How a painless patch could one day deliver vaccines

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When you pull up your sleeve to get your yearly flu shot, you might feel a twinge of anxiety as a health care provider readies the needle and syringe. Maybe you find yourself looking away or taking deep breaths to steel yourself, even though it's over in just a few seconds.

So what if there was a painless vaccine you could administer yourself? What if, rather than heading to the pharmacy, you could simply place the equivalent of a Band-Aid on your arm, leave it there for a few minutes to a few hours, then take it off and let your physician know you've been innoculated?

That's one of the main goals of vaccine patch technology. Multiple research teams have designed patches that use microneedle arrays made out of materials like stainless steel or sugar to deliver quick and pain-free vaccination by taking advantage of the key role that skin plays in training our immune system. One group is even developing a completely needle-free method to confer immunity.

Vaccination is a crucial public health measure against serious, preventable illnesses, but the fear of needles — or of vaccines themselves — can be a hurdle to protection for individuals and their communities. In many places around the world, extreme conditions or lack of health care can stifle accessibility to traditional vaccines, too.

Vaccine patches haven't yet been approved for commercial use, but both global vaccine experts and researchers have acknowledged their potential for years, particularly when it comes to making vaccines more accessible worldwide. Several patches have gone through human or animal trials, and at least two are currently being evaluated to potentially protect against COVID-19.

To bring this type of vaccine to market, a range of logistical and financial hurdles will have to be overcome. But if one or several of the many companies and organizations involved in

developing this technology are successful, we could one day live in a world where any vaccine we need is delivered right to our door.

Skin is our 'first layer of defense'

Skin probably isn't the first part of the body that comes to mind when you think about the immune system, but it plays a major role in protecting us from all of the invisible invaders we confront in our daily lives.

"All day long, you're getting exposed to viruses and bacteria and you usually don't even know it because your skin is doing a good job of taking them off," explained Louis Falo, a professor and chair of dermatology at the University of Pittsburgh School of Medicine.

The skin has three primary layers: the epidermis, the top layer made up of epithelial cells that slough off over time; the dermis, the middle layer that contains blood vessels, hair follicles, sweat glands and nerve endings; and the hypodermis, the bottom layer made up of connective tissue and fat that attaches the first two layers to the muscle and bone below. The epidermis contains five sublayers, and the dermis consists of two regions.

Within the dermis is a collection of dendritic cells whose primary job is to patrol your skin in search of foreign invaders like bacteria or viruses. When they come across anything that shouldn't be there, they capture it and start the process of teaching your immune system how to fight it off.

"When the skin gets insulted, invaded, or damaged, it sends a signal to the dendritic cells that there is a problem," Falo said. "Then [those cells] start grabbing stuff and migrating back into the central part of the body to generate the immune responses."

How vaccine patches work

Falo is involved in an effort at the University of Pittsburgh School of Medicine to create a vaccine patch to protect against coronavirus, dubbed "PittCoVacc," that features an array of 400 sharp-tipped, sugar-based microneedles, each of which is "about the width of a [strand] of human hair and about half a millimeter in length."

These needles house the vaccine's antigen: pieces of viral protein that resemble the spike proteins that coat the coronavirus' exterior, which are what the virus uses to invade our cells. That means the microneedles themselves are the vaccine, Falo said.

These screens show a magnified view of the PittCoVacc's microneedle array. Photo courtesy the University of Pittsburgh School of Medicine

"When you put that on a patient and you apply some gentle pressure, the hard needles are able to penetrate the outer layer of the skin. And then when they're in the skin, they absorb water and very rapidly dissolve," Falo explained. "When they dissolve, they release the antigen directly into the skin."

That's when dendritic cells can start training the body to make antibodies in response to the antigen.

The microneedle arrays in PittCoVacc are so small that they avoid nerves and blood vessels beneath the skin, so application is both painless and bloodless, Falo said. The patch also requires a very small concentration of the vaccine compared to traditional shots, which Falo explained makes it less likely to cause any adverse reactions in recipients.

Falo noted that the manufacturing process could be scaled up fairly quickly in order to produce the patches in larger quantities because each one holds such a small amount of antigen. Unlike traditional vaccines, which must be kept cold or frozen until they're ready to be injected into the body, vaccine patches like PittCoVacc are stable at room temperature. That means that they could be packaged, stored and shipped around the world "just like Band-Aids" at a low cost.

“The sugar actually encases the ingredients and forms a protective layer so that they don’t denature when they get warmer, so that they maintain their structure and their function when conditions normally would prevent that,” Falo said.

