IIHMR UNIVERSITY

www.iihmr.edu.in

Faculty Development Program for IIHMR Group of Institutions

COVID Vaccine: Development Process and Distribution

Date: September 26, 2020

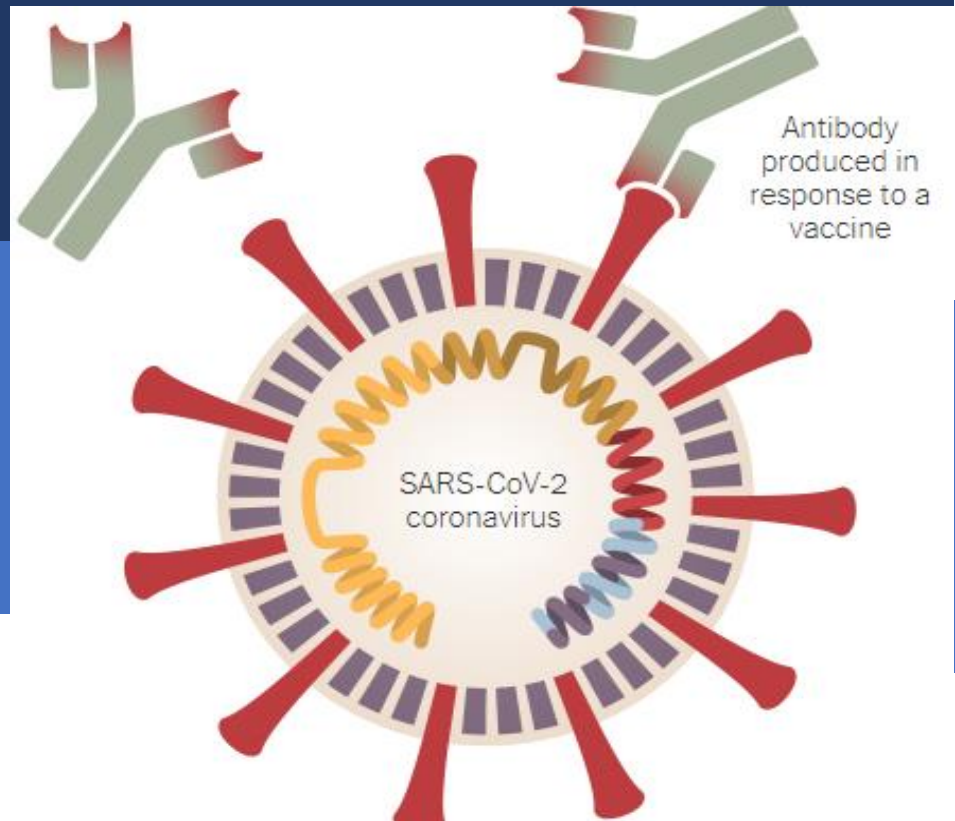
Dr Daya Krishan Mangal
Professor, Advisor (SDG-SPH)
IIHMR University, Jaipur

Dr. Daya Krishan Mangal, Doctorate in Medicine (Preventive and Social Medicine), University of Rajasthan, India; Fellow of Indian Public Health Association has served as a teacher in medical colleges of Rajasthan in different capacities for more than 25 years and also worked as Community Health Consultant, Government of Libya, Senior Research Scientist, The Futures Group International, Dy. Director IEC Bureau, Directorate of Health Services, Government of Rajasthan, Associate Professor at Health Management wing, Rajasthan Institute of Public Administration, and Officer on Special Duty with Government of Rajasthan on secondment. After seeking voluntary retirement from Government of Rajasthan in 2004, Dr. Mangal has worked with UNPFA India Country Office and at UNFPA's State Offices at Madhya Pradesh and Maharashtra for ten years. During his illustrious career of more than 35 years in public health, Dr. Mangal has made significant contributions at policy and programme levels in the areas of health system strengthening, health communication, health training and research. He possesses extensive experience of working in different cultural settings and with multi disciplinary teams. Dr. Mangal has published 25 scientific articles in peer reviewed National and International journals and contributed in several reports and chapters in books on public health issues. His current interests are Health systems strengthening, health systems research, quality of care and Reproductive Health.

COVID Vaccine: Development process and distribution

Dr Daya Krishan Mangal

FDP meeting on 26.09.2020



Outline of the Presentation

- Background
- Vaccine development
- Vaccine approval
- COVID vaccine status- Global and India
- COVID vaccines in phase 3: examples
- Distribution of COVID vaccine in India
- What will change with introduction of COVID vaccine

Background

- COVID 19 Global situation
  - Confirmed cases: **32110656**
  - **Confirmed deaths: 980031**
- India situation
  - Confirmed cases: **5818570**
  - **Confirmed deaths: 92290**
- Second highest tally of cased only behind US where total cases are **6868828** and deaths are 200725
- India is reporting far lower number of cases and deaths per million population compared to many countries globally.

- **COVID 19 Cases and deaths per million Population**

Countries	Cases	Deaths
Global	4123	126
US	21542	623
India	4148	66
Brazil	21736	653
Russia	7734	137
Colombia	15376	485

History of vaccines

- Smallpox vaccination by Edvard Jenner in 1796 is considered beginning of immunization.
- However, evidence suggests that variolation was practiced in China and India as early as 1000 AD
- Today we have effective vaccines against 27 diseases
- Vaccines play critical role in prevention and control of epidemic-prone diseases, such as yellow fever, cholera and influenza.
- COVID is the pandemic of 21 century and everybody is looking forward to vaccine against it for prevention and control.

COVID Vaccine: Development

Development of a New Vaccines

- Exploratory stage
- Pre-clinical stage
- Clinical development
- Regulatory review and approval
- Manufacturing
- Quality control
- Reaching vaccine to people

Exploratory and Pre-clinical stage

- **Exploratory stage involves**
  - Basic laboratory research and often lasts 2-4 years.
  - Federally funded academic and governmental scientists identify natural or synthetic antigens that might help prevent or treat a disease.
  - These antigens could include virus-like particles, weakened viruses or bacteria, weakened bacterial toxins, or other substances derived from pathogens.
- **Pre-clinical stage:**
- It uses tissue-culture or cell-culture systems and animal testing to assess
  - The safety of the candidate vaccine and its immunogenicity,
  - Or ability to provoke an immune response.

The Journey of Your Child's Vaccine

Before a new vaccine is ever given to people, extensive lab testing is done that can take several years. Once testing in people begins, it can take several more years before clinical studies are complete and the vaccine is licensed.

How a new vaccine is developed, approved and manufactured

The Food and Drug Administration (FDA) sets rules for the three phases of clinical trials to ensure the safety of the volunteers. Researchers test vaccines with adults first.

PHASE 1

20-100 healthy volunteers

- Is this vaccine safe?
- Does this vaccine seem to work?
- Are there any serious side effects?
- How is the size of the dose related to side effects?

PHASE 2

several hundred volunteers

- What are the most common short-term side effects?
- How are the volunteers' immune systems responding to the vaccine?

PHASE 3

hundreds or thousands of volunteers

- How do people who get the vaccine and people who do not get the vaccine compare?
- Is the vaccine safe?
- Is the vaccine effective?
- What are the most common side effects?

