Innovations in the Vaccine Landscape

So one of the things that I think it's really important to do right now is not just look at vaccines as they are in the here and now, but think about what they could look like in 10, 20, 30 years.

Innovation can mean different things to different people. It basically means making something that's new and better than what we had before.

And when it comes to vaccine innovation, we're really talking about two things: creating new vaccines that we need or improving something about the ones we already have.

In today's episode, we'll cover a few examples of vaccine innovation, from vaccine design to vaccine delivery. This is The Antigen, and I am your host Yasmeen Agosti.

Trypanophobia. Heard of it? It may sound like a virus or some bacteria but it's not. It's the official word used to describe the fear of needles.

Vaccines usually conjure up images of people wincing and babies crying. While there are a few oral vaccines out there – like rotavirus and typhoid for example, most vaccines do require a jab.

Some studies have shown that the fear of needles can play a role in why certain people don't get the vaccines they need. Needle phobia aside, there are some other really good reasons why people are trying to design new ways to give a vaccine.

Anna Mouser, from the Wellcome Trust, explains the idea of a vaccine patch that could be applied to the skin, similar to a band-aid. While the idea is still being developed and tested right now, if successful, it could make a huge difference in parts of the world where access is a challenge.

For me, one of the most exciting developments is microarray patches. They work by having thousands of teeny, tiny dissolvable needles in them that can't be seen or felt.

Researchers are currently studying microarray patches in laboratories and clinical trials. The hope is that once they can prove that a patch vaccine can work safely and effectively, they could be approved for use in people.

And if you think about what it would look like to deliver, say the measles and rubella vaccine or the polio vaccine, that way it's, it's hugely transformative. And one of the ways patches are exciting because of things that people might not even be aware of. So at the moment you have to store vaccines very, very carefully to ensure they're refrigerated so that the ingredients within them still work effectively. This is called the cold chain. And in many parts of the world it's extremely costly and difficult to keep vaccines refrigerated, as you might imagine. I mean they're delivered all over the

world. So patches could really make it so much easier to get vaccines to hard to reach areas and populations where at the moment it's incredibly challenging to reach. They also have the potential to cut waste and ultimately be something that people can even apply on themselves. So looking ahead, immunization could look very different in 10, 20 years. We might not even associate it with needles anymore in the same way. And that would have a small benefit just because for a lot of people they don't really like needles. And we do wonder sometimes the extent to which that can be a factor in people not going and getting the vaccines they needed.

You may remember from our Global Health episode something called “the last mile”. The term refers to the last part of the vaccine journey in developing countries that can be the hardest to complete – often due to lack of good roads, reliable transportation or difficult terrain. It’s a challenge that’s been turned into important opportunity for vaccine innovation.

Some countries are currently overcoming this challenge with drones.

Zipline, founded in 2014, uses drones to deliver certain vaccines, medicines and blood products to people in hard to reach places.

I spoke with Naa Adorkor Yawson, who works for Zipline in Ghana. When I asked Naa if she could give an example of the kind of terrain they deal with, she mentioned Lake Volta – one of the largest, artificial bodies of water in the world. The lake was created after the construction of the Akosombo Dam over the River Volta in the mid-1960’s.

We sell one health facility beyond our farm place called Yeji. And that facility is separated from that to say the rest of the country by the Volta Lake. So if you have to go to that facility, you have to go on a ferry and that ferry runs every two hours. So if you miss the ferry at 6:00 AM for example, the next time you can get onto the ferry to a farm to that area, the Yeji area, is two hours later, that will be 8:00 AM. So you can imagine in an emergency situation or in the situation where you're having a vaccination clinic and you have to vaccinate, there are people waiting to be vaccinated.

If I'm a health professional there and I need additional vaccines, I have to wait for the ferry to come cross the lake to the other side and then commute to the region, which is about three hours a week.

Before Zipline can begin delivering, there is advanced preparation, including mapping out the route to the health facility.

So what happens is that the process starts way before we even deliver the products. So it starts, let's say months before the facilities actually even ready to receive their product. So we go in, we have our engineering team, our GIS team going to the health facilities to map out a route. So our

drones fly autonomously, they are not controlled remotely. They fly on their own. So there's a need for us to map a route as transit plans, right from the health facility to our distribution center.

