Kenya Medical Association National Executive Committee Meeting

COVID19 VACCINE DEVELOPMENT AND ACCESS:
Overview, Timelines and Roll-out implications for Africa

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Scope of the presentation

- Review of the journey of vaccine development for COVID-19

- Reflect on the bottlenecks and way forward to current vaccine development & roll out efforts

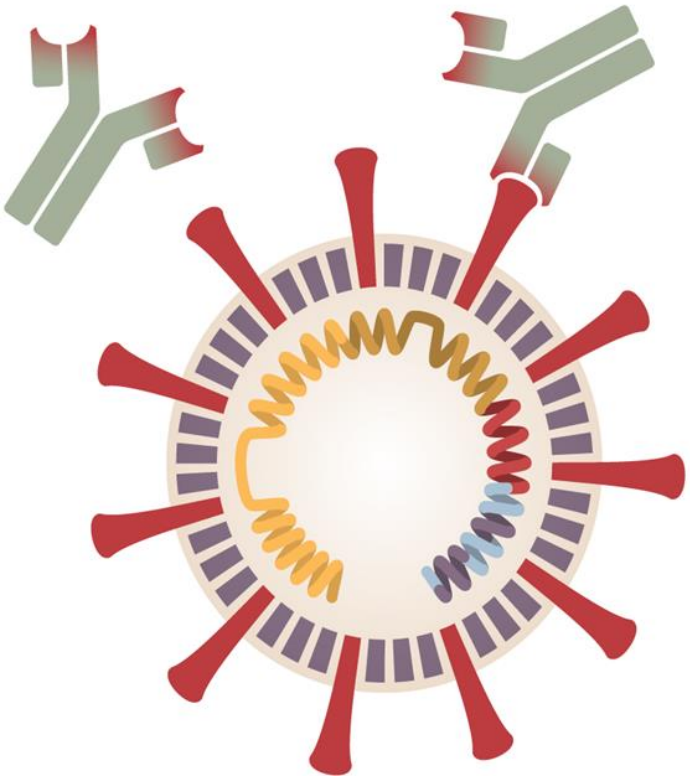
Disclosure

Relationships with commercial interests:

- **NONE**
- **No conflict of interest**

Vaccine development work

- Work began in Jan 2020 with the deciphering of the SARS-CoV-2 genome.
- The first vaccine safety trials in humans started in March, & now 10 have reached the final stages of testing, 2 are before FDA for approval.
- Some of these trials will fail, others may end without a clear result.



The Process

PRECLINICAL PHASE:

- Test a new vaccine on cells and then give it to animals such as mice or monkeys to see if it produces an immune response. We have confirmed 89 COVID preclinical vaccines in active development.

PHASE 1 SAFETY TRIALS:

- Give the vaccine to a small number of people to test safety and dosage as well as to confirm it stimulates the immune system.

PHASE 2 EXPANDED TRIALS:

- Give the vaccine to hundreds of people split into groups, such as children and the elderly, to see if the vaccine acts differently in them. These trials further test the vaccine's safety and ability to stimulate the immune system.

The Process

PHASE 3 EFFICACY TRIALS:

- Scientists give the vaccine to **thousands of people** and wait to see how many become infected, compared with volunteers who received a placebo.
- In June, the F.D.A. asked for evidence that vaccines can ***protect at least 50 percent of those who receive it.***
- In addition, Phase 3 trials are large enough to reveal evidence of relatively rare side effects that might be missed in earlier studies.

EARLY OR LIMITED APPROVAL:

- China and Russia have approved vaccines without waiting for the results of Phase 3 trials. *The rushed process has* ***serious risks.***

The Process

APPROVAL:

- Regulators in each country review the trial results and decide whether to approve the vaccine or not. During a pandemic, a vaccine may receive emergency use authorization before getting formal approval. Once a vaccine is licensed, researchers continue to monitor people who receive it to make sure it's safe and effective.

