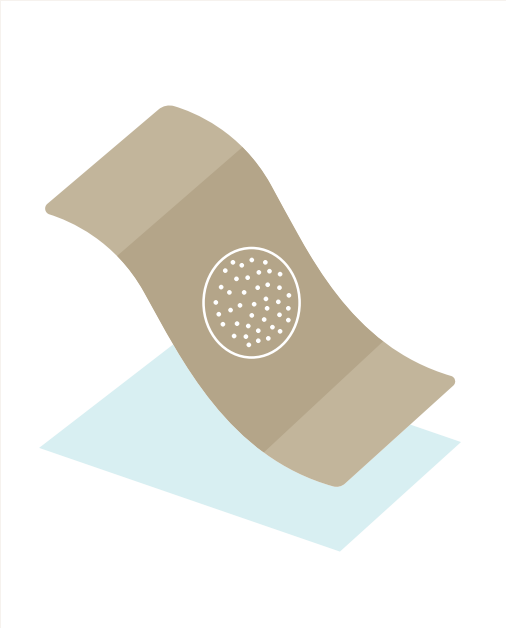
Microarray Patches for Vaccine Administration

WHAT IS THE TECHNOLOGY?

A microarray patch (MAP; also called a microneedle patch) is an emerging technology for administering vaccines that has the potential to modernize mass vaccination campaigns. MAPs have been proposed for use against measles, influenza, and other infectious diseases and could theoretically be developed for most vaccine-preventable diseases. Currently, MAPs are being evaluated by the CDC and PATH for global health applications, but they could be highly useful in emergency response settings as well.



Several different types of MAPs have been developed, the most promising of which is comprised of an array of small, water soluble, thermostable cones that are embedded with the antigen of choice and held against the skin by an adhesive bandage. Once applied and pressed into the skin, the cones dissolve within minutes, delivering the antigenic payload into the dermal tissue.

MAPs are a reliable, pain-free method of delivering an intradermal (ie, into the skin) injection that could minimize the amount of vaccine needed to confer immunity. Additionally, in the context of a severe pandemic or GCB event, they could enable self-administration of vaccines, which would not require advanced medical training or expertise. Immunologically, antigens delivered via intradermal administration are taken up by specialized antigen-presenting cells (APCs) that reside in the skin. These cells take in and process antigen from the vaccine, transmit it to the lymphatic system, and present the antigen to T and B cells. T-cells are able to recognize and kill virus-infected cells, and B-cells can make antibodies against an invading virus, thereby generating a protective immune response.

WHAT PROBLEM DOES THIS SOLVE?

In the setting of a GCB event involving an infectious disease amenable to vaccination, the ability to generate rapid, population-wide vaccine coverage will likely be a high priority and may be the only viable way to meaningfully protect large numbers of people. Unfortunately, recent experiences with infectious disease emergencies, notably the 2009 H1N1 influenza pandemic, have demonstrated that we lack the ability to rapidly immunize the US population, let alone the global population.

Severe epidemic and pandemic disease events like influenza, Ebola, and Zika have catalyzed initiatives to expedite vaccine research, development, and manufacturing.[39] However, relatively little attention has been paid to addressing the logistical and technological aspects of administering vaccines in an emergency—particularly for pandemics and GCB events, when vaccination will need to be completed rapidly. A primary bottleneck in this process is the small number of healthcare providers—relative to the susceptible population, which could potentially be the entire planet for a wholly novel pathogen—who would or could be pressed into service to implement a mass vaccination campaign during an emergency. This is especially true in the developing world, where even the routine provision of medical care, including vaccination, is an ongoing and persistent challenge.

Medical Countermeasure Distribution, Dispensing, and Administration

HOW DO WE DO IT NOW?

