Introduction to RadVax

Executive Summary

RadVax is an open-source vaccine that anyone can make. It is designed by a team of researchers connected to Harvard Medical School, and the intellectual property made available without copyright restriction. It is extremely affordable, costing less than $5 per person. RadVax is very flexible, and it is easy to make boosters to address new variants. The open-source design means that local control and ownership of vaccine production is entirely possible, and the infrastructure can be used to address both current and future pandemics.

Overview

RadVax is built on 3 well-established technologies: **nasal delivery**, which provides immunity where the virus enters/leaves the body; **chitosan nanoparticles**, which stimulate the immune system to fight an invader; and **lab-grown protein fragments**, which tell the immune system which invader to fight. Each of these technologies has been used safely for many years - RadVax is primarily a method of combining them. The method for combining the technologies uses simple techniques that are possible for anyone with basic laboratory skills.

Here is what each of the components do:

Nasal delivery

This just means spraying the vaccine directly into the nose (allergy sprays, and some flu vaccines use the same approach). Since no needles or injections are required, the vaccine can be **administered by anyone**, not just medical personnel. Nasal delivery also means that the system-wide immune response isn't as strong as with an injection. This makes the vaccine safer, but also means that it needs to be taken 3 or 4 times (instead of just 1 or 2 injections).

Chitosan nanoparticles

The chitosan nanoparticles serve two purposes. The first is as a transport system, which brings the protein fragments into the body. Because the nanoparticles are about the same size as the COVID virus, they travel to the same parts of the nasal tissues, bringing the protein fragments with them. The nanoparticles also help keep the protein fragments in place long enough for the body to respond.

The second purpose of chitosan is as an "adjuvant"; an adjuvant is a substance that stimulates the immune system, telling the body that it needs to fight an invader. Chitosan has been used in clinical trials, and found safe enough that the **EU has recommended it for use as an adjuvant**

in vaccines.

Lab-grown protein fragments

Your body learns to recognize invading viruses based on the shape of the virus' outer protein shell. So to teach the body what to fight, most COVID vaccines include small pieces of the virus' shell that are both distinct to the virus, and likely to be recognized by the immune system. These small pieces of protein are called "peptides". The world is full of peptides that we eat and breathe every day, without any problem since peptides themselves are generally harmless. They are made in the cells of plants and animals, and can't reproduce. It is only when a peptide is combined with an adjuvant that the body learns to attack.

One difference between the various COVID vaccines is how they introduce those peptides into the body. The Moderna, Pfizer, and AstraZeneca vaccines all trick the body into making these peptides. RadVax is a little bit different; it uses peptides that are made in a lab, and delivers them directly to the body (similar to the Novavax vaccine). While the delivery methods differ, the core principle is the same - **the combination of an adjuvant and the peptides teach the body what to attack**.

The choice of which peptides to use is one of the most important parts of any vaccine. Scientists make the decision based on several factors about peptides, including which peptides:

- can be dissolved in water (so they can be delivered to the body)
- can be recognized by the immune system (so the body can learn what to attack)
- are unique to the virus (so the body doesn't become sensitive to anything besides the virus)
- are likely to remain unchanged as the virus mutates (so that the immunity is long-lasting)

Safety and efficacy

Safety

RadVax was designed to be very, **very safe**; each component of the design was selected to err on the side of safety. Nasal delivery was chosen because it is a well-established, safe delivery method which has the additional benefit of focussing the immune response in the mucus membranes of the nose and sinuses. This means that the worst side effect is typically just a stuffy nose, or in a few cases a mild headache. Chitosan nanoparticles as a delivery/adjuvant was chosen because it has been used in clinical trials, has an excellent safety record, and was **already recommended for use by the EU**. It stimulates the immune system, but doesn't stimulate it too much. Lab-grown protein fragments (peptides) were selected carefully as well. Amongst other things, the scientists at RaDVaC have compared the peptide sequences against the entire human genome (using BLAST), to be sure that the peptides used won't be mistaken

for some part of the body. Possibly the best indication of its safety: all of the **RaDVaC team has not only taken RadVax themselves, they've also offered it to their families**. An estimated 1000 people have already taken RadVax under self-experimentation exemptions in the USA, and the most severe reported symptoms have been headache and congestion.