They go and process it and bring out a transit plan. Then that goes to the Ghana Civil Aviation Authority because they are the primary regulators for the air space. Once we receive the approval, we go back to the facilities and we train them on how to use the service.

Once the health facility is trained on how to use the Zipline service, things get simpler. They can order a vaccine drone delivery at anytime through a phone call, text message or even email if they have access to the internet.

So after we've packaged the product, we launch, it goes into the drone and it is launched to the health facility. Once the package is launched, we alert the health facility or whoever placed the order with us that the package is on its way. Once the drone arrives and drops off the products, we also send them a message and they quickly go in to pick up the product and use it immediately or store it for use at a later time.

The drones travel at 100 km/hour within an 85 km radius. They fly rain or shine, day or night. Naa shared with me that to date, Zipline provides medical drone services to about 300 health facilities and has delivered over six thousand vaccine vials to various areas in Ghana.

As you can see,drones can be one approach to solving the challenges of overcoming the “last mile.” But there are other issues to address, likemaintaining “the cold chain,” as described earlier – it’s a system of storing and transporting vaccines at the right temperature.

Alison Witkoff from the International Rescue Committee explains how certain settings are using solar panels and other technologies to do exactly this.

So in a lot of developing countries, for instance, there may not be electricity at the health center. So with vaccines you need to keep them stored at a certain temperature and it's usually a cool temperature. So if you think about the fact that you're in a sub Saharan African country and it's extremely hot and there's no electricity, once you get those vaccines to the health center, how are you going to keep them cold? How are we going to store them?

So we're starting to see a lot more solar panels in health facilities. There's also even solar powered refrigerators. So that's a really great innovation that's going to help be able to store those vaccines. Another interesting innovation is that there's vaccine vial monitor temperature labels. So these are labels that go on the vaccines.

And once the vaccine reaches a temperature that's above the temperature that it should be, the color on the vial changes and then that will signal to the health worker that they should no longer be using that vaccine because it's no longer effective.

It's also important for community health workers, or CHWs, to be able to keep track of the people who need them and when they need them. Innovations in mobile health are helping to address this issue in certain countries like Uganda and Somalia.

Some other innovations that we at the IRC are looking at are low cost but high impact innovation. So for instance in Uganda and Somalia we developed a mobile health platform technology. So it allows health workers to use mobile health technology on their phones to track children who have been vaccinated. It also allows them to see when children haven't come back to the health facility for their vaccinations. And then they can immediately work with CHWs who also this mobile phone technology to go out and track those children to do follow up and get them to come back for the vaccination that they've missed.

So far, we've talked about innovation in vaccine delivery to help improve access. But just as important, is the innovation happening in the development of entirely new vaccines.

Influenza vaccines, are a great example of one area where researchers are focusing their efforts.

Flu, is a common and contagious respiratory illness caused by influenza viruses. Flu illness can be mild to severe and when it is severe, the infection can lead to hospitalization and even death. Anyone can get the flu but children, elderly and those with certain health conditions are at higher risk of having complications like pneumonia.

Today, we have many kinds of flu vaccines out there, but the one thing they all have in common is that they are recommended to be given once a year.

Professor David Salisbury, in an associate fellow at the Center for Global Health Security at the Royal Institute for International Affairs at Chatham House in London, and explains why this is so.

For many years we had just the same sort of influenza vaccines manufactured every year in advance of the seasonal influenza epidemics. And it always was a guessing game because you never really knew in advance what strain of influenza virus was going to emerge. And influenza viruses change. They mutate very easily. And so the virus of last year may not be the virus of this year and there are three or four common strains of influenza. And each of those can vary. And that meant that some years the vaccine would be produced and would be a perfect match for the influenza strains that were circulating. And then other years it would not be a good match. And so

you might get one of your vaccine viruses to be a good match or two or three and nowadays four. But the risk of getting a poor match amongst four was pretty significant.

The impact of influenza on public health cannot be under-estimated. Here in the U.S., the Centers for Disease Control or CDC estimated that during last year's 2018-2019 flu season, there were more than 35 million flu cases, of which there were 490,000 hospitalizations and 34,000 deaths. You can find out more information about influenza on the CDC website.