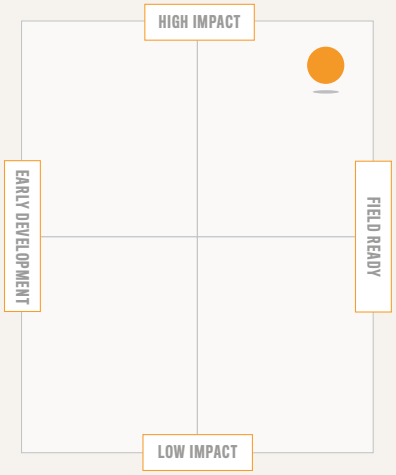
Today, most vaccines are administered using a needle and syringe. While this is a tried and true delivery method, it has several downsides, including the need for healthcare providers to administer the injection, the risk to healthcare providers of needlestick injuries and exposure to blood-borne pathogens, and pain for the recipient.

It typically takes weeks or months for a coalition of public health authorities, pharmacists, and healthcare providers to immunize large populations. Using MAPs would fundamentally change the vaccination process from one of administering vaccines to one of distribution and self-administration, resulting in significant savings of time and resources.

In theory, mass vaccination could be performed within days using MAPs for self-administration. During a GCB event, any time saved in vaccination operations—including R&D, production, distribution, and administration and dispensing—could translate into a significant number of illnesses prevented and lives saved.

WHAT DOES SUCCESS LOOK LIKE?

Widespread adoption of MAP technology could significantly decrease the time to complete immunization operations by enabling self-administration during emergencies. Pandemic vaccines could be distributed via more logistically efficient means—such as commercial shipping companies or the postal service—or they could use the current POD models that are already established. Public health and healthcare personnel would still be required to dispense or administer vaccines to some subsections of the population (eg, homeless individuals, those with allergies to the primary vaccine) and conduct necessary surveillance of adverse events, but the resources required to implement these programs would be significantly less than for a traditional mass vaccination POD. A worthy, but admittedly ambitious, goal would be the eventual elimination of the needle and syringe administration of all vaccines, which could potentially lower barriers to obtaining routine vaccinations like measles, mumps and rubella (MMR); diphtheria, tetanus, and pertussis (DTap); and seasonal influenza.



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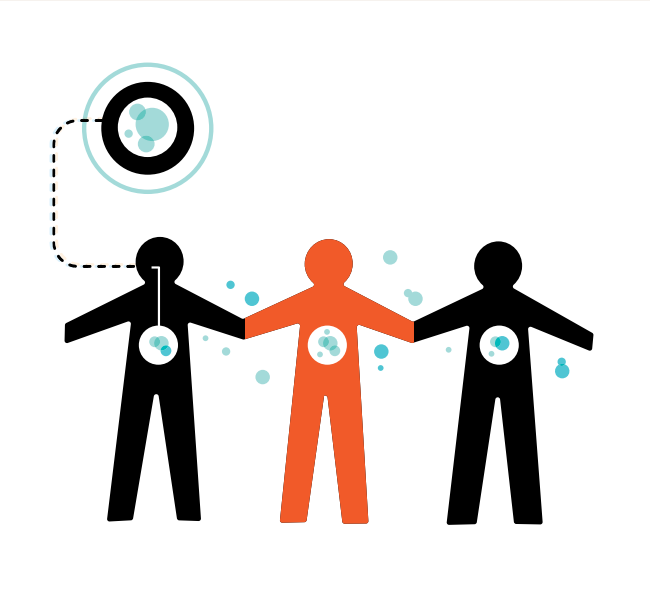
Self-Spreading Vaccines



WHAT IS THE TECHNOLOGY?

Self-spreading vaccines—also known as transmissible or self-propagating vaccines—are genetically engineered to move through populations in the same way as communicable diseases, but rather than causing disease, they confer protection. The vision is that a small number of individuals in the target population could be vaccinated, and the vaccine strain would then circulate in the population much like a pathogenic virus. These vaccines could dramatically increase vaccine coverage in human or animal populations without requiring each individual to be inoculated. This technology is currently aimed primarily at animal populations. Because most infectious diseases are zoonotic,[40] controlling disease in animal populations would also reduce the risk to humans.