RadVax should be safe to use even with special populations, such as elderly people, children, and pregnant or breastfeeding mothers. Many of the people who have taken RadVax already are well into their 80s, and haven't reported any unusual side effects. There's no reason to believe there's any particular risk with administering RadVax to children, but it's extremely difficult to get a small child to breathe in deeply while nasal spray enters their nose, and therefore challenging to administer effectively. We should always be especially cautious when considering nursing or pregnant mothers. Primarily because at that age, children are developing so rapidly that small effects can be harmful in later years. But in this case, there's no reason to believe there's any particular risk. The immune response is mild (no fevers reported, etc), and concentrated in the nasal tissues; it's certainly less dangerous than acquiring COVID. Women in countries that are already reaching herd immunity might prefer to forgo RadVax, since their environment will be fairly safe. Women in places where they still have a high chance of getting COVID should check with their doctors, to see if RadVax is a good choice for them.

Efficacy

The efficacy of RadVax is not yet clear; the RaDVaC group is trying to find government partners to begin clinical trials for efficacy. That said, there are strong theoretical reasons to believe that RadVax provides very **good protection at the mucus membranes in the nasal area**. This helps do two things:

- prevent you from acquiring COVID (because the virus enters the body by breathing in)
- prevent you from spreading COVID (because you breathe out virus growing in the nose)

Unfortunately, testing for this localized immune response is difficult. Some RadVackers with the necessary equipment have done so, and reported signs of local immunity, which is both expected and encouraging.

The other difficulty in evaluating efficacy is that RadVax stimulates a different part of the immune system from most vaccines. The part of the immune system activated is determined primarily by the adjuvant; RadVax uses chitosan, which primarily activates T-cells. Most other vaccines instead primarily activate B-cells. B-cells work by identifying invading viruses, and then recruiting other parts of the immune system to attack. It is easy to test for B-cell activation, because they produce antibodies which circulate in the blood. T-cells, in contrast, don't directly attack the virus; instead they attack your own cells if they have been taken over by the virus. This makes T-cell response much harder to evaluate, even though it can be very effective.

RadVax and commercial vaccines

You can take RadVax in addition to a commercial vaccine, as there should be no negative interactions between them. RadVax recruits a different part of the immune system than commercial vaccines (T-cells, as opposed to B-cells), so it is a complement, not a substitute. It will provide additional protection to you and your family that you can't get from commercial vaccines, so you should still take both. RadVax has a few strengths that commercial vaccines don't, both on the personal level, but also on a public-policy level.

Personal benefits

Taking two different vaccines can produce synergistic effects, making RadVax + commercial a better choice than commercial alone: https://www.npr.org/sections/health-shots/2021/05/05/993882203/giving-2-doses-of-different-covid-19-vaccine-could-boost-immune-response

Unlike nasal-delivery vaccines, injections do not produce mucosal protection. So you can still acquire COVID, although the commercial (injection-based) vaccine will make it much easier for your body to fight the virus. Nasal-delivery vaccines can produce an immune response right at the point where the virus enters the body, which can **prevent you from catching COVID in the first place**.

Because RadVax is both safe and simple, it's also very flexible. The peptides used in RadVax have already been updated several times, both as scientists learn more about the virus, and as new variants evolve. RadVax is currently in its 10th generation, and is based on the latest knowledge about which peptides produce an immune response. It includes an optional peptide that should be **especially helpful for training the immune system of people who have Hispanic, Southeast Asian, or Native American ancestry**.

Most commercial vaccines for COVID are based on very early research. They use peptides that are part of the spike portion of the shell (which is what the virus uses to enter our cells). The advantage at the time was that scientists could be sure it was distinct to the virus, even early on when we didn't know much at all about how COVID attacks us. The disadvantage is that this is one of the things most likely to change as the virus evolves, leading to "vaccine escape". Unfortunately, our medical regulatory system doesn't easily allow for changes in the formulas used. Right now, the **COVID virus is evolving faster than our regulatory system can keep up with it.**

RadVax was based on later research, and uses a slightly different approach. First, rather than focussing on the spike protein, the RaDVaC team compared SARS-COV-2 (the COVID virus) to SARS-COV-1 (the original SARS from 2002), to see **which parts of the virus had remained unchanged** over 2 decades. They also looked at the immune response of people who had acquired SARS-COV-1, to see which parts of the virus they were still immune to. They used this information to choose peptides that should both **prevent vaccine escape**, and provide **long-**

lived immunity.

And while RadVax doesn't focus on the spike protein, RadVax is certainly able to use peptides related to the spike protein. The latest generation (Gen 10) of RadVax does have an optional peptide that should help **defend against the new, more dangerous variants** (Brazillian strain P.1, English strain B1.1.7, and South African strain 501Y.V2). In general, RadVax is very flexible, and it is easy to make boosters to address new variants. They hope to soon have a peptide to address the Indian strain B.1.167.