COMBINED PHASES:

- One way to ***accelerate*** vaccine development is to combine phases.
- Some coronavirus vaccines are now in Phase 1/2 trials, for example, in which they are tested for the first time on hundreds of people.

PAUSED:

- If investigators observe worrying symptoms in volunteers, they can put a trial on pause. ***After an investigation, the trial may resume or be abandoned.***

FDA strict guidelines to coronavirus vaccine makers seeking early approval

- Proof an experimental vaccine is at least 50% effective
- Vaccine makers to follow volunteers for a median of two months after the final dose- two shots spaced three to four weeks apart.
- Document at least five cases of severe COVID-19 observed in the participants who have received a placebo, - in order to determine the risk of respiratory disease induced by vaccination — a key safety worry for both developers and regulators.

Types of Vaccines based on development process

Adenovirus vaccine

- Wild Adenoviruses, genetically engineered to express viral antigens found in SARS-CoV-2, usually those of spike protein that coronavirus uses to break into human cells.
- When put into a vaccine, adenoviruses trigger an immune response in the human body, protecting against CoV.
- This is a new technology: no adenovirus vector vaccines for other diseases are yet widely available, though vaccines for HIV, influenza, Ebola and malaria using this platform are in clinical trials and an Ebola vac has been briefly deployed.
- ChAdOx1 nCoV-19 vaccine candidate from Oxford University's Jenner Institute. (ChAdOx1 stands for "chimpanzee adenovirus Oxford 1.")

Adenovirus vaccine

- The Chinese company CanSino Biologics — the medical science arm of the People's Liberation Army, no less — has completed Phase 1 trials with an adenovirus vector vaccine called Ad5-nCoV.

- Johnson & Johnson, via its subsidiary Janssen, uses a genetically modified human adenovirus technology it calls AdVac.
  - This is a proven platform, which was used to produce thousands of doses of company's Ebola vaccine deployed in the Congo in November 2019.

- Adenoviruses are not the only viral vectors that can be used:
  - Merck is working on a potential COVID vaccine using an engineered vesicular stomatis virus, previously used successfully in its Ebola vaccine.
  - Another collaboration Merck is involved in uses an attenuated live measles vaccine.

Adenovirus vaccine

CanSino reported positive results in a Lancet paper on May 22.

- This is the first Phase 1 COVID vaccine clinical trial published in a peer-reviewed paper, -108 healthy adults all showing an immune response to the adenovirus vector vaccine.

- Since adenovirus is already widespread in the population, some of those in the trial had already been naturally infected with it, dampening their immune response. -- Will Oxford's chimp adenovirus vaccine perform better? Time will tell, but meanwhile CanSino is proceeding to Phase 2 trials with a six-month study of 500 adults in Wuhan.

Adenovirus vaccine

The Oxford team published a preprint on May 13 showing that ChAdOx1 prevented rhesus macaques monkeys from getting pneumonia when infected with SARS-CoV-2. That's the good news — the vaccine protected against disease.

- The bad news was that the vaccinated monkeys still became infected, and nose swabs showed the same amounts of virus in samples taken from both vaccinated and non-vaccinated animals.
- This means in theory that vaccinated people could still be infectious even if they don't actually get symptoms of the disease.
- Still, it would be a massive step forward if we could just "push the disease from pneumonia to a common cold," in the words of one expert.

Adenovirus vaccine

- Oxford University has partnered with the global pharmaceutical company AstraZeneca for vaccine now being renamed AZD1222.
  - On May 21 it announced an agreement to produce 400 million doses
  - On June 5 AstraZeneca's CEO said they intend to produce 2 billion doses of vaccine - Phase 3 trials planned involving thousands of participants in UK, US, Brazil, S.A.
- Johnson & Johnson has the corporate muscle to produce vaccine doses in large quantities to allow vaccine availability for emergency use in early 2021."

ANY DRAWBACKS?