There are 2 main types of self-spreading vaccines: recombinant vector vaccines and live viral vaccines. Recombinant vector vaccines combine the elements of a pathogenic virus that induce immunity (removing the portion that causes disease) with a transmissible viral vector. Cytomegalovirus is one candidate vector for recombinant vaccines, because it is highly species-specific and moderately transmissible. Live viral vaccines are attenuated, meaning that the vaccine viruses are much less pathogenic than wild-type and would be similar to the oral polio vaccine or the live attenuated influenza vaccine (LAIV) in that those vaccines can sometimes transmit from person to person.

Although there are substantial technical challenges in genetically engineering viruses, synthetic biology tools such as CRISPR/Cas9 are likely to aid researchers in overcoming these hurdles in the coming years. Self-spreading vaccines have already been used to protect wild rabbits from myxomatosis and to control Sin Nombre virus in rodent populations. Additional work is targeting Ebola virus in apes and bats, Lassa virus in rats, and bovine tuberculosis in badgers.

WHAT PROBLEM DOES THIS SOLVE?

The most practical and useful application of self-spreading vaccines would be to control disease spread in wild animal populations (also known as sylvatic spread). A vaccine would be administered to a few selected animals in hotspots among target populations including nonhuman primates, bats, or rodents. The vaccine would then spread within the target population, eliminating the need to vaccinate each animal. Successful disease control in animal populations could limit the number of infected animals and thereby reduce the opportunity for the disease to spill over into humans, thus stopping outbreaks in humans before they ever emerge. Such a sylvatic strategy would reduce the overall number of outbreak opportunities in humans, but it could not interrupt an outbreak once it becomes established in humans.

In the event of a grave public health threat, self-spreading vaccines could potentially be used to broadly inoculate human populations. Like the approach in animals, only a small number of vaccinated individuals would be required in order to confer protection to a larger susceptible population, thus eliminating the need for mass vaccination operations, including PODs.

Medical Countermeasure Distribution, Dispensing, and Administration

HOW DO WE DO IT NOW?

Current mass vaccination strategies require each individual to be inoculated with 1 or more doses of vaccine. For humans, this can be accomplished at PODs or doctors' offices, by healthcare providers, but for wild animal populations there is the added challenge of animals being difficult to track and catch.

One relatively successful approach to vaccinating wild animal populations is through use of oral baits. For example, oral rabies vaccine baits have been dropped aerially into animal habitats to reach vulnerable species like foxes and bats. This approach relies on development of a suitable and stable vaccine and timely bait uptake, and it may not reach all vulnerable animals. Nevertheless, it has contributed significantly to rabies elimination in a number of geographic areas,[41] and it is also being used for other diseases like Lyme disease.[42]

In human pandemics, each element in the pipeline of vaccine production, distribution, and administration would have significant difficulties in scaling effectively to address the crisis. For example, if vaccine cannot be produced at scale, or if the healthcare system cannot flex to accommodate the administration of millions of doses of vaccine, the effectiveness of the response will be diminished.

WHAT DOES SUCCESS LOOK LIKE?

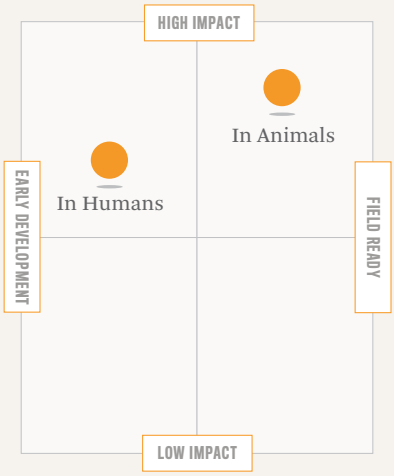
If used in animals, successful implementation of self-spreading vaccines would prevent spillover of pathogens with pandemic potential into human populations without the need for difficult and costly mass vaccination operations in animal populations. For example, inoculation of relatively few bats and nonhuman primates against Ebola could potentially limit or eliminate human outbreaks. Sufficient coverage could even eradicate animal diseases, permanently eliminating these risks to both animals and humans.

