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Vaccine development

- Exploratory stage
- Pre-clinical stage
- Clinical development
- Regulatory review and approval
- Manufacturing
- Quality control.

Phases

Phase I: small trial to determine basic safety and immune response.

Phase II: a larger trial to to study the candidate vaccine's safety, immunogenicity, proposed doses, schedule of immunizations, and method of delivery.

Phase III: a randomized and double blinded trial which involves the experimental vaccine being tested against a placebo.

Approval

EUA (emergency use authorization) is based on a determination from interim analysis of a Phase III efficacy study that demonstrates that the known and potential benefits of the vaccine outweigh the known and potential risks.

Vaccines

At One to One Health's COVID Services, we focus on personal responsibility to navigate the pandemic.

One facet of personal responsibility is education: finding good information and applying it. We have generated this special issue for you as part of your educational process to dispel any myths, and recognize concerns over vaccination.

Many vaccines are being developed to combat Covid-19. Categories of vaccines can be confusing, so we have simplified only for clarity. We have purposefully excluded discussion of the category of DNA-based vaccines, as there is little focus on DNA-based vaccines in humans. Note that the Covid-19 vaccines have not been fully trialed in children (under 18). We have labeled some vaccines based on their countries of origin, and although many vaccines are in development in those countries, we focus on the vaccines furthest along in development. Currently, 237 vaccines are in development worldwide. 38 vaccines for Covid-19 are in clinical trials, and 10 are in phase 3 clinical trial or have submitted to regulatory review to begin immunizing the population.

If you have had COVID-19, you still need a vaccination.

Vaccines 201

- Fear of vaccines is real, and likely relates to vaccines in recent history that have had disastrous side effects. These vaccines have been **virus-based**.
- The historical RSV vaccine had horrible side-effects and deaths. The RSV vaccine set vaccine development technology back decades.
- mRNA vaccines and virus-like protein particle vaccines have *no kinship or relationship* to the viral-based vaccines
- New vaccine platforms will change how we prevent viral infections in the future by having the ability to be used as an "on-the-shelf framework" for development. New vaccines will be able to be created in days to weeks (not months to years) to combat potential pandemics.
- Injectable vaccines generate long term immunity with IgG antibodies. These work throughout our body, but to a lessor extent in the mucosal linings (intestines, mouth, nostrils and upper respiratory system).
- IgA antibodies are important in the mucosal linings, and are generated by oral formulations.

We believe in vaccinations, as they have substantially eradicated diseases such as Polio and Smallpox. Vaccines have been successful in preventing cervical cancer from HPV. Although some vaccines have had horrible outcomes and even made some diseases worse (Dengue and RSV), we believe that the vaccines we discuss do not fall into this worrisome category. The technology (which you will read about) is completely new, novel like the coronavirus that is causing the pandemic. We can't wait to receive our COVID-19 vaccination.

Many people don't want to take the new COVID-19 vaccine "because vaccines can't even prevent the Flu". The argument is that, in the case of influenza, we don't know the exact Flu virus for vaccination and therefore have to guess which flu virus will predominate a year from now. Let's be clear: we know exactly which virus SARS-CoV-2 is, and we know what we are vaccinating against, making this argument invalid.

Flu vaccines can make people feel like they HAVE the flu. In all reality, it's our robust immune system reacting to the vaccine that makes us feel all "viral-y", and is an expected response. This reaction is reported to occur as well with the COVID-19 vaccines, especially with the second dose. Anticipating this response by using a medication like acetaminophen prior to and during the immediate post-vaccine period can help.

We are not virologists, however one of us majored in microbiology. We are both physicians who have been following the vaccine development since March. Back then, one of us predicted that Moderna, and the other that Novavax, would be the earliest and most highly efficacious vaccine out of those candidates. We both in the end probably will be right.

In no way do we want to portray ourselves as immunologists, or some kind of vaccine authorities. We are concerned physicians who are sick of this pandemic, are focused on the health of our community, and want to make a difference. We hope you will share this educational special issue.

We believe in vaccination against COVID-19.

Sincerely, David and Lisa

1. MRNA vaccines: Moderna and Pfizer/BioNTech

- Other examples include Zika and targeted cancer vaccines.
- Technology was introduced in 1990.
- Made of messenger RNA chains wrapped in lipid coating
- The protein made is spike protein or part of the spike.
- mRNA-1273, the Moderna COVID-19 vaccine candidate, remains stable at 2° to 8°C (36° to 46°F), the temperature of a standard home or medical refrigerator, for 30 days.
- Your genes are not affected by this vaccine

How it works:

✦Man-made mRNA chains are wrapped in a lipid coating (fat nanoparticle)

✦The lipid coating "binds" with human cell walls and dumps its mRNA into the cell

✦mRNA is then "read" by the ribosomes to make protein molecules

✦The immune system finds these "cell made" protein molecules and makes antibodies to them

✦Immune cells then take these antibodies to our lymph nodes where memory cells are formed

Other interesting facts:

A boost of vaccine helps create better memory cells so that killer cells and antibody-producing cells can be created quickly if ever exposed to the same virus in the future.

