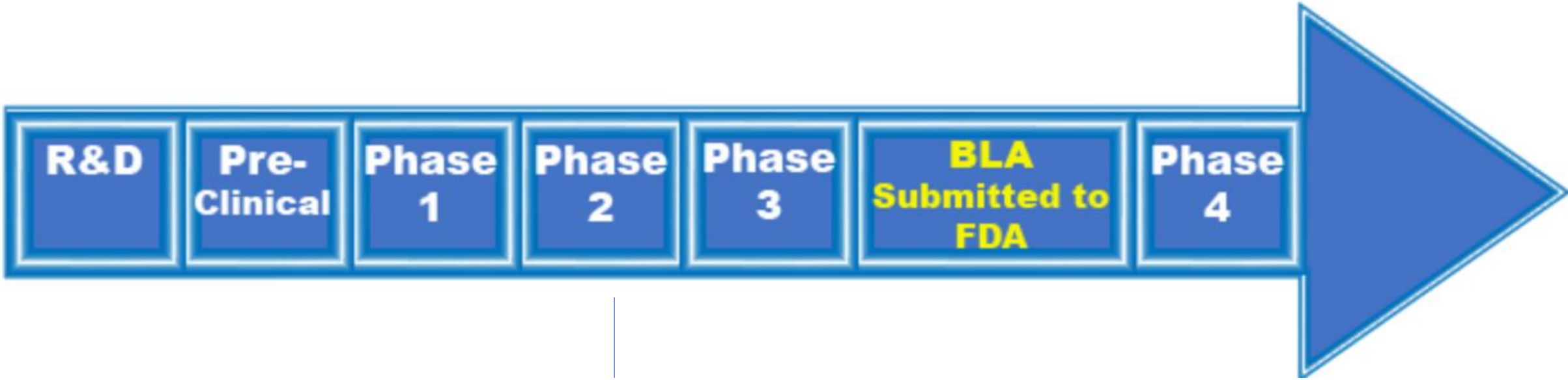
FDA and the COVID-19 Pandemic

Merlin Robb, MD

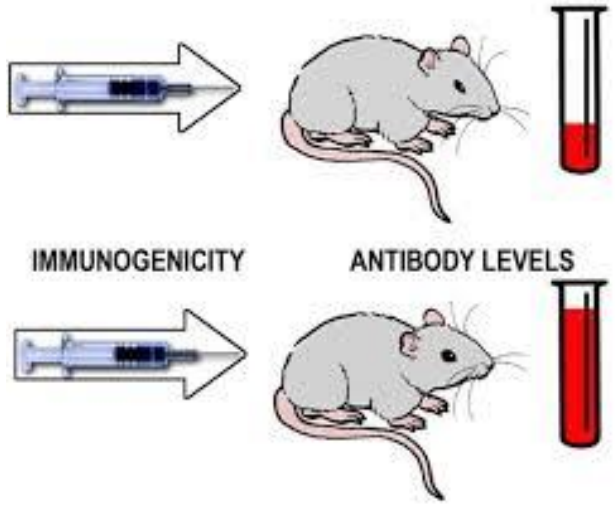
10 May 2021

FDA review



Departure from routine in a state of Emergency to permit broad use of a product prior to submission of a Biological License Application and BLA approval

Initial phase of discovery for new vaccines
Pre-clinical (laboratory) studies
(Data from these studies will be reported to FDA)