For human use, targeted release of weakly transmissible self-spreading vaccine early in an outbreak could create herd immunity in communities and prevent an outbreak from becoming a pandemic. If introduced later, after an outbreak has become widespread, self-spreading vaccines could still help to protect susceptible individuals and limit the number of new cases and prevent catastrophic outcomes.

While self-spreading vaccines could help reduce illness and death in a severe pandemic, this approach comes with several big challenges. One important component of the current vaccination approach for humans is the informed consent process. In order to receive a vaccine, individuals (or their legal guardians) must be informed about the risks of vaccination by a healthcare provider and provide their consent before being vaccinated. Those who decline are not forced to receive a vaccine. In the case of self-spreading vaccines, the individuals directly vaccinated would have this option, but those

to whom the vaccine subsequently spreads would not. Additionally, self-spreading vaccines would potentially infect individuals with contraindications, such as allergies, that could be life-threatening. The ethical and regulatory challenges surrounding informed consent and prevention and monitoring of adverse events would be critical challenges to implementing this approach even in an extreme event.

Finally, there is a not insignificant risk of the vaccine virus reverting to wild-type virulence, as has sometimes occurred with the oral polio vaccine—which is not intended to be fully virulent or transmissible, but which has reverted to become both neurovirulent and transmissible in rare instances. This is both a medical risk and a public perception risk; the possibility of vaccine-induced disease would be a major concern to the public. Modeling efforts suggest that making self-spreading vaccines weakly transmissible might reduce the risk of reversion to wild-type virulence by limiting the number of opportunities for the virus to evolve. However, weakly transmissible vaccines would have to be introduced to more people to obtain sufficient immunity in the target population.



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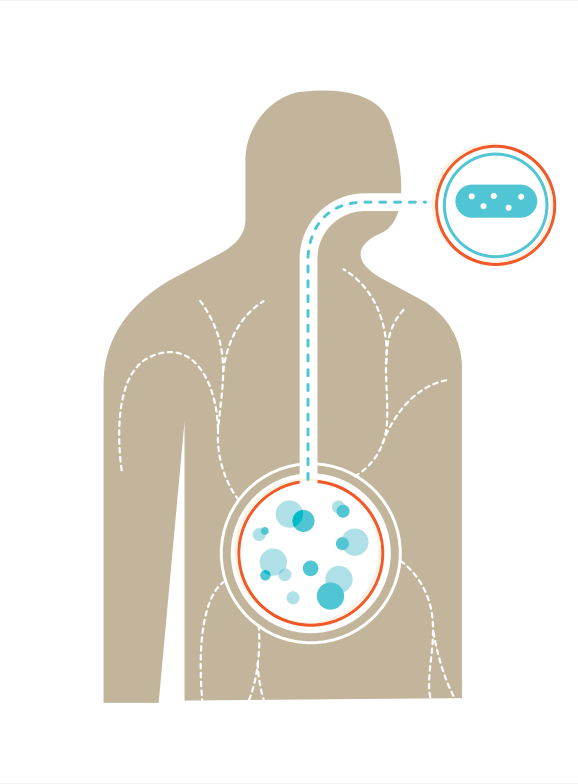
Ingestible Bacteria for Vaccination



WHAT IS THE TECHNOLOGY?

