are part of the immune system.

**Antibody response may be ephemeral**

> “Give a man a fish and you feed him for a day. Teach him how to fish and you feed him for a lifetime,” said Chinese philosopher Lao Tzu, founder of Taoism.

Tzu might have been referring metaphorically to the immune system’s response to viral infection: an initial rush of antibodies that fades as a longer-lasting cell-based memory builds that primes the body to rapidly release antibodies upon a future encounter with the pathogen.

Antibodies are proteins, so they don’t make more of themselves as cells might. That’s why antibodies collected from plasma from a person who’s recovered from COVID-19 lasts a few weeks. It’s also why an “antibody medicine” like Regeneron’s dual-antibody REGN-COV2 provides only short-term protection, a bridge until a vaccine becomes available.

To remain effective over a reasonable period of time, a vaccine must mimic the memory component of an immune response, which arises from B and T cells and is therefore called the “cellular” immune response. The shorter-term release of antibodies into the bloodstream is the “humoral” immune response ("humor" means fluid).

A strong antibody response to a vaccine may be a harbinger of lasting B and T cell protection, but vaccines may be marketed before their durability is known – a complete understanding of how long a vaccine’s protection lasts can take years. The vaccine against the mumps, for example, went on the market in 1967, but in 2006, several colleges had outbreaks, among students whose childhood mumps vaccine had worn off. A booster extends the coverage.
Clues to a COVID-19 vaccine’s durability come from natural immunity from past coronavirus infections. The antibody response to SARS and MERS persisted less than a year. But so far, the cellular immune response to SARS, the older of the two, has lasted eleven years.

Clinical trials to evaluate COVID-19 vaccines in people consider both antibody production and the building of cellular immunity. And a vaccine can be even more protective than natural immunity.

“A vaccine elicits memory B and T cells so the immune system remembers how to fight the disease in the future. Natural infection is not likely to produce durable immunity and vaccination will be essential to produce herd immunity to reduce the probability of viral transmission,” said Arlene Sharpe MD PhD co-director of the Evergrande Center for Immunologic Diseases at Harvard Medical School and Brigham and Women’s Hospital on a recent zoom that MassCPR, a group of Boston-area institutions that formed in early March in response to the pandemic, held.

Making antibodies

The immune system isn’t as easy to visualize as a skeleton splayed out in a Halloween decoration, the flattened entrails of a roadkill, or the circulatory system, which even Groucho Marx in the film Horse Feathers could easily explain. (“Let us follow a corpuscle on its journey through the body.”)
Instead, the immune system is an army of billions of cells and their secretions that stand ready to attack newly encountered pathogens, remember old ones, and at the same time recognize “self,” protecting the body’s own tissues. The cells travel in clear lymph fluid, passing through lymph nodes that filter out debris.

The immune system reacts in three stages. First, physical barriers keep pathogens out: skin, earwax, waving cilia in the throat, stomach acid, diarrhea. Next, innate immunity unleashes a bath of inflammatory molecules that are a generalized response to infection.

Finally comes adaptive immunity, which is specific and provides the ‘memory’ that a vaccine emulates. In addition to T and B cells, innate immunity includes the wandering, blobby macrophages, which engulf pathogens and are festooned with bits of a pathogen’s surface – antigens – that alert other immune defenses.

Antibody production begins when a stimulated B cell divides in the bone marrow, giving rise to two types of cells. One, a plasma cell, has a clear oblong area that is a ginormous Golgi apparatus, which processes 2,000 antibodies per second that enter the circulation.

The second “daughter cell” of a dividing B cell is a memory B cell. Like the name suggests, a memory B cell hangs around, and if the pathogen shows up again, jumps into action and pumps out more antibodies, cutting off the new infection fast.

An important part of the antibody response is that it’s “polyclonal” – differently-shaped antibodies are produced, each recognizing and binding to a different part of a pathogen, like using different weapons to tackle different parts of an enemy’s body.

Some antibodies just bind to a pathogen, but others “neutralize” it, and those are the ones that make a vaccine or immune response effective. Yet certain other antibodies actually enhance infection; vaccines are designed to block this from happening.

**T cells call the shots**

T cells come in several varieties and exert complex effects.

- Helper (aka CD4) T cells activate B cells and release interleukins, which also stimulate B cells.
- Killer (aka cytotoxic or CD8) T cells directly attack cells stuffed with viruses, which antibodies can’t do.
- Regulatory T cells (T regs) check the entire response so it doesn’t destroy healthy cells.

Tracking T cells is important in evaluating potential vaccine durability. And although we only have a half-year of data, the natural infection suggests that antibody responses may be short-lived or not strong enough.
“Investigators are reporting the antibody response in humans infected with COVID who recover tends to drop relatively quickly. To some people that’s an alarm bell and they guess that a vaccine will show little durability. But following recovery from an acute infection, a decline in antibodies is normal B cell biology and is exactly what we predict,” said Daniel Barouch, MD, PhD, professor of medicine, Harvard Medical School and director, Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center.