The first flu vaccine in the U.S. was licensed in the 1940's. And since that time, we've seen the field of flu vaccines evolve greatly.

But we've also seen changes in the influenza vaccines that we use. They all used to be grown in eggs and that meant that you used to have millions and millions of eggs all being used to grow the virus. We're moving away from that now. And many producers are using cell culture where you use cells into which the virus can grow, infects the cells, it grows in the cells. And then the virus comes out of the cells and you then use that to make your vaccine.

We used to have just three viruses on a vaccine. Many now have four. We're also seeing some of the vaccines having things called adjuvants. Now these are chemicals and they're nontoxic chemicals that are in the vaccine that improve your immune response to the vaccine. And so adjuvanted vaccines are emerging now and becoming routine. We also have high dose vaccines where for some people, particularly the elderly, where their immune response may not be as good. Having a high dose vaccine can boost their immune response.

There are now efforts under way to create something called a universal flu vaccine. People are looking to do this so that we don't have play the guessing game each year when it comes to matching the vaccine to an ever-changing virus.

Dr. Peter Palese, Professor and Chair of the Department of Microbiology at the Icahn School of Medicine at Mount Sinai Hospital in New York, does research on this topic and explains one approach they are currently investigating.

There is always a better mousetrap. I think we are thinking of making better vaccines and one of those approaches is a universal influenza virus vaccine. And the definitions of that are slightly different for different people and different organizations. We talk here about our efforts at Mount Sinai, we would like to make a, not only a better vaccine, but a vaccine which does not have to be given every year, but with which can last for 20 years or even a lifetime, one and second, that it will protect against all future strains, against all the influenza A & all the influenza B virus strains, in the future.

There are two main types of influenza virus – type A and type B – and it's these two types which cause the flu season that we experience each year.

Flu A and flu B, each have multiple versions circulating around in a single flu season. People commonly refer to these different versions as flu strains.

To make things even more complicated, especially when it comes to making a flu vaccine – these flu strains change from year to year.

So, I asked Dr. Palese if he could describe the virus and how understanding its structure could help scientists to design a universal influenza vaccine to target the right part.

So if one looks at the virus, it's like a soccer ball or football. It's a little round little, uh, sphere. And on the outside, uh, there are proteins, which are recognized by our immune system. And these proteins are actually what changes mostly. So we don't make much of an immune response against the inner components of the influenza virus. But mostly, uh, we make, uh, antibodies, which is our immune response against the outside and the outside of the virus changes from year to year.

Scientists like Dr. Palese are looking closely to find the right part or antigen on the outside of the flu virus that does not change much over time, while still ensuring that it can stimulate the immune system to fight off the infection. Their hope, is that by doing this, they can design a single flu vaccine that will protect a person against many different flu strains for a long period of time.

Up until this point, The Antigen has focused on *prevention* vaccines, which are used to prevent serious infectious diseases.

There are now vaccines being developed to actually *treat* a disease that's not an infection - cancer. These are called *treatment or therapeutic vaccines*. And there are already several which are licensed, including ones to treat some forms of prostate and skin cancers.

Dr. James Gulley, is with the Center for Cancer Research at the National Cancer Institute, and an internationally recognized expert in cancer immunotherapy. He explains what a therapeutic cancer vaccine is all about.

So what is a therapeutic vaccine? You might know of the rabies vaccine where after you get bitten by a rabid animal, you get a series of, of shots that prevent you, hopefully from getting the rabies disease much the same way once you already have cancer. These therapeutic vaccines, they're designed to get your body's immune system to recognize and attack the cancer cells that are already there.

So, in a sense, cancer cells are *like* germs in that they don't belong in our bodies. And our immune system is designed to recognize and attack anything that doesn't belong there.

But a key difference between a cancer cell and germs is that cancer cells are a lot better at tricking the immune system into leaving them alone. They do this, by holding up something like a molecular "stop sign"; basically, telling the immune system 'hey don't worry, everything is fine here'.

So, I asked Dr. Gulley how a cancer vaccine can teach immune cells to get past this molecular stop sign, technically referred to as an immune checkpoint.

Typically what we see is that these cells can get into the tumor, but they are often held in check because the tumor can put up this stop sign for the immune cells and these immune cells cannot function.