Bacteria can be genetically engineered to produce antigens in a human host, acting as a vaccine, which triggers immunity to pathogens of concern. One such vaccine platform (Vaxonella, created by Prokarium) turns a genetically engineered attenuated strain of the *Salmonella enterica* bacterium into an in vivo bioreactor to create recombinant vaccines. These bacteria are placed inside capsules that, once swallowed, dissolve in the small intestine and release the bacteria. Through natural processes, these bacteria traverse the intestinal mucosa through microfold cells, which carry them to aggregated lymphoid follicles known as Peyer's patches. Within these lymphoid follicles, antigen presenting cells (APC), such as dendritic cells and macrophages, naturally respond and phagocytose an invading bacterium. Once inside these human immune cells, the engineered bacterium begins to express antigens that trigger the APCs to stimulate all arms of the immune system. The bacterium itself is then quickly destroyed by the body's immune cells.

Typhella, a vaccine for typhoid fever, has already been made using this platform and has been shown thus far to be safe and effective in 5 phase I and 3 phase II clinical trials. The ease with which the *Salmonella enterica* strain can be genetically manipulated lends itself to producing a wide range of vaccine antigens.

WHAT PROBLEM DOES THIS SOLVE?

Simplified and low- cost administration makes oral vaccines an attractive option, but previous oral vaccines have had challenges related to efficacy and safety. Some oral vaccines are inferior to those delivered via injection because they are unable to elicit a sufficient immune response through the gut. Other vaccines, like the oral polio vaccine, may be protective and effective for outbreak response, but they can revert to a disease-causing form and spread from person to person.

Through the use of synthetic biology, the Vaxonella platform overcomes several of the limitations that have prevented widespread use of oral vaccines. Because, in this case, antigen is being made within the body's own cells, there is no need for the costly protein purification techniques used to develop antigen in a laboratory. Additionally, by using the bacteria's natural protein expression system, antigens can be created more easily than they could

be in the lab. And because the bacteria would produce antigen in APCs and not before, it is possible to express antigens that would normally be toxic to the chassis bacteria themselves. This allows the platform to make vaccines with antigens that, due to their toxicity, are not compatible with other vaccine platforms. Finally, using attenuated bacteria with genetic deletions greatly reduces the chance of the bacteria reverting to wild type and causing disease.

There are several logistical and social barriers that this type of oral vaccine would also help overcome. The Vaxonella platform produces thermostable vaccine products that can be stored at 40°C for several weeks, making vaccination more cost-effective and logistically easier because cold chain is not necessary. Oral formulation of this type of vaccine also avoids the need to have healthcare providers administer it. And avoiding the pain and discomfort associated with needle pricks will also increase patient compliance.

HOW DO WE DO IT NOW?

Many vaccines made using current methods rely heavily on cold chain to ensure product quality, which can account for up to 50% of distribution costs.[43] This is a major barrier in producing cost-effective vaccines for low-resource settings, where there is already an increased risk of infectious disease outbreaks due to weakened healthcare and sanitation infrastructure and malnutrition.

Subcutaneous and intramuscular injections remain the primary form of vaccine administration, but healthcare providers are needed to administer vaccines, making it logistically challenging to respond to an emergency in a timely and efficient manner.

There are currently only a handful of licensed oral vaccines, because of difficulties in effectively transporting viral antigens across the gut epithelium. Furthermore, complex viral antigens display intricate folding structures that make them very technically difficult, time-consuming, and costly to produce as traditional subunit vaccines for injection.

WHAT DOES SUCCESS LOOK LIKE?

This type of oral vaccine platform could enable the development of a vaccine within a substantially reduced time frame, at a fraction of the current cost. Without the need for cold chain, distribution and dispensing would be greatly facilitated, and ease of administration could ameliorate much of the logistical burden medical responders currently face, allowing more people to be vaccinated.

Success of this type of vaccine platform in an emerging epidemic would still depend heavily on improvements in timely identification of disease-specific antigens as well as having the necessary supportive regulatory environment in place. It is currently estimated that in a pandemic situation where the disease is known, optimistically a vaccine using this type of platform could be developed in about 2 months, plus additional weeks to scale up production. Advances in disease-specific antigen-identification platforms would expand the applicability of this technology to deal with emerging infectious diseases.