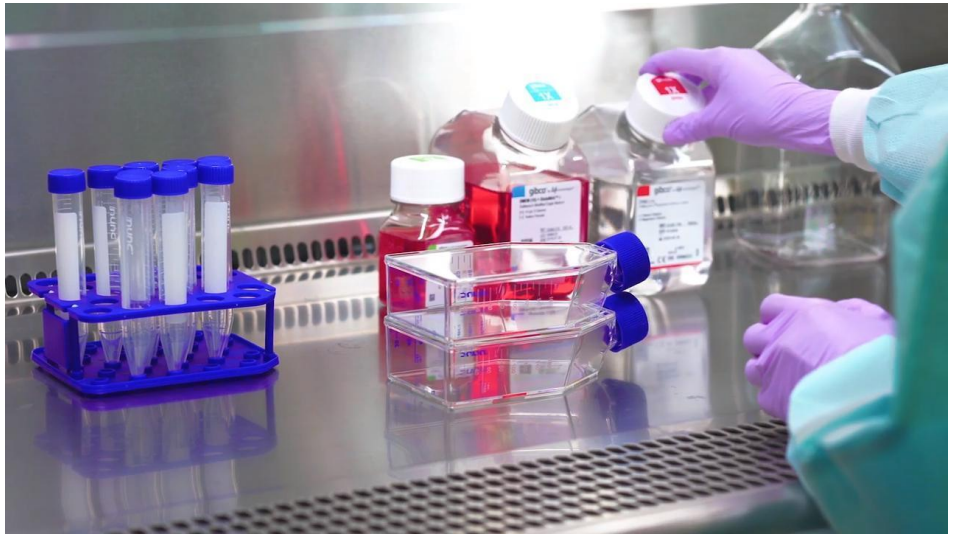
Work in the laboratory is called the ***pre-clinical phase***

- After the vaccine product is created in the lab, researchers need to characterize the product:
  - Structure
  - Function – what does it do in the body
  - How does the immune system react (also called antigenicity)

Animal studies –

- To demonstrate that the vaccine can stimulate the immune system to do (immunogenicity)
- To show that it can protect against disease (efficacy)
- Animal studies can include small animals (rodents, hamsters) and non-human primates (monkeys, macaques)
- Challenge studies: give the animal the vaccine, then expose them to the pathogen to see if the vaccine protects them

Pre-clinical laboratory work, continued



Laboratory work is also used to look at <u>safety</u> of the product:

- Expose to living cells grown in the laboratory
  - used to check whether the vaccine could be harmful to cells;
- Give to small animals to check whether it causes any adverse effects
  - Short term
  - Repeat dose over time (n+1)
- All the laboratory experiments have to be done according to specific quality standards—to make sure the results are reliable
  - called “Good Laboratory Practice”

Beginning clinical testing

FDA permission is required before testing the vaccine in humans (*clinical testing)*

The first step is an **Investigational New Drug application (IND)**

Assembles:

- The *pre-clinical data* from the laboratory studies
- Information about the manufacturing technology
- Tests results showing the *quality* of the vaccine (purity, no contaminants, etc)
- The *clinical trial protocol*—the research plan for doing human trials

FDA reviews all the information submitted about the product to determine whether it is safe enough to move forward in testing in people.

FDA has a time limit of 30 days to decide;

FDA can issue three kinds of responses:

- **Safe to proceed** (green light)
- **Non-clinical hold** notes to improve or clarify the study plan (green light, but comments to be addressed)
- **Clinical Hold** – issues need to be addressed before human trials can start (red light)

How FDA processes and approvals changed with the Public Health Emergency

- COVID vaccines are allowed to be used by the public without having to submit a full FDA license application (Biologics License Application, or BLA) and without obtaining full FDA approval
- The Emergency Use Authorization, or EUA, process allows the FDA to let the public use a product (vaccine or treatment) after considering key aspects of production, product characteristics, and evidence of benefit which exceeds risks
  - In contrast, a typical licensing (BLA) review takes 6-9 months (may be fast tracked to 4 months)
  - In the BLA process, production facilities must be inspected as a requirement for BLA
- An EUA has the same key core principles and areas of focus as a full licensing process, but does not require the final production facility and long-term data needed for a BLA
- **In all cases, sponsors need to follow Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP) and Good Clinical Practices (GCP)**

US Government response to the pandemic (2): Formation of Operation Warp Speed (renamed: the Countermeasures Acceleration Group—CAG)