- Live viruses, even if attenuated, can be risky in immunocompromised people.
- Neither Oxford nor CanSino scored full successes with their first attempts.

RNA vaccine

- While conventional vaccines work by presenting the body's immune system with the inactivated real virus or antigens derived from it, injecting mRNA into cells means that they produce the required viral proteins directly inside the human body.
  - **"A big advantage of mRNA vaccines is that scientists can skip the lab production of proteins by directly injecting the molecular instructions to make the protein into the human body itself."**
- In this case the RNA sequence is taken from the SARS-CoV-2 virus genome, stimulating an immune response that should later stop the CoV virus.
  - **One advantage to mRNA vaccines is a cheaper, faster production process, making them potentially the most scalable to tackle a global pandemic.**

RNA vaccine

- Companies trying this approach:
  - Moderna - now approved, and being given in USA
  - The Imperial College, London;
  - The German-based company BioNTech, which is working in alliance with the drugs giant Pfizer; - now approved, and being given in USA and UK
  - CureVac, another German-based company.
  - A Chinese consortium from Fudan University, Shanghai JiaoTong University and RNACure Biopharma is employing a second strategy of using mRNA to create “virus-like particles” in the body to activate an immune response.
- More detail on Moderna and Pfizer/BioNTech shortly
- CureVac announced “positive pre-clinical results” for its lead COVID vaccine candidate on May 14 and received approval to start a Phase 1 clinical trial on June 17 in Germany and Belgium.

Inactivated pathogen

- The most traditional approach — the inactivated virus stimulates the immune system to produce antibodies, using killed or weakened virus.
- The Chinese company Sinovac,designed a vaccine by isolating SARS-CoV-2 samples from infected hospital patients and growing the virus in cell lines before inactivating it with a chemical agent. It is called PiCoVacc (for “purified inactivated SARS-CoV-2 vaccine”).
  - In a paper published in Science on May 6, - “induced SARS-CoV-2-specific neutralizing antibodies in mice, rats and non-human primates.” It also “provided partial or complete protection in macaques” against deliberate infection with the virus. On June 13 Sinovac posted initial results for a Phase 1/2 trial involving several hundred people: 90% of the volunteers tested positive for protective antibodies.

Inactivated pathogen

- An international team has a different approach, using a vaccine that is already widely deployed: the BCG vaccine.
- Because BCG already has a decades-long history of safe use as a vaccine, trials to see whether it is effective against COVID have gone straight to Phase 3.
    - Trials are currently underway among 10,000 frontline health workers in Australia, run by Murdoch Children's Research Institute, and in the Netherlands among a further 1,500 health workers.

ANY DRAWBACKS?

- Growing large volumes of viruses to use in vaccines is a long and arduous process, so the traditional approach will be the slowest to scale up globally. Believe it or not, most attenuated virus vaccines are made using huge numbers of chicken eggs.

DNA vaccine

- Technique does involve injecting a fragment of circular DNA, called a plasmid, into human cells.
- This introduced DNA codes for SARS-CoV-2 viral proteins that are then expressed by the cell and help prime the immune system to fight off an attack by COVID-19.
- Like mRNA, this is a new technology — no DNA vaccines have ever been fully developed and utilized in humans to prevent disease.
- The leading developer is Inovio, which worked with a DNA candidate vaccine against MERS.
- Several other teams are also working on DNA vaccine candidates for the novel coronavirus, including one at the Harvard Medical School.

DNA vaccine

- On May 20, Inovio scientists published trial results in the journal Nature Communications for its COVID candidate DNA vaccine, INO-4800.
    - This showed “robust binding and neutralizing antibody as well as T cell responses in mice and guinea pigs,” according to the company, raising hopes that INO-4800 might also stimulate a strong immune response in humans.
    - Inovio’s vaccine is already in human trials in Philadelphia and Kansas City and South Korea.
- Separately, the Harvard-led team announced in a paper published in Science on May 20 that various DNA candidate vaccines expressing different forms of the SARS-CoV-2 spike protein had succeeded in immunizing rhesus macaque monkeys.