FDA licenses the vaccine only if:

- It's safe and effective
- Benefits outweigh risks

Vaccines are made in batches called lots.

Manufacturers must test all lots to make sure they are safe, pure and potent. The lots can only be released once FDA reviews their safety and quality.

The FDA inspects manufacturing facilities regularly to ensure quality and safety.

FOR MORE INFORMATION, VISIT HTTPS://WWW.FDA.GOV/CBER

If the FDA licenses a vaccine, experts may consider adding it to the recommended immunization schedule.

https://www.cdc.gov/vaccines/parents/infographics/journey-of-child-vaccine.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fparents%2Finfographics%2Fjourney-of-child-vaccine-text.html

Clinical development – Three phase process

Phase I trial

- Small groups of people receive the trial vaccine.
- Typically a small trial done in about 10-50 people mainly to assess safety. Whether the vaccine candidate is safe in humans.
- In Phase I they also sometimes see if the vaccine makes the right kind of antibodies or not, but primarily it is a safety trial.
- Phase I trail typically takes a few weeks.

Clinical development – Three phase process

Phase II trial

- The clinical study is expanded, and vaccine is given to people who have characteristics (such as age and physical health) like those for whom the new vaccine is intended.
- It is larger trial with more than 100 volunteers. Dosage testing e.g. 1 injection of 20 micrograms or should I give two injections of 10 micrograms each.
- What should be the frequency with which I should give the vaccine? Usually a single injection doesn't work, then at least two to three shots.
- In phase II, we will also look at how the immune responses have developed in the various arms of the trail.

Clinical development – Three phase process

Phase III trial

- The vaccine is given to thousands of people and tested for efficacy and safety.
- Phase III trail is a very large efficacy trial.
  - Here we ask whether those who get the vaccine are protected, compared to those who don’t get the vaccine. This is typically tested in thousands of volunteers.
- Usually done in an area where the infection is prevalent. Otherwise we will never have enough people getting naturally infected to be able to make a distinction between those who are protected versus those who are not.

Clinical Development – Three phase process Cont….

- Scientists give the vaccine to **thousands of people** and wait to see how many become infected, compared with volunteers who received a placebo.
- These trials can determine if the vaccine protects against the coronavirus.
- In June, the F.D.A. said that a coronavirus vaccine would have to protect at least 50% of vaccinated people to be considered effective.
- In addition, Phase 3 trials are large enough to reveal evidence of relatively rare side effects that might be missed in earlier studies.

Phase 4 Process

- **Phase IV trial is** formal, ongoing studies after the vaccine is approved and licensed for tracking side effects.

Regulatory framework in India and US

Regulatory guidelines for vaccine registration

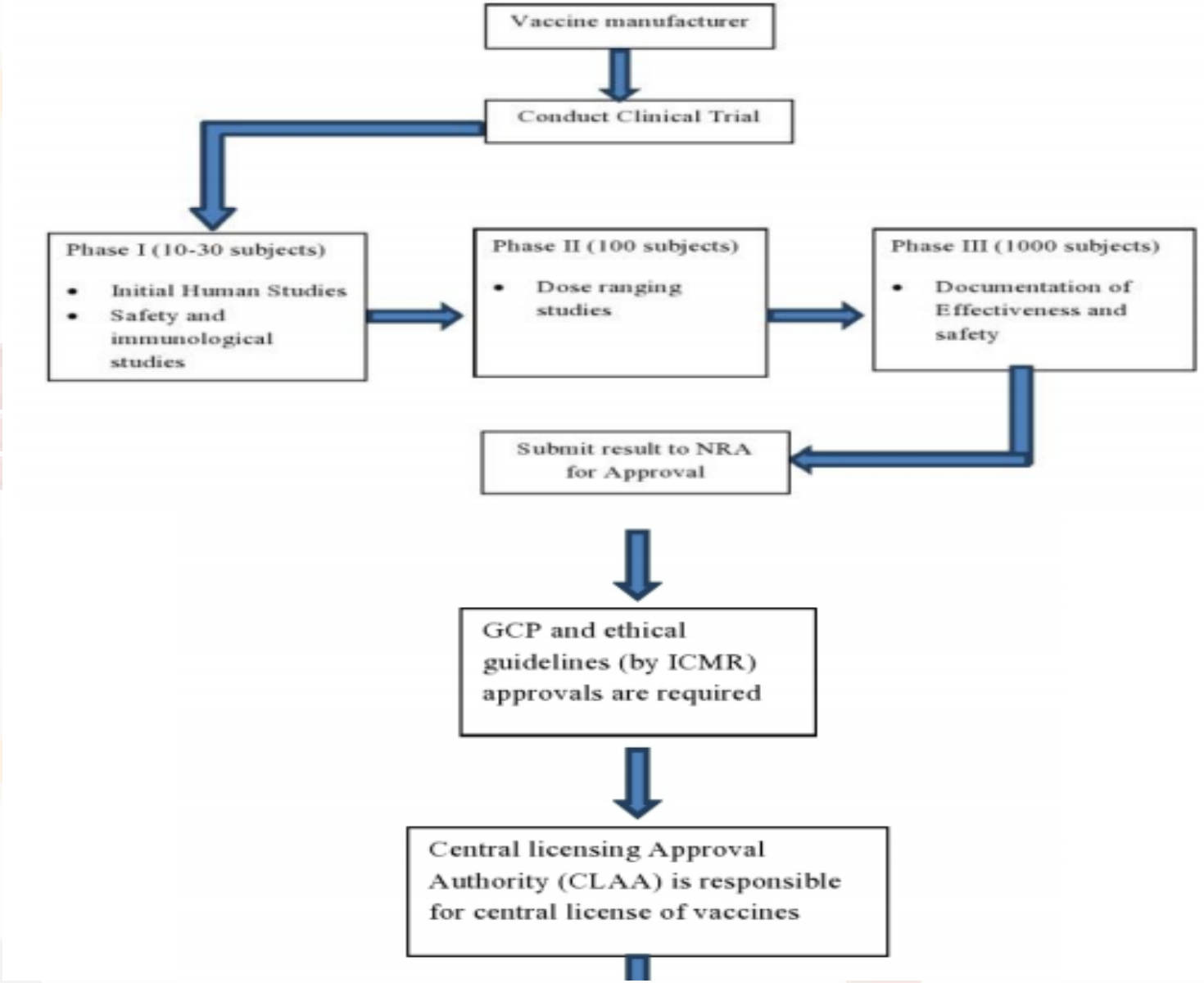
India

- Ministry of Health and Family Welfare,
- National Technical Advisory Group on Immunization (NTAGI),
- Indian Council for Medical Research (ICMR),
- Central Drugs Standard Control Organization (CDSCO),
- Central Licensing Approval Authority(CLAA)

USA

- CBER (Centre for Biologics Evaluation and Research)
- Vaccines and Related Biological Products Advisory Committee (VRBPAC)
- Biologics License Application (BLA)