- US government agencies formed an integrated operational approach to development of COVID-19 vaccines and treatments: “Operation Warp Speed”
- Health and Human Services (HHS)
  - National Institute of Allergy and Infectious Diseases (NIAID) and other elements of the National Institutes of Health (NIH)
  - Centers for Disease Control and Prevention (CDC)
  - Biomedical Advanced Research and Development Agency (BARDA)
  - Food and Drug Administration (FDA)
- Department of Defense (DoD)

Manufacturing quality: COVID-19 vaccines

Manufacturing requirements—

- **Identity** – verify the product is present, how much and absent any adulteration
- **Purity** – all vaccines have materials from production processes like cell line debris etc
- **Potency** – verifies the product does what is expected

Need consistent, quality control process and product profile after a minimum of 3 production runs

- At a scale to confidently predict large volume production needed for national needs
- Full scale production at final facility for market required for BLA
- Validation of most but not all analytics (all must be validated for BLA)

Specific Requirements for pre-clinical and toxicity studies

- Th-1 dominance of immune response (VAERDS)
- Repeat dose tox studies were allowed to be in parallel to initial human study

FDA oversight of clinical trials

- FDA weighs in on key issues relating to scientific validity of the trial and safety of human participants
- Trial design—will the trial be able to generate the right kind of data to show safety and efficacy?
- Study population—are the relevant populations included?
- Efficacy considerations—are the specific tests used and trial endpoints the right ones to show whether the vaccine works? How strong does the evidence need to be?
- Safety considerations—does the trial have enough protections for the people enrolled?
- Statistical considerations—is the sample size large enough and is the statistical analysis appropriate?

Clinical trial population in early phase (phase I) COVID-19 vaccine trials

Older adult participants (e.g., over 55 years of age) may be enrolled if they do not have medical conditions leading to a high risk of severe COVID-19.

Some safety data in younger adults should be collected before enrolling older adult participants, especially for vaccine platforms without prior clinical experience.

Early clinical studies should also exclude participants at high risk of SARS-CoV-2 exposure

Collect and evaluate clinical safety and data on the immune response for each dose level (that is, how much vaccine product is given) and for each age group

Clinical trial population in COVID-19 vaccine efficacy (phase II/III) trials

- Efficacy trials should represent all ages and health conditions associated with COVID-19 infection and its complications
- Trials do not need to screen for, or exclude, participants who previously had SARS-CoV-2 infection.

FDA strongly encourages the enrollment of populations most affected by COVID-19, specifically **racial and ethnic minorities**.

Efficacy trials should include plans for continued follow up and analysis of safety and effectiveness outcomes in the event that a safe and effective vaccine becomes available

FDA requirements for data on efficacy and safety in phase II/III efficacy trials

Specific Requirements for the Efficacy Data

- Primary endpoint may be virologically confirmed SARS CoV-2 or COVID-19
  - OWS enforced harmonization of endpoint for PCR verified COVID-19
- Point estimate of efficacy above 50%
- Study size gives a lower bound of the 95% Confidence Interval > 30%
- A median of 2 months of follow-up for the study population
- At least 5 cases of severe COVID-19 disease with a favorable split between vaccine and placebo groups

Safety data

- At least 3000 participants with exposure to dose planned for BLA
- Monitor reactogenicity in a subset for 7 days
- Monitor adverse events for 28 days and serious AE or medically attended AE for duration of study
- IDMC recommended
  - OWS required a single DSMB for all of these efficacy trials (except Pfizer)

US government response to the pandemic (1)
Declaration of public health emergency

- On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a **public health emergency** related to COVID-19 and mobilized the Operating Divisions of HHS.[1] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[2]

- The new Administration Secretary of HHS, Dr. Xavier Becerra re-issued a declaration of a public health emergency related to COVID-19 on 15 April 2021

US Government response to the pandemic (3): Operation Warp Speed vaccine development strategy

Invest in big pharma capable of scaling up production and distribution

Parallel and redundant development of multiple vaccine platforms (different types of vaccines)