One of the first reports showed antibodies decreasing by half in just 37 days among a small sample of people who had mild cases. That’s similar to SARS and MERS, in which antibodies fade away within a year. But so far, reports of phase 1 clinical trial results for two COVID vaccines are encouraging.

**Moderna’s and Oxford’s vaccine candidates boost antibodies and T cells**

The first interim report, published in *The New England Journal of Medicine* July 14, found that all 45 participants who received one of three doses of Moderna’s mRNA-1273 vaccine made antibodies, more with the higher dose. Binding antibodies appeared by day 15 and neutralizing antibodies after a second dose on day 28. Neutralizing antibodies are a biomarker of vaccine protection for other respiratory viruses, so that’s good news.

“Responses are comparable to what occurs with natural infection, and perhaps a little higher. Data are encouraging; the strategy elicits immune responses that are targeted against the virus,” said Lindsey R. Baden, MD, associate professor of medicine, Harvard Medical School and director of clinical research, Brigham and Women’s Hospital. The study used antibodies in plasma from recovered patients as a control for the natural immune response, and the vaccine exceeded that comparison.

Even better news: participants made T cells. Helpers appear first, which pump out a specific soup of cytokines, and then after the second dose of vaccine, killers appear, making sure that any remaining viruses can’t replicate.

The phase 1 trial showed that the middle of three doses is best for tempering efficacy with side effects. Phase 2 began in May and phase 3, began on July 27. Overall, depending on the number of trials that
Modernma’s vaccine (mRNA-1273) is designed to enhance visibility to the immune system. The target cell translates it into an engineered version of the virus’s spike protein that tames the inflammatory response. The spike is also tweaked to be more stable than the natural one.

On July 20 the second clinical trial report came from the Oxford COVID Vaccine Trial Group’s candidate ChAdOx1, in *The Lancet*. That vaccine consists of the genetic instructions for the spike protein delivered in a chimpanzee virus.

Like the mRNA vaccine, Oxford’s candidate is given in doses 28 days apart. And it, too, evokes both a humoral (antibody) and cellular (T cell) response.

So far, the numbers of vaccinated people are small, but the reports are optimistic.

**You can’t rush science: Potential dangers to fast rolling out of a vaccine**

With clever variations on the clinical trial theme, like overlapping phases and designing spike proteins to be more visible to the immune system, it may indeed be possible to barrel through phase 3 clinical trials that test a statistically significant number of people. But post-marketing surveillance, a normal part of drug development, is going to be critical.

The participants in the MassCPR zoom marveled that vaccine development for COVID-19 is so far taking 5 to 10 months, compared to the historical 5 to 10 years.

“We are only months into knowing about this virus, so any longevity of the immune response we have to interpret with care because our understanding of the biology and durability of the biology will take time.
The virus will evolve and we have to take that into consideration,” said Baden. He showed data from monkeys that suggest a long-lasting effect is possible.

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Practically speaking, the phase 3 trials will take time because the participants aren’t being injected with virus, for ethical reasons. Instead, investigators must wait for the volunteers to encounter the virus in their communities, to see if a smaller percentage of vaccinated people become infected than the unvaccinated control groups. And that’s why a vaccine “by the end of the year would be quite a surprise for many of us,” said Ken Mayer, MD, of the Fenway Institute.

“We’ll have increasing clarity as the next 3 to 6 months proceed with a suite of clinical trials underway or soon to be. Most optimistic is late fall for first availability for an Emergency Use Authorization. But a tremendous number of things would have to go perfectly to achieve that. Early 2021 is more realistic,” said Barouch. An “EUA” brought COVID-19 treatment remdesivir to patients before the official FDA approval.

Baden agreed that early 2021 is more feasible. He points out the potential savings of 6 to 12 months from beginning to manufacture candidate vaccines before their clinical trials conclude, well before. “Financial risks are acceptable, safety not, and that’s why it will take at least 3 to 6 months more.”

Once a vaccine is out there, attention will turn to epidemiology. What percentage of the population must be vaccinated or have natural immunity to induce herd immunity? And how many people will actually take
If several vaccines make it to the finish line, how will people be assigned to them? People over age 65, for example, would benefit most from a vaccine that includes an adjuvant, which is a chemical that affects the immune response. A vaccine candidate from Australian biotech company Vaxine Pty Limited, for example, includes a complex sugar that lowers the risk of the vaccine triggering an excessive immune response. The sugar adjuvant has worked well in vaccines against influenza, hepatitis B, and West Nile virus, according to Nikolai Petrovsky, PhD, research director at the company.

Assessing the all-important T cell response will take time, too, because that’s the way the cellular immune response unfurls in nature. Gradually. A full immune response is a finely-tuned process that is a consequence of millennia of evolution – not of politics, PR, potential profits, or wishful thinking.

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