Registration Process of vaccine in India

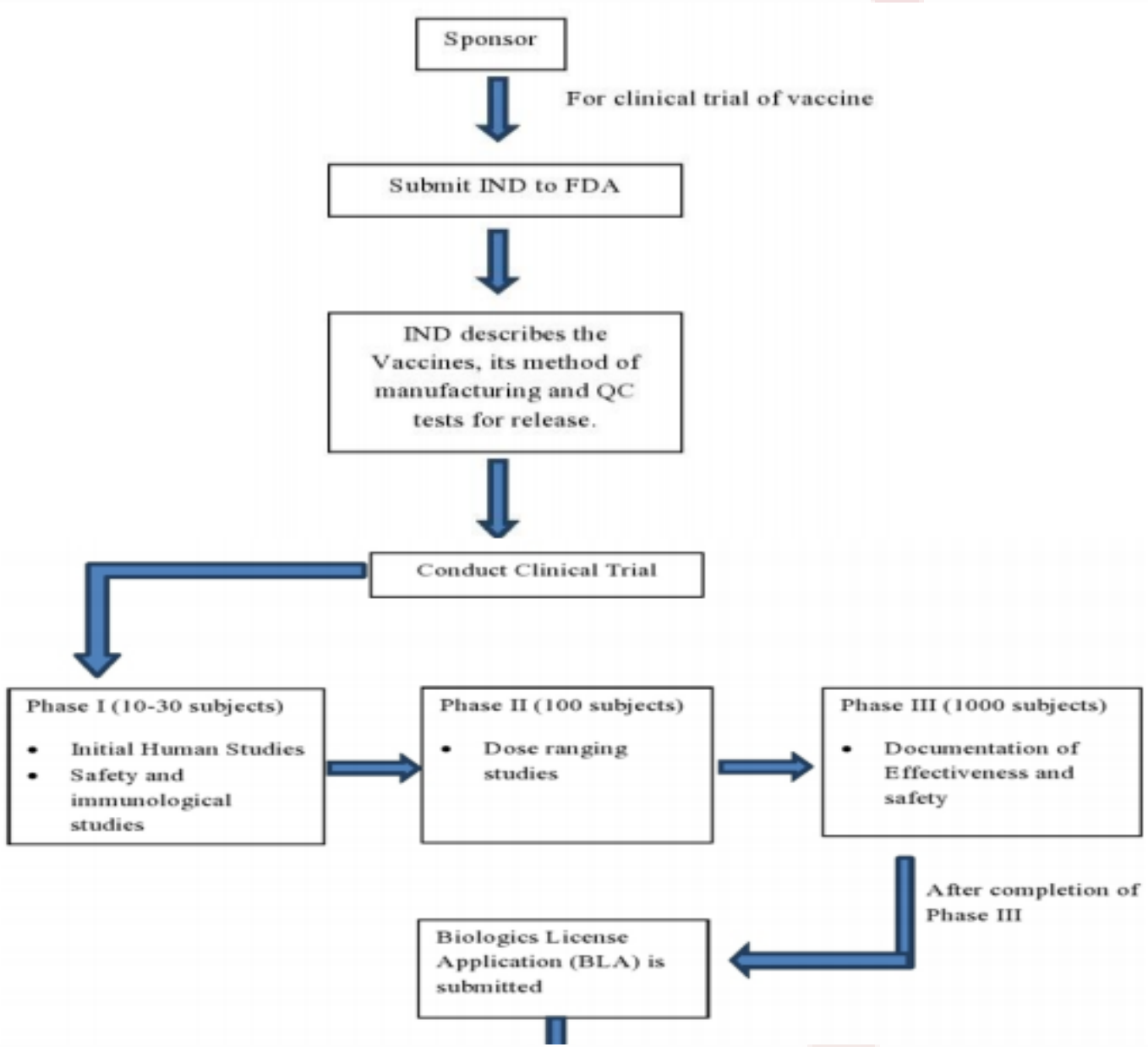


Vaccine product approval process, http://www.fda.gov/Biologics Blood Vaccines/Development Approval Process/Biologics License Applications BLA Process/ucm133096.htm
. BLA(Biologics License Application)process, http://www.fda.gov/ biologics blood vaccines/ development approval process/biologics license applications BLA process/default.htm
U.S Food and Drug Administration, "Vaccine and Related Biological product advisory committee" http://www.fda.gov/AdvisoryCommittees/ Committees Meeting Materials/Blood Vaccines and Other Biologics/Vaccines and Related Biological Products Advisory Committee/

Registration Process of vaccine in India

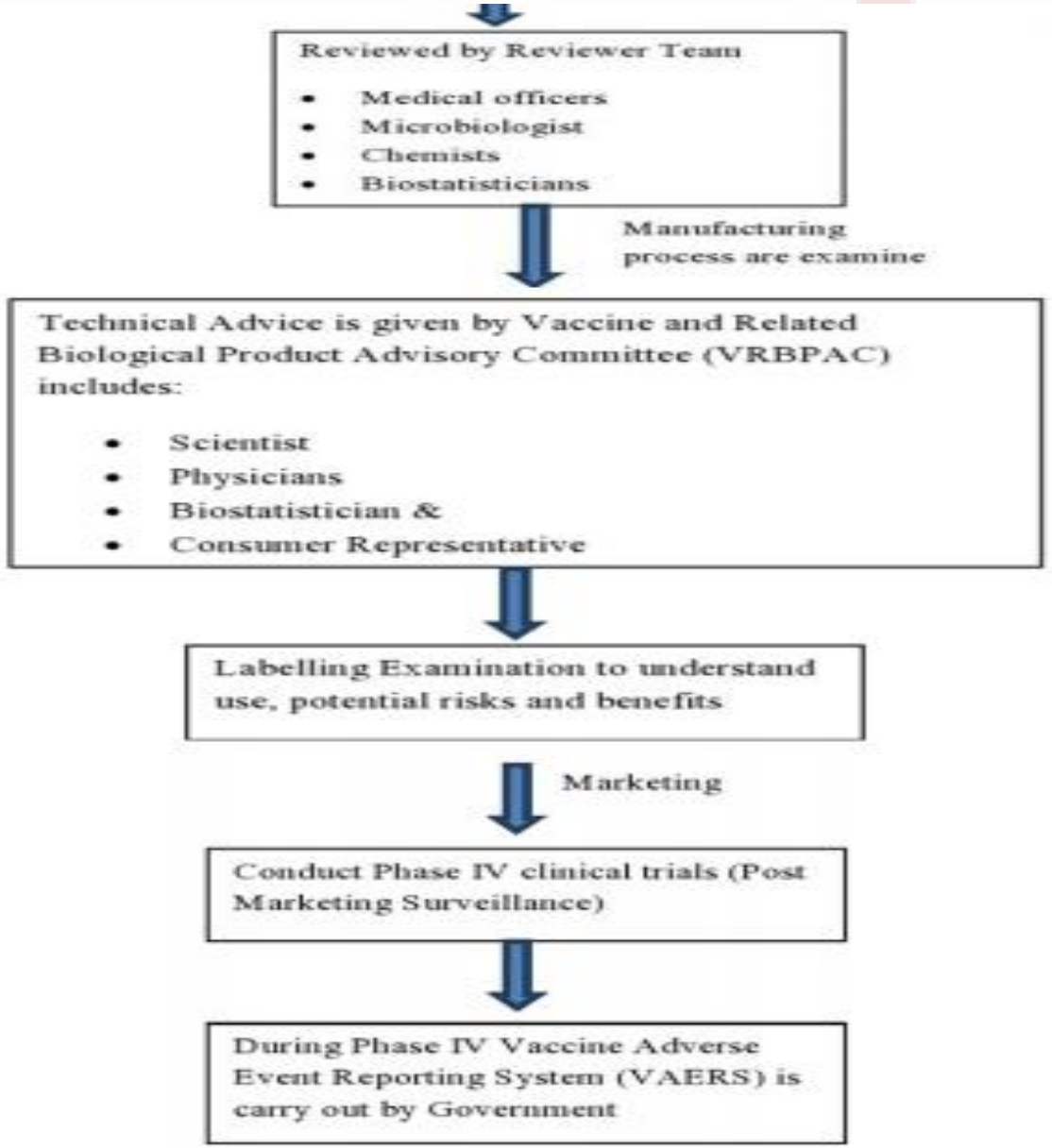
Vaccine product approval process, http://www.fda.gov/Biologics Blood Vaccines/Development Approval Process/Biologics License Applications BLA Process/ucm133096.htm
. BLA(Biologics License Application)process, http://www.fda.gov/ biologics blood vaccines/ development approval process/biologics license applications BLA process/default.htm
U.S Food and Drug Administration, "Vaccine and Related Biological product advisory committee" http://www.fda.gov/AdvisoryCommittees/ Committees Meeting Materials/Blood Vaccines and Other Biologics/Vaccines and Related Biological Products Advisory Committee/