2 companies (Pfizer and Moderna) using **mRNA vaccines**– entirely novel approach

- Novel and therefore high risk that it might not work, but accelerated time-line
- Distribution challenging and scalable production unknown

2 companies using a **adenovirus vector vaccine** product – Janssen and Astrazeneca

2 companies using a **protein subunit vaccine** – Novavax and Sanofi

- Many licensed products
- Safe with good track record for distribution
- More difficult to produce but scalable
- Low risk but slow time-line

Vaccine development strategy: how the timeline for vaccine development was shortened

Normally, each step in the process happens in sequence

In Operation Warp Speed, with massive amounts of US government funding, many steps were done in parallel to save time

- Pre-clinical testing and early manufacturing effort occurred in parallel
- The government committed to paying for the manufacture of vaccine for phase 3 trials from the beginning of the project
- The government also supported phase 3 testing of multiple vaccine products

Operation Warp Speed also:

- Re-purposed the NIH and other federal research networks to conduct COVID-19 vaccine trials
- Had products advance through phase I to phase III as soon as key data available
- FDA provided specific guidance on
  - Characterizing COVID-19 disease
  - Requirements for successful submission of an application for Emergency Use Authorization (EUA)
- FDA worked with the companies (sponsors) frequently to ensure efficiency

Operation Warp Speed set up standards for the clinical trials

- OWS forged a group to harmonize, track, and share “lessons learned” for the different vaccine trials
- All the different vaccine studies used the same basic resaerch plan
- Operational Warp Speed helped enhance site capacity
  - Provided trailers for the sites to use for clinical trials (study visits)
  - Provided transportation of materials used for the studies
    - Provided PPE
  - Set uniform standards for monitoring of participants with COVID-19 in the clinical trials:
    - Pulse oximetry (measuring oxygen) required for all COVID cases
    - Availability of experts to advise about the trials
    - Endpoint definitions—that is, provided uniform standards for what was measured in each of the trials
  - OWS set up a process for
    - expert review of the endpoints in the trials
    - Planning the statistical analysis
    - Determining how many clinical trial endpoints were required for interim analysis
-

How was the Emergency Use Authorization (EUA) process faster than the regular FDA licensing process?

- FDA worked with companies on timing and content of submissions
  - Rapid review of data, protocols and safety information at each stage of development
- FDA organized **Vaccine and Related Biologic Product Advisory Committee (VRBPAC)** within very short time after submission of EUA
  - FDA reviews all data
  - FDA takes the raw data and re-analyzes independently of the sponsor's own analysis
- The VRBPAC is a group of experts in vaccines for prevention of disease
- At the VRBPAC meeting:
  - Company presents their data for supporting an EUA
  - FDA presents their analysis of data and their judgement
  - Public testimony is allowed for a defined period at the meeting
  - VRBPAC members discuss data
  - VRBPAC take a formal vote on whether to approve the EUA