ANY DRAWBACKS?

- As with mRNA, there have never yet been DNA vaccines –
- Inovio has been around for four decades but has yet to develop a single approved product.

Viral proteins

- Genes that code for proteins from the pathogen — in COVID's case, mostly the notorious spike protein — are spliced into different viruses, which are then mass-produced.
  - Sanofi Pasteur, the vaccines division of Sanofi, is repurposing its earlier SARS vaccine efforts into COVID. Its recombinant DNA approach in cell lines has already been licensed to produce an influenza vaccine,
  - A team at the University of Pittsburgh, whose members had already worked on SARS and MERS and quickly repurposed their spike protein vaccine to target SARS-CoV-2. Its purified protein can be delivered in a "microneedle array," a fingertip-sized patch of 400 tiny soluble needles that affixes to the skin like a Band-Aid.
  - Novavax has developed a way to package SARS-CoV-2's spike proteins into nanoparticles that should enhance immune response by better mimicking the virus.

Viral proteins

- In Canada, Medicago began producing virus-like particles of the coronavirus — expressed in leaves of Nicotiana benthamiana, a wild relative of tobacco — just 20 days after the viral genome was published.
- Sanofi's has brought forward Phase 1/2 trials from December to September.
  - On 24 June Sanofi said Phase 3 trials could begin by December, and that it expects to have 100 m doses of vaccine prepared by the end of the year – even before it has been proven to work. If all goes to plan, another 1 billion doses can be manufactured in 2021.
- The Pittsburgh team won the race to produce the first peer-reviewed paper on a COVID vaccine trial, reporting in mid-March that its microneedle vaccine had "elicited potent antigen-specific antibody responses" when tested in mice.
  - However, Phase 1 human trials have not yet begun, and the scientists warn that getting results "would typically require at least a year and probably longer."

Viral proteins

- Novavax has received investments totalling $388 million from the Coalition for Epidemic Preparedness (CEPI) to advance clinical dev of its vaccine NVX-CoV2373.
  - Phase 1 trials began on May 26 in Australia in 131 human volunteers.
  - The company is developing scaled-up production that could potentially deliver 100 million vaccine doses by the end of 2020, and 1 billion doses starting in 2021.
- Medicago announced positive results for a trial of its COVID candidate vaccine in mice on May 14, and aims to start human trials in the summer.
  - It can already produce 120 million doses of the vaccine per year in its current facilities, and aims to scale up to 1 billion per year by 2023.

ANY DRAWBACKS?

- As with growing viruses directly, growing large amounts of viral proteins takes time.

Cell lines may be quicker than chicken eggs but scaling up to the billions of doses will take a lot longer than the mRNA/DNA approach.

So where are we with all these vaccines and vaccine candidates?

Moderna RNA vaccine

- Moderna's vaccine (mRNA-1273) was the first to be injected into human volunteers, in mid-March.
  - May 18 - announced that its vaccine candidate had stimulated an immune response with the production of neutralizing antibodies in eight human volunteers in its Phase I trial generated global media coverage and a stock market rally.
  - Moderna completed Phase 3 trials with over 30,000 participants and received FDA emergency approval this month
  - Manufacturing capacity is being lined up for 500 million to one billion doses by 2021.
  - The company is confident enough to have announced a partnership – on 25 June – with a production agreement signed "to support production of an initial 100 million doses of the vaccine candidate intended to supply the U.S. market starting in the third quarter of 2020", and hundreds of millions of additional doses thereafter.