Registration Process of vaccine in USA



Vaccine product approval process, http://www.fda.gov/Biologics Blood Vaccines/Development Approval Process/Biologics License Applications BLA Process/ucm133096.htm
. BLA(Biologics License Application)process, http://www.fda.gov/ biologics blood vaccines/ development approval process/biologics license applications BLA process/default.htm
U.S Food and Drug Administration, "Vaccine and Related Biological product advisory committee" http://www.fda.gov/AdvisoryCommittees/ Committees Meeting Materials/Blood Vaccines and Other Biologics/Vaccines and Related Biological Products Advisory Committee/

Registration Process of vaccine in USA



Vaccine product approval process, http://www.fda.gov/Biologics Blood Vaccines/Development Approval Process/Biologics License Applications BLA Process/ucm133096.htm
. BLA(Biologics License Application)process, http://www.fda.gov/ biologics blood vaccines/ development approval process/biologics license applications BLA process/default.htm
U.S Food and Drug Administration, "Vaccine and Related Biological product advisory committee" http://www.fda.gov/AdvisoryCommittees/ Committees Meeting Materials/Blood Vaccines and Other Biologics/Vaccines and Related Biological Products Advisory Committee/

Registration process of Vaccine

India	USA
National Regulatory Authority (NRA) is responsible for regulation of vaccine	Center for Biological Evaluation and Research (CBER)is responsible for regulation of vaccine
Central Licensing Approval Authority (CLAA) is responsible for obtaining license	Biologics License Application (BLA) is responsible for obtaining license
Form 44 and T- license is required to get approval for conducting clinical trial	IND (Investigational New Drug application) is required for conducting clinical trial
8-12 weeks are required for complete evaluation of application for registration of vaccine	180 days are required for complete evaluation of application for registration of vaccine
Registration fees- INR 50,000	Registration fees- $ 212,787

Approval of Vaccine

- EARLY OR LIMITED APPROVAL: China and Russia have approved vaccines without waiting for the results of Phase 3 trials. Experts say the rushed process has serious risks.

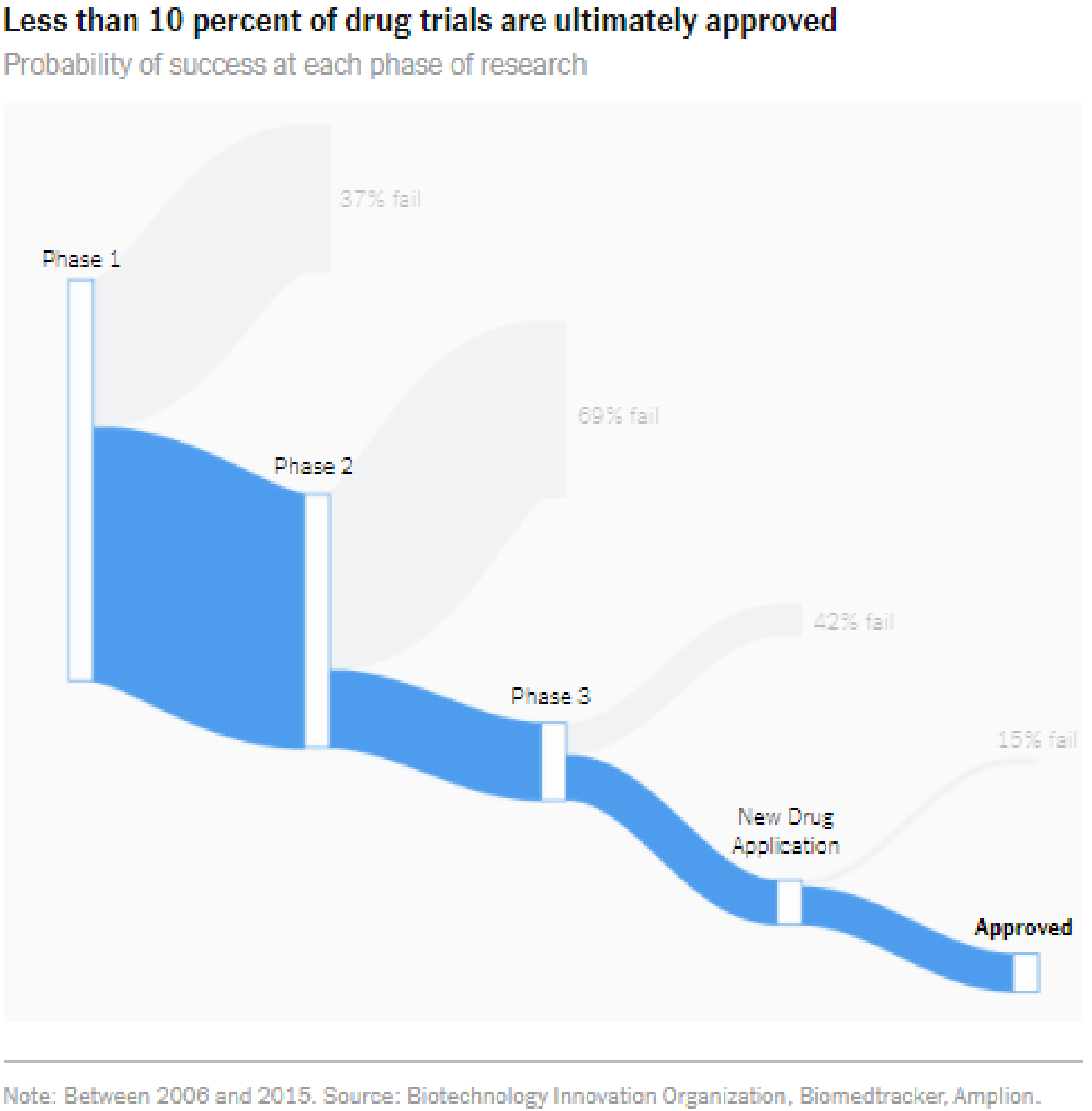
- APPROVAL: During a pandemic, a vaccine may receive emergency use authorization before getting formal approval. Once a vaccine is licensed, researchers continue to monitor people who receive it to make sure it's safe and effective.