Moving from the EUA to CDC recommendations on public health use of the vaccines

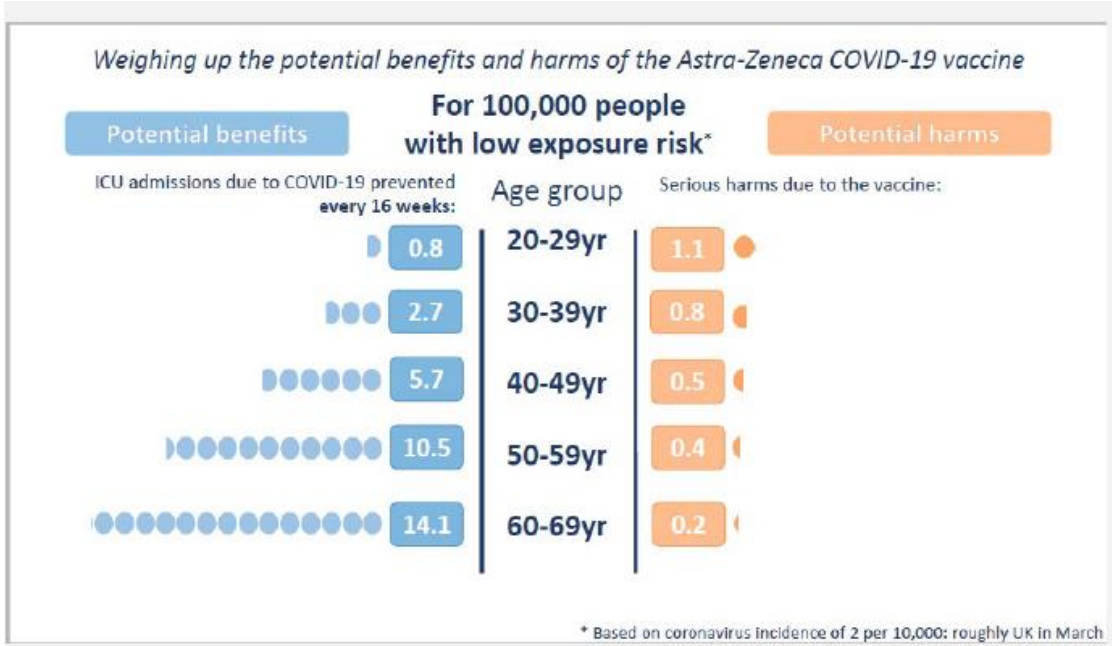
- CDC worked with FDA to immediately follow an EUA with a meeting of the **Advisory Committee for Immunization Practices (ACP)** which guides CDC recommendations for implementation of a vaccine
  - Company presents efficacy and safety data to the Advisory Committee (ACIP)
  - CDC takes the data and reviews independently, looking at
    - Safety
    - Efficacy
  - ACIP considers whether the vaccine should be used in a national immunization program
  - If the ACIP approves use of the product, this leads to CDC recommendations for implementation of the product in the public health system

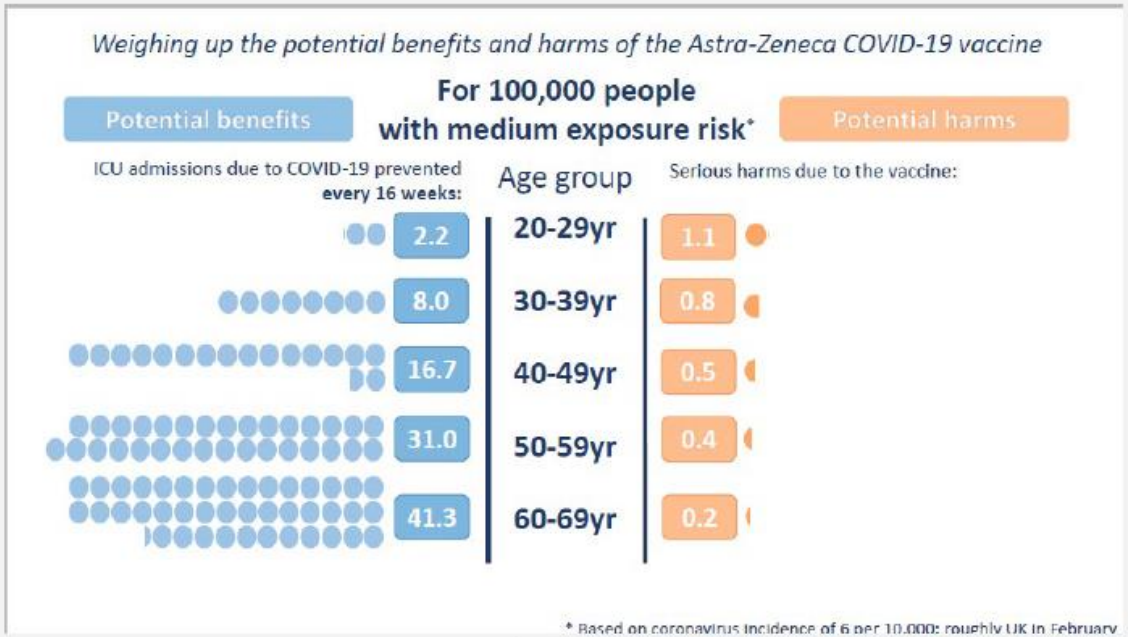
FDA and CDC requirements for safety follow up for the EUA vaccines