PittCoVacc hasn’t yet entered clinical human trials, but it has been tested in mice. Although mice can’t actually contract coronavirus — their cells don’t have the same ACE2 receptor structure that allows the virus to bind to and enter ours — preliminary results have shown that the mice created the antibodies Falo’s team would hope to see in people who received their vaccine.

Not all microarray patches use the same technology. The biopharmaceutical company Verndari, Inc., has designed a small microneedle array patch it calls the “VaxiPatch” that features stainless steel needles as opposed to the sugar-based ones used in PittCoVacc’s design. Each microneedle has a small well built into its side that holds just 10 nanoliters of liquid vaccine.

When the patch is assembled, all of the moisture within that droplet evaporates, leaving behind a “sugar glass” to deliver the antigen itself. Verndari’s COVID-19 vaccine is derived from a subsection of the coronavirus’ spike protein called the receptor binding domain.

Sample model of the VaxiPatch™ microneedle array dermal patch at the UC Davis Laboratories, Sacramento, CA. Photo Credit: Rudy Meyers Photography

“A sugar glass is like hard candy,” Daniel Henderson, co-founder and CEO of Verndari, said. When you apply it to a patient, “the moisture in the skin dissolves off this sugar glass from a solid back to a liquid, delivering the vaccine painlessly via the patch.”

The VaxiPatch is meant to be removed after about five minutes. After that, it leaves behind a temporary blue dye pattern on the skin. If the VaxiPatch is eventually approved for commercial use, Henderson expects that it would first be administered to patients in a traditional medical setting in order to reduce the risk of misapplication. But in a potential scenario where the patch could be sent directly to people’s homes, Henderson photo of that blue dye pattern and sending it to their health care provider as proof of vaccination.

Before the COVID-19 pandemic, the company developed a protein-based flu vaccine to be delivered using its VaxiPatch. Data so far suggests that the patch could be shelf stable for up to a month and withstand temperatures up to 60 degrees Centigrade, or 140 degrees Fahrenheit, which Henderson said would make it ideal for global distribution.

Traditional vaccines generally need to be stored in a strict, cold temperature range, which makes distribution expensive and especially difficult in places that lack a strong health care infrastructure. Another major cost, Henderson pointed out, is the health care provider who is trained to safely and sterilely administer the shot itself. Eliminating both of those requirements could dramatically reduce the amount of money it takes to get vaccines to those in need.

Henderson pictures a system where recipients could send their used patches back to Verndari, or perhaps their health care provider, who would then take care of disposal. Returned VaxiPatches could also be evaluated in a lab setting to calculate how much of the vaccine was actually delivered to the skin based on how much, if any, was left over after it was discarded.

The VaxiPatch that has been designed to protect against COVID-19 is currently moving through preclinical animal studies at the University of California, Davis. If that research yields promising results, the company can file an Investigational New Drug (IND) application with the FDA, which would consider greenlighting Phase 1 clinical trials in humans.

But Henderson's aspirations for the technology stretch beyond this pandemic to the many other pathogens that people need protection from across the world.

Verndari and Falo's teams are not the first to pilot this technology. In 2017, researchers at the Georgia Institute of Technology and Emory University led a Phase 1 clinical study in humans that was funded by the National Institutes of Health. It featured a "dime-sized" microneedle patch designed by a team led by Mark Prausnitz of the Georgia Institute of Technology that was intended to protect against the flu.

That patch has 100 microneedles that dissolve in the skin over the course of a few minutes and can then be peeled off and "discarded like a used bandage strip." Like other vaccine patches, it's also shelf stable and doesn't require refrigeration.

According to a report from the National Institutes of Health, researchers randomly divided 100 participants into four groups. One group applied the patch to themselves, another was given the patch by a health care provider and a third was given a placebo patch. The final group received a traditional flu shot, also from a health care provider.

After that, the team used blood samples to determine each participant's immune response to their respective vaccination route. Researchers found that those who received either the patch or the shot had similar responses, and that "participants who applied the patch themselves showed robust immune responses." Though more trials must be run to investigate its safety and efficacy, they concluded that patch recipients so far suffered "no serious related side effects," although some reported "faint redness" and "mild itching that lasted two to three days."

A vaccine without needles?

Although microneedle arrays are a popular option for vaccine patches, they're not the only innovation being considered to potentially revolutionize the way we're immunized. Ben Miller, a researcher and professor at the University of Rochester's Medical Center, helped develop a patch that avoids puncturing the skin.