- 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.

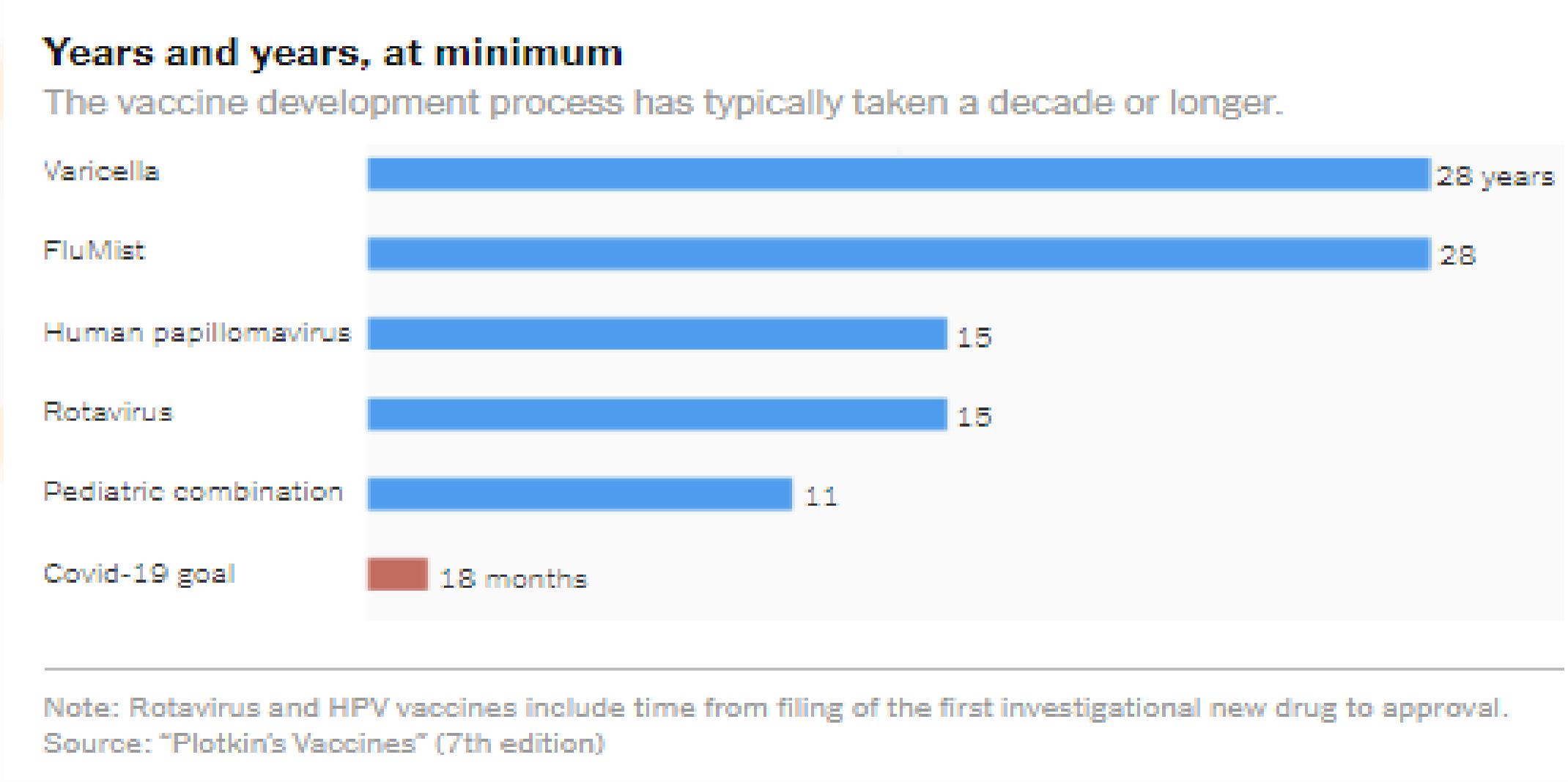
*Note: The combined Phase 1/2 trial is considered in both Phase 1 and Phase 2

Less than 10 percent of drug trials are approved

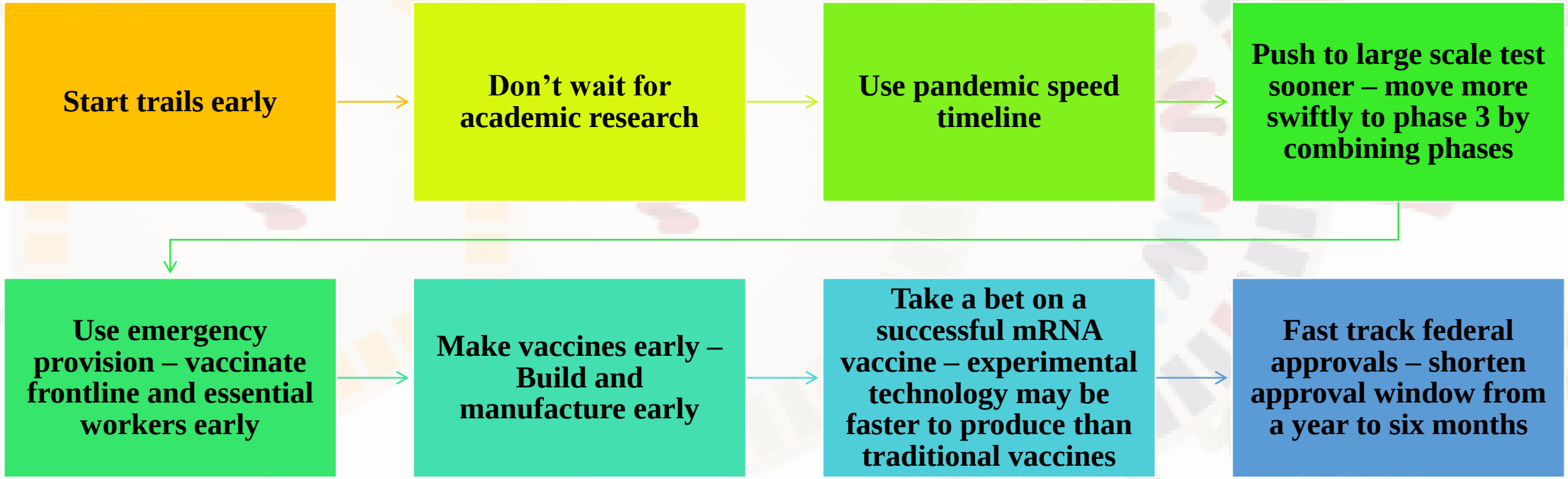
- Despite the unprecedented push for a vaccine, researchers caution that **less than 10 percent of drugs** that enter clinical trials are ever approved by the Food and Drug Administration.