The platform is non-infectious, and has no real mutagenic risk because it is not inserted into our genetic code. Our cells break it down over time so it doesn't stick around.

The best part is that your own body makes the antigen to which the antibodies are formed.

Moderna (MRNA-1273):

mRNA encodes whole spike protein. This new technology has been reported to be **95%** efficacious. In theory and in study, the *side effects should be low*, and boosting should be well tolerated. Many different antibodies can be produced to multiple points on this spike protein.

**EUA filed in U.S. and to be reviewed on December 17, 2020.*

Pfizer/BioNtech (BNT162b2)

mRNA encodes part of the spike protein. This new technology is reported to be **95%** efficacious. In theory and in study the *side effects should be low*, and boosting should be well tolerated. Many antibodies can be produced to the receptor binding domain, but excluding the tail of the spike reduces the number of different antibodies that could be produced.

**EUA filed in U.S. and to be reviewed on December 10, 2020. Vaccinations have begun under EUA in the UK.*

II. Virus-like Particle / Protein subunit: Novavax

- Current examples include Gardasil (HPV), Recombivax (Hepatitis B) and Shingrix (Shingles)
- Made of a man-made protein molecule which is the antigen you want the immune system to react to, creating antibodies and killer cells
- Virus-like particles involve connecting multiple protein molecules together so on the surface they look like a virus molecule to the body
- Your genes are not affected by this vaccine

How it works:

✦The "man-made" protein molecules are injected and recognized as "foreign".

✦The "foreign" protein causes cells (dendritic cells) to present and help produce antibodies.

✦The antibodies are taken back to the lymph nodes and memory cells to make antibodies and killer cells are created.

Other interesting facts:

A boost of vaccine helps create better memory cells so that killer cells and antibody-producing cells can be created quickly if ever exposed to the same virus in the future.

The platform is non-infectious, and has no real mutagenic risk because it is not inserted into our genetic code. Our cells break it down over time so it doesn't stick around.

Your body's own cells easily pick up the proteins and present the antigen for the formation of antibodies.

Novavax (NVXCoV2373)

This nano-particle vaccine is formed by joining multiple man-made spike proteins together by the tail. Structurally, it looks a lot like a coronavirus because it has a star-like appearance. The nano-particle is injected, and the body's immune system makes antibodies to the "man-made" spike protein.

As so many particles are injected with this vaccine, the immunity generated should be terrific, and it is whole spike protein. It has had great results through phase 2 trials and is due to have phase 3 reporting in early January.

**We look for filing for US and UK EUA in early to mid-January if results are as advertised.*

III. Viral Vector Vaccines: (Russian, AstraZeneca(Oxford), J&J/ Janssen

- Current examples include: Ebola and Dengue vaccines
- Made of active but not harmful virus which doesn't cause a human infection
- It carries the antigens of a disease-causing pathogen of which we want antibodies
- The gene that encodes the antigen we want expressed is spliced into the noninfectious viruses' genetic code
- Most of the Covid-19 vaccines studied throughout the world are viral-vector based and use the adenovirus platform
- In general, humans deal well with adenoviruses on an immune level

•*How it works:*

✦Replicating (virus reproduces in cell) and non-replicating virus carriers are used

✦When the vaccine is given, cells take up the virus with its gene code. When the cells start replicating the virus's genes, it also does the same with the code for the protein antigens of which we want antibodies created

✦Similar to the other vaccines, the antibodies are created and taken back to the germinal centers (lymph nodes) and immunity is created by stimulating memory B-cells and the killer cell system

Other interesting facts:

These vaccines have been successful in preventing diseases such as Ebola and Dengue fever.

Technically, you can attach any protein molecule gene into the virus code to get the antibody immunity you desire.

AstraZeneca (Oxford) vaccine (AZD1222):

This viral-vector vaccine uses a chimpanzee adenovirus to carry the proteins of SARS-CoV-2. It renders antibodies to spike protein, other surface proteins, and nuclear proteins. More helpful antibodies (not just spike) can be produced from this vaccine. A potential problem is that the adenovirus carrier probably has no antibodies currently in the recipients of this vaccine, however when boosting occurs (second dose), antibodies can have been created to the chimp adenovirus and an inflammatory immune reaction could occur to the adenovirus carrier. To be clear, this is not an infection with the adenovirus, but a reaction like we sometimes see when we get flu shots. It *could* reduce the effectiveness of the vaccine. Interestingly, by mistake during phase 3 trials, almost 2,800 British study participants received half dose first and whole dose boost vaccination. This group had the best immunity being 90% efficacious vs full dose first/full dose boost which was only 70% efficacious. There was a pause in Phase 3 trial for this vaccine. It was determined that a patient who received this vaccine developed transverse myelitis (form of paralysis). This patient had multiple sclerosis prior to vaccination and transverse myelitis is highly associated with MS.