MODERNA RNA VACCINE

- Moderna recruited 30,000 volunteers across the United States to participate in its phase 3 trial.
  - Found to be 94.5% effective
  - A quarter of the participants are 65 years or older.
  - White people make up 63 percent of the volunteers; 20 percent are Hispanic; 10 % are Black; and 4% Asian Americans.
  - They randomly assigned volunteers to get either the Moderna vaccine or a placebo.
  - The trial was blinded, placebo controlled meaning that neither the volunteers nor the people running the trial knew who got what.
  - The 95 people who got sick with Covid-19 reflect the diversity: (15 were 65 or older; the group included 12 Hispanic volunteers, four Black participants, three Asian Americans and one multiracial person) and efficacy and safety appeared the same in all of the subgroups.

Pfizer's Vaccine

- Pfizer developed the vaccine with its partner BioNTech NOW report that its coronavirus vaccine is **95** percent **though initially they reported 90%** effective and had no serious side effects
- The data showed that the vaccine prevented mild and severe forms of Covid-19
- And it was 94 percent effective in older adults, who are more vulnerable to developing severe Covid-19 and who do not respond strongly to some types of vaccines.
- The trial results — less than a year after researchers began working on the vaccine — shattered all speed records for vaccine development, a process that usually takes years.

How do Moderna's early results compare with Pfizer's?

- Pfizer provided less detail in its announcement last week on Nov. 9 than Moderna did on Monday, Nov. 16.
- Pfizer's outside board of experts analyzed 94 volunteers and estimated that the effectiveness of its vaccine was over 90 percent.
- They did not specify how many people who got sick had received the vaccine or the placebo.

- **Nevertheless, the estimates for the two vaccines far exceed the F.D.A.'s requirement that coronavirus vaccines have an efficacy of more than 50 percent.**

- Pfizer did not report how many volunteers had severe Covid-19, or what fraction of those people got the vaccine. Findings like these are expected to come out in the next few weeks.

How do Moderna's early results compare with Pfizer's?

- The Pfizer and Moderna vaccines are similar not only because they use mRNA but also because they coax our cells to make the same viral protein, called spike.
  - Other vaccines that don't use mRNA also make the spike protein their target. The success of Moderna and Pfizer may bode well for them as well.

- **Moderna vaccine may be preferred to Pizer vaccine in that**
  - It can be kept at – 20 degrees temperature
  - Can be transported while frozen at - 20degrees compared to Pfizer's -70 degrees requirement
  - It is easier to distribute - favorable cold chain needs
  - Electiveness of 94.5 C – though now Pfizer has reported 95% -- higher than what they had earlier reported as 90%

What do the Pfizer and Moderna reports mean together?

- Pfizer and Moderna used the same basic design to build their vaccines.
- Both vaccines contain a genetic molecule called messenger RNA, which is wrapped in an oily bubble.
  - The bubble can fuse to a muscle cell and deliver the RNA. Encoded in that molecule are instructions for building a single coronavirus protein called spike.
  - When a vaccinated cell releases copies of the spike protein, the immune system learns to make antibodies against it.
- While scientists have investigated mRNA vaccines for years, no vaccine has yet been licensed as safe and effective to use in people.
- Neither trial has uncovered serious side effects from the vaccines, although studies on their safety are continuing.

How are other vaccine makers faring?

- A number of teams have created vaccines based on another virus called an adenovirus, that slips into cells, delivering the gene for the spike protein.
  - In early November, a sponsor of a Russian vaccine announced that its adenovirus-based vaccine, called Sputnik V, was over 90 percent effective.
  - Outside experts wanted to see more data, however, because the announcement was based on just 20 sick volunteers — far fewer than in the Moderna and Pfizer trials.

- AstraZeneca and Johnson & Johnson are also conducting Phase 3 trials on adenoviruses that carry the spike protein gene.
  - And other companies, including Novavax and Medicago, are running advanced trials on vaccines that deliver the spike protein itself, or pieces of it, to the body.

How are other vaccine makers faring?