Trend in Vaccine development



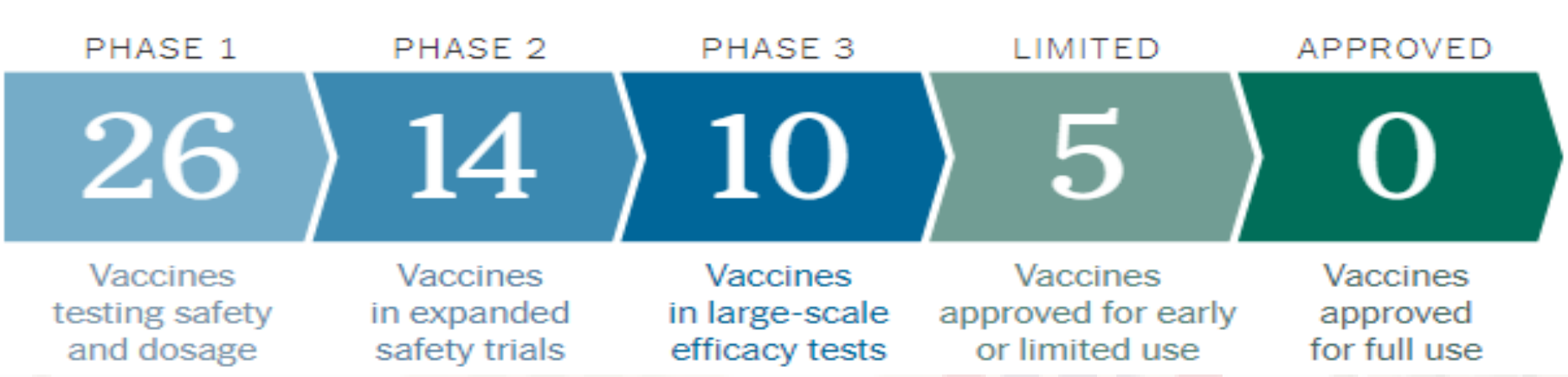
Coronavirus Vaccine: Development stages in Emergency situation



COVID Vaccine- status: Globally and in India

Coronavirus Vaccine tracker

- Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by next year.
- Researchers are testing **35 vaccines** in clinical trials on humans, and at least 88 preclinical vaccines are under active investigation in animals.



Updated September 23, 2020

Land Scape of corona vaccine-22 September 2020

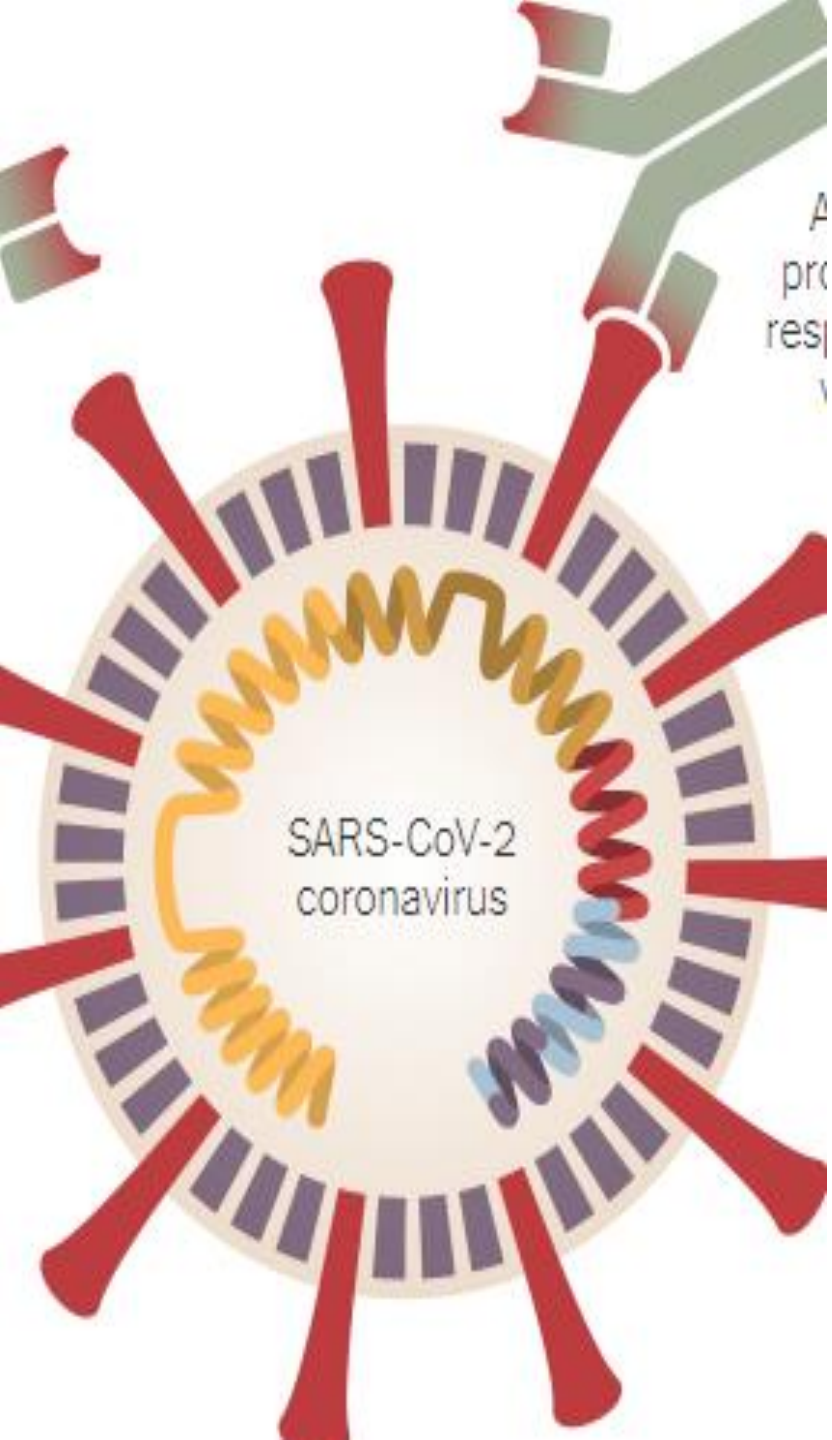
- file:///C:/Users/D.K.%20Mangal/Downloads/novel-coronavirus-landscape-covid-19-(5)%20(2).pdf

List of vaccines - Phase 3

	Sponsor	Trial Phase	Instituition	Funding	Country
Inactivated Vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	3	Henan Provincial Center for Disease Control and Prevention	Ministry of Science and Technology, China	China
CoronaVac	Sinovac	3	Sinovac Research and Development Co., Ltd.	Sinovac Research and Development Co., Ltd.	China
mRNA-1273	Moderna	3	Kaiser Permanente Washington Health Research Institute	Operation Warp Speed; NIAID, BARDA ($483 million)	England
Ad5-nCoV	CanSino Biologics	3	Tongji Hospital; Wuhan, China	CanSino Biologics	China

Country wise – Vaccine for Coronavirus

Country	Pre clinical	Phase 1	Phase 2	Phase 3
Autralia		2	1	
Canada	1			
China	1		2	3
England		1	1	1
Germany	1	2	1	
US	7	4	2	
India			2	
Russia		1		
Singapore		1		
Thailand	1			
Korea		1		
Taiwan		1		
Italy		1		
Belgium		1		



COVID Vaccine development timeline and update

- The first vaccine safety trials in humans started in March, but the road ahead remains uncertain.