Johnson and Johnson / Janssen Vaccine

A similar viral-vector vaccine to the Oxford vaccine, but it uses a *human* Adenovirus (Ad26) as the vector. It is single shot vaccine as reported with no boost. We suspect the boost would have reaction issues due to Ad26 vector on first injection. That being said, phase 2 trials went well and is reportedly doing well in phase 3 trial.

Russian Vaccine:

This vaccine is very interesting, but very little is known as trials either were not performed or were skipped prior to immunizing the population. What we do know is that the viral-vector vaccine is based on two separate adenovirus carriers. The first vaccination is given with one adenovirus carrying the genes for SARS-CoV-2 proteins, and the boost is a *different* adenovirus carrying the *same* SARS-CoV-2 proteins. This intriguing concept would avoid the inflammatory response generated on boost if the same adenovirus were used. We need to keep our eyes on this platform, as it has great potential!

Chinese vaccines:

China has at least two vaccines that are being used currently. Their current vaccines are viral-vector vaccines using similar adenovirus carriers as the J&J vaccine. The reports out of China are encouraging, but they have not been studied outside of China. Early reports are that they are 90% efficacious.

Viral vector-based oral vaccine

Vaxart

Vaxart is the furthest along with their all "oral" adenovirus-based viral-vector vaccine. They are in phase 1 trials, having done well with laboratory animals. IgA antibodies should be generated by this vaccine. The IgA antibodies are important, as that is what is seen in our upper respiratory tree, mouth, and nostrils. In theory, an oral vaccine yields IgA antibodies, and thus *sterilizing* immunity (like oral polio vaccine does with attenuated whole virus). It also might be how we boost in the future.

IV. Whole Virus Vaccines: Polio, Measles/Mumps/Rubella, Influenza

- Made of the infectious pathogen from which we desire immunity
- Two forms exist: inactivated and attenuated
- The inactivated types are non-replicating forms of the virus. It has all or most of the antigens, but it can't infect or replicate in the cell. (IPOL -injected polio vaccine- and Flu vaccines)
- The attenuated type is basically a weakened virus that can still infect and replicate, however it has a very low ability to cause disease. OPV (Oral Polio Vaccine) consists of a mixture of live attenuated poliovirus strains of each of the three serotypes, selected by their ability to mimic the immune response following infection with wild polioviruses.

How it works:

✦The whole virus vaccine evokes an immune response because it shares the same proteins as the real virus. It has either no ability to infect (inactivated) or has low effectiveness (attenuated).

✦The antibodies are exactly matched to the real virus because the proteins are essentially the same.

Interesting Facts:

The oral polio vaccine replicates in your intestine and gives sterilizing immunity to polio. It is shed in your feces and passive immunity can be given to anyone who comes into contact with your stool through fecal/oral routes.

The injectable polio vaccine does not replicate but causes an immune response that gives immunity to *disease.* It will not kill intestinal infection of polio virus because those immune cells are not in the intestines. In other words, disease is prevented, but infection is not.

The basics: IgG antibodies come from injected vaccines and IgA antibodies from oral vaccines. If you have an injectable vaccine, the IgG antibodies can allow infection in the mucosal surfaces, but it will kill the virus if it were to become systemic. If you have an oral vaccine and a virus (like SARS-CoV-2) tries to infect the mucosal surfaces, the IgA antibodies will kill it before it can infect your whole body. This kind of immunity is called *sterilizing immunity*. Both injectable and oral vaccines will confer immunity to disease.

In the U.S. we immunize against polio with an injection. Polio can infect our intestines, but it will not cause paralysis and will not systemically infect us with the disease. Oral polio is not given in the U.S. any more due to an incidence of 1/100,000 people developing a paralysis-like syndrome similar to polio, but not as severe.

Currently, 18 **Inactivated Whole Virus** vaccines are being studied for Covid-19 with some in Phase 1 clinical trials. These vaccines are being studied in China, India and Kazakhstan. Special laboratories are required in the US, UK and Europe to study SARS-CoV-2, thus no whole virus vaccines are in development within the US or Europe.

Similarly, 4 **Live Attenuated Whole Virus** vaccines are being studied for Covid-19 in India and Turkey. All are in pre-clinical trials.