Public-policy benefits

RadVax is especially useful for developing countries, because it uses a different method for delivery, and thus has an **entirely different supply chain**. The supply chain for commercial vaccines has already been saturated (https://www.scientificamerican.com/article/new-covid-vaccines-need-absurd-amounts-of-material-and-labor1/). There are concerns that supplies have been stretched so thin that production of standard childhood vaccines such as MMR, or polio has nearly stopped. In contrast, the **supply chain for RadVax can be used without creating further public health risks**.

It also provides **vaccine equity**. Currently the industrialized nations are first in line for the commercial vaccines, so commercial vaccines won't be available for poor nations anytime soon. For example, the USA is holding back over 30 million doses of AstraZeneca (enough to vaccinate the entire country of Peru). In addition, commercial producers sometimes renege on their commitments to poor countries (Pfizer backed out of an agreement to supply 10 million doses to Colombia). RadVax can be produced **locally in-country**, since it only relies on a few ingredients, which are widely available. **Countries can begin making RadVax themselves**, without relying on international corporations which may or may not come through on their commitments.

Producing RadVax

Regulatory approval

Currently the biggest obstacle to using RadVax is the absence of regulatory approval. Conducting the required clinical trials using the traditional approach for vaccines can require tens of thousands of participants, and take many months. The placebo arm of such a trial will necessarily include hundreds of people who acquire the disease, and spread it in their communities, resulting in further deaths. In addition to these human costs, the financial costs of population trials are high.

One alternative to population trials is instead to use a "challenge trial", which involves deliberate exposure of volunteers to the virus, under controlled conditions. The World Health Organization has recently issued guidelines for the ethical use of challenge studies <<CITE>>, recognizing

that the much **faster pace of development can save lives globally**. In addition to saving lives due to shorter trial times (which take weeks, rather than months), challenge trials require far fewer participants, and so can be cheaper to run.

It may also be possible to create a "safety trial", which can serve as an improvement on the challenge trial design, by **further reducing risk to the participants**. This can be accomplished through a combination of careful selection of volunteers such as younger adults (who have a much lower risk of serious illness from COVID), or people who have already recovered from previous COVID infections (and who reportedly have much milder symptoms upon secondary infection <<CITE>>). Another method has been proposed by the RaDVaC organization, which is to first test the efficacy of the vaccine by exposing participants to a related coronavirus which is much more benign (such as HCoV-OC43), rather than direct exposure to SARS-CoV-2.

Manufacturing

The final stage of RadVax is produced at the point of administration, and is **very easy to make**. It takes only basic laboratory skills to make RadVax, so anyone with a bachelor's degree in chemistry, biology, or a related field can learn to make it in about an hour. Once the ingredients are acquired, the process itself can be done in less than an hour.

There are only 5 ingredients:

- distilled water
- salt (sodium chloride)
- TPP (trisodium phosphate, a widely-used food additive)
- chitosan nanoparticles (ideally in the form HACC, available from lab suppliers)
- peptide sequences (hundreds of companies worldwide do custom sequencing)

The most complicated part of the manufacturing process is creating the synthetic peptides. There are two basic options: purchasing the peptides from an existing company, or developing the capacity to produce peptides within-country. The quantities required to immunize a nation are well within the production capacity of many companies, who can produce many kilograms per month (1 kg can immunize approximately 2 million people). Alternatively, a country that wanted to have the flexibility to create booster shots to address variant strains could choose to begin production locally. For repeated use over a period of years, the required equipment would pay for itself many times over.

Distribution

RadVax is an excellent choice for developing countries. Many commercial vaccines use complicated technology, require intensive capital investment, and have stringent supply chains. RadVax, in contrast, uses accessible technology, and uses labor more than capital (both factors which favor developing economies).

Nasal-delivery vaccines are widely used in lab and experimental settings. They are not commonly used for general vaccines, though, because they typically require multiple doses in order to build an immune response. One notable exception is the nasal flu vaccine. We can get away with a weak immune response in this case because basically everyone has had the flu before, so the body already has defenses against it... we just need to teach it about the new variants. However, there are several challenges to using a nasal vaccine, including the RadVax, at scale. In rich/developed countries, time is at a premium, and it's difficult to get people to come to a doctor's office four times in order to complete a vaccination. In developing countries, on the other hand, time carries less cost, so multiple doses are less onerous.

Another challenge is the short shelf life of RadVax (around two weeks). Unlike the industrial vaccines, it can't be frozen, so it needs to be used fairly soon after being made. This is fine for use in a laboratory setting, but is not very effective at industrial scales (where it's better to have a shelf life measured in years). Partly because the shelf life is so short, RadVax is a labor-intensive option (as opposed to most commercial vaccines, which are capital-intensive). It needs to be made in relatively small batches, for use shortly after creation. So it will probably be made by individual clinics, for administration to their patients. This labor cost isn't affordable for rich countries, but is much more of an option in developing countries.