➢Gam-Covid-Vac - combination of two adenoviruses, Ad5 and Ad26, both engineered with a coronavirus gene by Gamaleya Research Institute, part of Russia's Ministry of Health

- Approved for limited use – Sep 23, 2020

➢Chinese company CanSino Biologics - Adenovirus called Ad5

➢Chinese company Sinovac Biotech - An inactivated vaccine called CoronaVac.

➢The Wuhan Institute of Biological Products –Sinopharm's vaccine to use on health care workers.

- EARLY OR LIMITED APPROVAL: China and Russia have approved vaccines without waiting for the results of Phase 3 trials. Experts say the rushed process has serious risks.

- APPROVAL: 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.

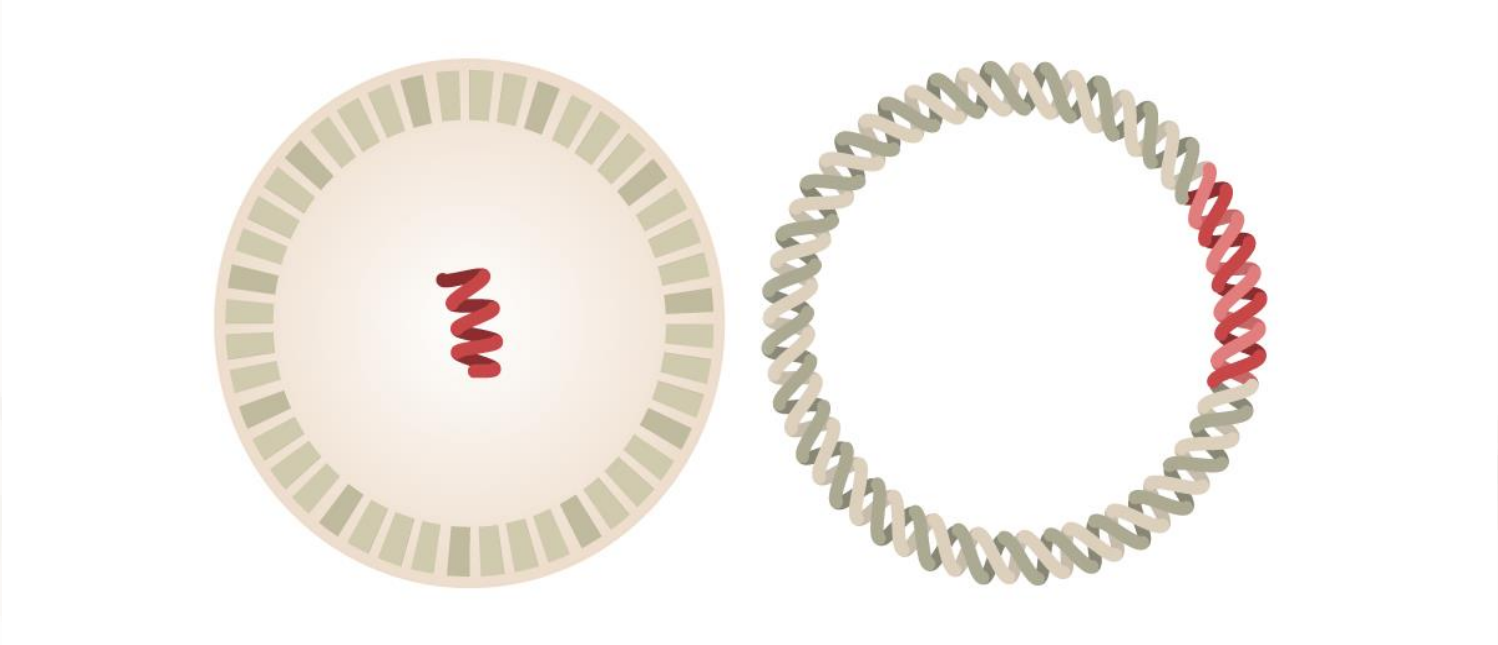
*Note: The combined Phase 1/2 trial is considered in both Phase 1 and Phase 2

Vaccine Types

- **There are 4 main types of vaccines:**
  - Live-attenuated vaccines.
  - Inactivated vaccines.
  - Subunit, recombinant, polysaccharide, and conjugate vaccines.
    - RNA vaccine
  - Toxoid vaccines.

Genetic vaccines

- *Vaccines that use one or more of the coronavirus's own genes to provoke an immune response.*



APPROVED Vaccine- Russia

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

- The **Gamaleya Research Institute**, part of Russia's Ministry of Health, launched a Phase 1 trial in June of a vaccine they called Gam-Covid-Vac Lyo.
- It is a combination of two adenoviruses, Ad5 and Ad26, both engineered with a coronavirus gene.
- In July, the chair of the upper house of Russia's Parliament said the country might start vaccine production by the end of the year.

  On Aug. 11, President Vladimir V. Putin announced that a Russian health care regulator had approved the vaccine, renamed Sputnik V, before Phase 3 trials had even begun.
- Vaccine experts decried the move as risky, and Russia later walked back the announcement, saying that the approval was a "conditional registration certificate," which would depend on positive results from Phase 3 trials.
- Those trials, initially planned for just 2,000 volunteers, were expanded to 40,000.

Approved for Early use

Gamaleya Vaccine Fact Sheet

ФНИЦ эпидемиологии и микробиологии имени Н.Ф. Гамалеи

- **Codename**: Gam-Covid-Vac
- **Type**: Adenovirus vector vaccine (Ad5 / Ad26)
- **Mechanism**: Spike protein
- **Dose**: 10 x 10^{11} viral particles x 21 days apart
- **Recruitment Target**: 40,000
- **Recruitment Status**: 3000 (9/04/2020)
- **Primary Outcome**: New COVID-19 infections
- **Estimated Completion** (clinicaltrials.gov): 05/01/2021

Medscape

Approved - CHINA

- The Chinese company **CanSino Biologics** developed a vaccine based on an adenovirus called Ad5, in partnership with the Institute of Biology at the country's **Academy of Military Medical Sciences**.
- In May - promising results from a Phase 1 safety trial
- July - Phase 2 trials demonstrated the vaccine produced a strong immune response.
- In an unprecedented move, the Chinese military approved the vaccine on June 25 for a year as a "specially needed drug."
- CanSino would not say whether vaccination would be mandatory or optional for soldiers.
- On August 9, the Saudi health ministry announced that CanSino Biologics would run a Phase 3 trial in Saudi Arabia, and later in the month they also started a trial in Pakistan