- University of Oxford-AstraZeneca
  - A study published in *The Lancet* in July showed that phase I/II trials of a single dose of ChAdOx1 nCoV-19 produced neutralising antibodies in more than 90% of participants. The vaccine also produced a T-cell response.
  - AstraZeneca and the University of Oxford said yesterday 27/12/2020 they have achieved a "winning formula" for efficacy, to provide close to "100 percent protection" against severe COVID disease requiring hospitalization
  - The UK government announced on Dec 23 that the developers had submitted their data with Approval expected to be granted to roll out the shot on Jan 4

How are other vaccine makers faring?

- Earlier trials had shown varying outcomes in the AstraZeneca shot's efficacy. The vaccine initially showed an average 70 percent effectiveness but that level jumped to 90 percent depending on dosage.
- Behind this average figure from large-scale trials in the UK and Brazil was a 62% effectiveness for those who were vaccinated with two full doses of the shot.
- For volunteers who received a half-dose first and then a full dose one month later, however, the vaccine was found to have 90% efficacy.
- AstraZeneca's vaccine can be stored, transported and handled at normal refrigerated conditions of between two and eight degrees Celsius (36-46 Fahrenheit) for at least six months.

How are other vaccine makers faring?

- Janssen
  - Phase 3 clinical trials of Janssen's vaccine began in the UK this week.
  - Like the Oxford candidate, Janssen's Ad26.COV2.S is an adenoviral vaccine.
  - The UK has agreed to buy 30 million doses of the Janssen vaccine.
  - It can be stored at normal refrigeration temperatures of 2C to 8C for at least 3 months. It can remain stable for 2 years when stored at -20C.

How are other vaccine makers faring?

- Novavax
  - Novavax expects to fully enrol phase 3 clinical trials of its NVX-CoV2373 candidate in the UK by the end of November. Trials in the US and Mexico will start by the end of the month.
  - The vaccine was created using recombinant nanoparticle technology to generate antigen derived from the coronavirus spike combined with a proprietary adjuvant to enhance immune response.
  - Interim data from the UK trial is expected in the first quarter of 2021.
  - The Government has secured delivery of 60 million doses.
  - The vaccine is stable at normal refrigeration temperature of 2C to 8C.

How are other vaccine makers faring?

GSK-Sanofi Pasteur

- The candidate vaccine ucombines recombinant protein-based technology from Sanofi to produce an influenza vaccine and GSK's pandemic adjuvant technology.
- A phase 3 trial is expected by the end of 2020.
- The UK Government has ordered 60 million doses.
- Standard storage temperatures of between 2C and 8C are understood to be a requirement of the GSK-Sanofi candidate vaccine.

How are other vaccine makers faring?

Valneva

- Valneva's VLA2001 vaccine is a vero-cell based highly purified inactivated whole virus vaccine based on the manufacturing platform of its Japanese encephalitis vaccine.
- The UK Government has an agreement to buy 60 million doses in the second half of 2021, with options of more than 40 million doses in 2022, and a further 30 million to 90 million doses during 2023 to 2025.
- VLA2001 is expected to require standard refrigeration at 2C to 8C.

In Summary

- There is some degree of immunity after the first dose of the COVID-19 vaccines, but it's not optimal and we don't know how long it will last.
  - We do know definitively that immunity increases dramatically after the second dose and lasts considerably longer.
- A "bridging study" in children will probably begin in mid-January to make sure that the COVID-19 vaccines' efficacy and safety data are comparable to those of the successful adult vaccine trials.
  - It's not necessary to vaccinate children before we reopen schools.

In Summary

- April could be "open season" for the general public to start receiving COVID-19 vaccines, as long as the current rollout to priority groups goes smoothly.
  - We could have "umbrella protection" establishing herd immunity — by the end of summer 2021.
- People who are hesitant to get a COVID-19 vaccine should be reassured that the approval process has been independent and transparent, made by people who have no allegiance to the federal government or to pharmaceutical companies.
- Like all RNA viruses, this coronavirus has been mutating, and a new variant that has shown up in the United Kingdom may be more contagious.
  - However, there is no evidence that it is more virulent or that current vaccines will not be effective against it.