Currently, this process of getting immune cells to attack tumors requires a one-two punch with both medicines and vaccines. The medications, which are called immune checkpoint inhibitors, essentially work to stop the stop sign. And then, the vaccine takes over the job from there.

And so just putting a bag over the stop sign, if you will, that doesn't allow any immune cell to become more functional. One way to do that is to give a vaccine where you can get the immune system to say, here, this is the target. We want you to go around and look for this target. And then the immune cells will go around, look for that target that's in the vaccine, find it in the tumor cells, and then they're ready to go.

That target can be a substance or a protein that a cancer cell makes and displays on its surface. Picking the right target or antigen is the very same idea used in classic vaccinology.

So we need to have some target for the immune system to look at and sometimes that target is a gene that's overexpressed the protein is, is overexpressed in tumor cells. And these can lead to off-the-shelf-based vaccines where perhaps the vaccine is against CEA, carcinoma embryonic antigen, which is expressed in colon cancer for instance, or a prostatic acid phosphatase expressed in prostate cancer. And these targets are expressed in some normal tissues, but they're overexpressed in cancer tissues. What the immune system can do is, is find those cells and kill them.

Dr. Gulley is referring to one approach when it comes to designing cancer vaccines – a one-size-fits-all. This kind of cancer vaccine targets an antigen that you find in many people who have the same type of cancer.

There is another approach to designing cancer vaccines – one that's customized, and only meant for one person and their specific cancer. These are called neo-epitope or neo-antigen vaccines.

These vaccines, which are not yet licensed, will be more complicated to make because again it's made to fight one cancer in one person.

And that may take time and it's possible in some cases that, uh, there's not going to be enough time to make the vaccine for a given patient cause this could take 12 weeks or so.

Right now, the strategy is to give cancer vaccines in combination with other cancer treatments. In this way, the cancel cells can be approached from multiple directions.

It may be different approaches for different cancers, but I think that therapeutic vaccines by themselves, I think you need the immune system to be able to recognize the cancer and that's where a vaccine can be very useful. I hope that there's going to be a future where we're going to be able to use combination immunotherapy approaches with vaccines, checkpoint inhibitors and other things to allow those immune cells to work best in the tumor micro environment. And hopefully by doing that we'll be able to eradicate more tumors and have complete responses and cures.

I asked Dr. Gulley if cancer vaccines could teach immune cells to protect someone for a long period of time, just like we see with certain prevention vaccines for infectious diseases.

You can turn those cells into memory cells that could potentially be around so that later on, if there are some dormant cells that try and raise their head, potentially you could then have the immune system recognize them, turn back on and, and kill those cancer cells before they cause any clinically significant cancer.

The idea of using the immune system to fight cancer is not a new one. As far back as 1890's a bone surgeon named Dr. William Coley attempted to treat cancer by injecting tumors with bacteria. But it wasn't until we had a much better understanding of both the immune system and various kinds of cancer that the field of immunotherapy really took off.

And I like to think of vaccines as a way of training the immune system to recognize targets in the tumor. You know, there's many ways to get the immune system engaged. We can either take immune cells out, uh, modify them and give them back to the patient. That I would say is akin to somebody giving somebody something like a, somebody giving a fish to somebody so they could have a meal for that day. Whereas a vaccine is teaching the immune system how to go at a specific target in the tumor. And so that's more akin to teaching somebody how to go fishing. And potentially then that could lead to feeding that person for a lifetime or having the immune system being engaged in fighting the cancer for a lifetime.

On our next and very last episode, we'll wrap up everything we learned thus far and continue to look forward to the future.

We'll examine the potential of vaccines to help fight emerging global health threats – like antibiotic resistance and new disease outbreaks like coronavirus. As well as understanding the potential of vaccines to help us lead healthier lives, from the moment we're born to older age.

A lot of people talk about disease X. It sounds like it's out of a Hollywood film, but coronavirus is an example of disease X. It's a disease we haven't seen before. One that we don't know. And so there's a process then of identifying that disease, decoding it and understanding how it works and then using that knowledge to build a vaccine. And I think we're getting better at doing that rapidly, but we've got a long way to go.

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