Approved for limited Use

CanSinoBio Vaccine Fact Sheet

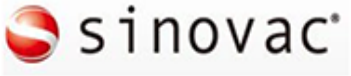
- **Code Name**: Ad5-nCoV
- **Type**: Adenovirus vector vaccine (Ad5)
- **Mechanism**: Spike protein
- **Dose**: 5 x 10^{10} viral particles ONCE
- **Recruitment Target**: 40,000
- **Recruitment Status**: ??? (Single site in Pakistan?)
- **Primary Outcome**: New COVID-19 infections
- **Estimated Completion** (clinicaltrials.gov): 12/30/2021

Medscape

Sinopharm Vaccine Fact Sheet

- **Code Name**: ???
- **Type**: Inactivated virus
- **Mechanism**: Whole virion
- **Dose**: 2 doses, 21 days apart
- **Recruitment Target**: 50,000
- **Recruitment Status**: 50,000 (9/7/2020)
- **Primary Outcome**: New COVID-19 infections
- **Estimated Completion** (clinicaltrials.gov): 3/16/2021

Sinovac Vaccine Fact Sheet



- **Code Name**: CoronaVac
- **Type**: Inactivated virus
- **Mechanism**: Whole virion
- **Dose**: 2 doses, 14 days apart
- **Recruitment Target**: 8870 (healthcare practitioners)
- **Recruitment Status**: 1215+ (data hard to come by)
- **Primary Outcome**: New COVID-19 infections
- **Estimated Completion** (clinicaltrials.gov): 9/30/2021

Vaccine development in India

um Institute, Zydus Cadila, Panacea Biotec, Indian Immunologicals, Mynvax and Biological E are among the domestic pharma cines in India.

	Mechnism	Sponsor	Trial phas
	Inactivated vaccine	Bharat Biotech, National Institute of Virology	Phase 2
	DNA Vaccine (Plasmid)	Zydus Cadilla	Phase 2
	Replication deficient viral vector vaccine (adenovirus from Chimpanzees)	The university of Oxford, AstraZencea, IQVIA, Serum Institute of India	Phase 3
logicals	A subsidiary of National Dairy Development Board (NDDB), has inked an agreement w Griffith University to develop a vaccine for coronavirus		
	Setting up a joint venture firm in Ireland with US-based Refana Inc to develop a vaccin 19.		

Seven Vaccines in Phase 3

- **RNA Vaccine - Pfizer and Moderna**
- **Inactivated vaccine – Sinovac and Sinophram**
- **Vector Vaccine – CanSinoBio, AstraZeneca, Gamaleya**

RNA Vaccine – RNA is injected, your cells take it up, and they make the protein on their own. The vaccine is produced inside your body.

Vector Vaccine - Use an existing virus, modified to express a SARS-CoV-2 protein as a Trojan horse, to rev up the immune response

RNA Vaccine – Pfizer and Moderna

- Pfizer – encodes the receptor binding domain of SARS-CoV-2, two doses
- Target is 30,000 – But 44,000 patient clinical trial to increase diversity
- Efficacy in data will be available by October but safety data takes longer
- Estimated completion – 4/19/2021

- Moderna – Encodes the spike protein
- Like Pfizer approach
- 30000 patient clinical trial

- https://www.youtube.com/watch?v=qJlP91xjvsQ

Inactivated vaccine – Sinovac & Sinophram

- Sinovac – Clinical trial of 8870 healthcare workers
- Smart approach – smaller study with adequate power
- Estimated completion – 9/30/2021

- Sinophram - approved for use by the Chinese military, completed a 50,000-person clinical trial in the Middle East
- No data available on testing
- Estimated Completion – 3/16/2021

- **CanSinoBio**
  Uses adenovirus 5 vector to introduce spike protein. Adenovirus 5 is the workhorse of vector-based technology.
- But there's a problem: A lot of us have had it already. A 2004 study found that 37% of individuals in the United States have neutralizing antibodies to adenovirus 5.

- **AstraZeneca** using a chimpanzee adenovirus as their vector.
- To avoid the "already immune" problem.
- Clinical trail of 20,000 of their 30,000-patient
- A case of transverse myelitis led the study to be halted.
- It has since been restarted. Is there a protein on that chimp adenovirus that could lead to cross-reactivity with some human protein?

- Gamaleya - A combination of adenoviruses 5 and 26, otherwise have a similar approach.
- Russia famously approved the use of this vaccine before the phase 3 study was completed.
- As of September 4, only 3000 of the target 40,000 individuals in their Phase 3 study have been recruited.
- Concerns about the data quality of their phase 1/2 study, published in the *Lancet*, may temper enthusiasm for this particular vaccine.

Grim Truth behind Vaccine development

- A vaccine would be the ultimate weapon against the coronavirus and the best route back to normal life.
- The grim truth behind this rosy forecast is that a vaccine probably won’t arrive any time soon.
- Clinical trials almost never succeed. We’ve never released a coronavirus vaccine for humans before.
- Our record for developing an entirely new vaccine is at least four years — more time than the public or the economy can tolerate social-distancing orders.

Ahead on first phase of vaccine development

- The outbreaks of SARS and MERS, which are also caused by coronaviruses, spurred lots of research.
- SARS and SARS-CoV-2, the virus that causes Covid-19, are roughly 80 percent identical, and both use so-called spike proteins to grab onto a specific receptor found on cells in human lungs.
- This helps explain how scientists developed a test for Covid-19 so quickly.
- However, the potential Covid-19 vaccines now in the pipeline might be more likely to fail because of the swift march through the research phase

- **Vaccine Distribution: Reaching End User**

Vaccine distribution plan

Distribution challenges

- Cold chain
- Sterile vials and syringes and needles
- Prioritization of susceptible population
- Training of services providers
- Communication for acceptability
- Provision of vaccine

- Distribution plan in India
- National Expert Group on Vaccine administration on COVID 19 Has put together distribution strategy for India.
  - Use UIP infrastructure for delivery
  - Electronic Vaccine Intelligence network (E-VIN) for UIP will be used to monitor supply and availability

COVID Vaccine Distribution

- When a safe and effective vaccine is found, COVAX (led by WHO, GAVI and CEPI) will facilitate the equitable access and distribution of these vaccines to protect people in all countries. People most at risk will be prioritized.
- Draft Land scape of COVID 19 Vaccine

file:///C:/Users/D.K.%20Mangal/Downloads/novel-coronavirus-landscape-covid-19-(5).pdf

- Nine candidate vaccine are phase 3 in different countries
- Four candidate vaccines are in phase 3 in India

WHO Initiative for equitable distribution of COVID vaccine

- **COVAX is the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator**
- The ACT Accelerator is a ground-breaking global collaboration to accelerate the development, production, and equitable access to COVID-19 tests, treatments, and 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.
- https://www.youtube.com/watch?v=5opR6x6NMpQ&feature=youtu.b

Let us listen to what Dr Tedros, WHO ED talks on the CPVID Vaccine

- https://youtu.be/LUAsKbH7yeY

What will change after Vaccine is available

- Vaccine approval is step 1.
- But when enough number of people will be vaccinated? This depends on several interrelated factors:
  - Logistics, trained human resource, cost chain, acceptance and affordability
- Effectiveness of vaccine and coverage will be key
    - These will decide that life returns to normal

Thank you

Assumption – We already understand the Coronavirus – Normal timeline