Miller explained that our skin cells are held together by " tight junctions," or a network of proteins that "act like molecular Velcro." Loops stick out of each protein and lock in to loops on other proteins, and that structure prevents anything from getting through our skin barrier.

"The way you screw up Velcro is you put something into it that kind of blocks those hooks and loops from getting together," Miller said. "And so what we decided to do was [make] a synthetic molecule that looks like one of those loops that's on the outside of a cell."

Miller's team drew on research by his collaborator Lisa Beck on eczema, a common condition that causes permeable patches of skin that are more susceptible to outside irritants. Research suggests that those with eczema may have lower levels of the protein claudin-1, which is "essential for preventing leakiness of the skin barrier ."

Their patch introduces a synthetic protein called a peptide that temporarily blocks claudin-1 in the small area of skin directly under the patch. If ever approved for use in humans, Miller said, it could be introduced through a kind of topical cream within the patch.

That peptide "opens a door" in the skin and allows an antigen to enter, where it can be captured by dendritic cells to start the process of learning an immune response. By the time the patch is taken off, which Miller estimates might be about 12 hours after initial administration, the barrier closes back up the way it was before.

"You just kind of temporarily open a window in the skin at the molecular level, deliver the

material in and then that closes back up," Miller explained. "When you're done, you just pull the patch off and it's totally safe to dispose of it."

So far, Miller's patch has shown to be nontoxic and "completely reversible" in cell cultures and in animal studies. In a 2019 preclinical study, researchers injected mice with a primer flu vaccine to mimic the way that we receive flu shots. Some mice then received the patch while others were given a regular booster shot.

"What we found was that the patch method was very similar, almost exactly the same as the intramuscular injection method," Miller said."

In order to move his team's vaccine patch technology forward, Miller hopes to put their patch through larger-scale animal trials and, if those results are promising, human trials over the next one to three years.

Making vaccine patches a reality

Any vaccine patch will need to be both affordable for recipients and distributors and able to be mass produced in order to make it to market. William Moss, executive director of the International Vaccine Access Center (IVAC) at the Johns Hopkins Bloomberg School of Public Health, pointed out that brand new infrastructure would need to be established to produce these patches at a large scale — an investment that no government or company so far has been willing to make to move that process along.

Robert Pettigrew, former director of the National Institute of Biomedical Imaging and Bioengineering, was involved in the 2017 NIH Phase 1 clinical trial that evaluated a microneedle patch to protect against the flu. As with any kind of technology, he said, none of these patches will likely be 100-percent effective in every person. Some recipients may also have a reaction to materials used in the patches.

"Some people may press too hard, some people may not press hard enough" if they were to administer the patches themselves, Pettigrew said. "Some people may have too little [body fat] under the epidermis and some may have too little. You can imagine all sorts of little variations from person to person."

Pettigrew does believe, however, that vaccine patches could be effective in a high percentage of people, and that the technology itself could be "transformative."

The main selling points of vaccine patches — the fact that they don't need to be refrigerated and don't necessarily need to be administered by a physician — have long appealed to experts working to vaccinate people in remote parts of the world. In sub-Saharan Africa specifically, Moss said, poor health infrastructure can prevent people from accessing immunization services. It's also difficult to deliver vaccines to areas of conflict or humanitarian crisis.

Global health organizations have been fighting for years to eradicate measles via vaccination in certain regions of the world that suffer greatly from the disease. The measles vaccine, which is already stored dry and mixed with a diluent on site before administration, would be a perfect candidate for a vaccine patch.

“If we had safe and effective microarray patches for measles vaccination, that would really be a game changer,” Moss said.

Moss noted that it’s difficult to amass the funding and resources to push vaccine patches through the expensive process of clinical testing. Pharmaceutical companies are more interested in patch technology for drug delivery rather than vaccines, which he said “aren’t big money makers.”

Although Moss is skeptical that a patch will be one of the first COVID-19 vaccines to make it across the finish line, he is hopeful that renewed attention toward the technology could bring it closer to a reality. If one of those patches garners significant investment, it could help establish a regulatory and, potentially, a high-volume manufacturing process for future patches. And experts agree that could have significant potential to revolutionize the way we immunize people across the globe, including against illnesses like measles.

Vaccine patch technology could “really [democratize]” vaccination, Pettigrew said. “It brings modern science and modern medicine to everybody in a way that is not delivered to the extent that it could be.”