What happens next?

- Both the Moderna & Pfizer trials are continuing data collection The two companies have FDA approval for an emergency use authorization for vaccinating the public.
- US Army General Gustave F. Perna, chief operations officer for Operation Warp Speed, told reporters in a recent briefing USA is on track to finish distributing 20 m doses of COVID-19 vaccine by the first week in January.
- CDC committee of experts decided priority vaccination for:
  - HCWs – paid/unpaid involved in COVID-19 care
  - Long term care facilities residents – med/personal care – unable to care for self or live independently – these are easy to access and vaccinate; make up 2-3 million (6% of all USA COVID cases) and 40% of COVID deaths

What happens next?

- The UK was the first to approve and start use of Pfizer/Biontech vaccine in UK
  - **Priority to:**
    - **Elderly in care homes AND Health care workers**

    Then
    - **More than 80 year olds and Health care workers**

    Then
    - **60-70 year olds**

    Then
    - **Younger than 60 with comorbities**

    Then
    - **The rest – in 2021**
- Germany has embarked on massive production of coolers and refrigerators for use around Europe
- Pfizer & Moderna working with airlines for huge cargo planes with mobile freezers & constant temp monitoring for the distribution of the vaccines

COVAX

- COVAX - is the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator for global equitable access to CVD19 vaccines
- COVAX is co-led by Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI) and WHO.
- Its aim is to accelerate the development and manufacture of COVID-19 vaccines, and to guarantee fair and equitable access for every country in the world.
- What COVAX offers
  - Doses for at least 20% of countries' populations
  - Diverse and actively managed portfolio of vaccines
  - Vaccines delivered as soon as they are available
  - End the acute phase of the pandemic
  - Rebuild economies

The COVAX Agreement

- The new deals announced under COVAX include the signing of an advance purchase agreement with:
- AstraZeneca for 170 million doses of the AstraZeneca/Oxford candidate
- A memorandum of understanding (MoU) with Johnson & Johnson for 500 million doses of the Janssen candidate, which is currently being investigated as a single dose vaccine..
- Already existing agreements COVAX has with the Serum Institute of India (SII) for 200 million doses – with options for up to 900 million doses more – of either the AstraZeneca/Oxford or Novavax candidates, as well as a
- statement of intent for 200 million doses of the Sanofi/GSK vaccine candidate

Why we need COVAX

- Developing a vaccine against COVID-19 is the most pressing challenge of our time - and nobody wins the race until everyone wins.
- The global pandemic has already caused the loss of hundreds of thousands of lives and disrupted the lives of billions more.
- As well as reducing the tragic loss of life and helping to get the pandemic under control, introduction of a vaccine will prevent the loss of US$ 375 billion to the global economy every month.
- Global equitable access to a vaccine, particularly protecting health care workers and those most-at-risk is the only way to mitigate the public health and economic impact of the pandemic.

What happens next - AFRICA?

- COVAX (led by WHO, GAVI and CEPI) will facilitate the equitable access & distribution of these vaccines in all countries. People most at risk will be prioritized.
- Almost all African countries have signed to this
- Each country will receive 20% of its population doses of vaccine – for free – with accompanying cold chain equipment, then the country buys the other 80%
- Countries have to evaluate the data and approve the vaccines locally and individually
- Most African countries can handle the -20 degrees Moderna temp requirements, and even the -70 degrees Pfizer requirements in some areas – due to experience with the -80 degrees Ebola vaccines

What happens next - AFRICA?

- Need to address stigma and mental health and long term effects of COVID among recovering patients
- Vaccine hesitancy
  - In general – I don't think this will be a problem anywhere –
    - vaccination status will be tied to international travel and access to most amenities
  - Need for confidence building and community engagement and social mobilization
  - Biggest worry are hesitant health workers


Thank you