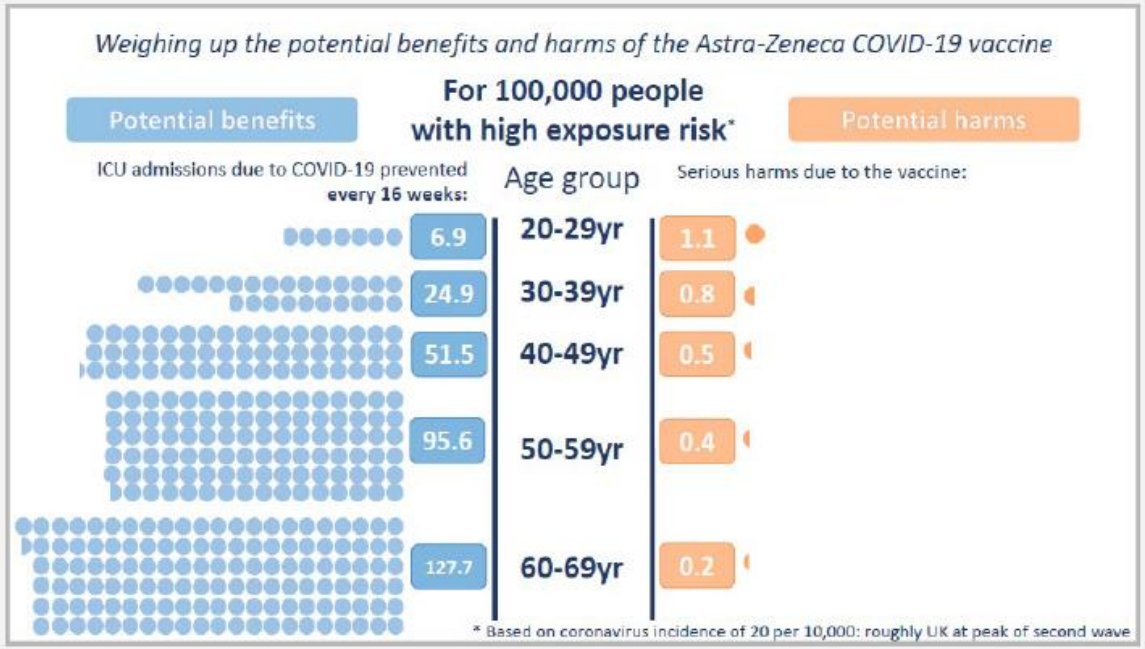
- Safety surveillance
  - VAERS
  - V-Safe
- FDA required expedited reporting for any Serious Adverse Events (SAEs) or deaths associated with the use of the vaccines
- FDA imposed one clinical pause (the Astra Zeneca vaccine) and reviewed data for a new safety pause (J&J, vaccine)
- FDA recently paused vaccinations using the J&J vaccine because of a newly recognized safety signal of blood clots (thrombocytopenic thrombotic syndrome);
  - CDC reviewed data and elegantly evaluated risks and benefits, and determined that benefits outweigh risk

- European regulatory agencies have reviewed these same kinds of events (blood clots) for the Astra Zeneca vaccine and came to a similar conclusion

WHO Analysis of Risk and Benefit for the Astrazeneca Vaccine in Europe







Summary

- FDA has a rigorous licensing process to review clinical trial data and preclinical studies for new vaccines
- The process includes looking at safety, efficacy, and quality of product manufacturing
- For the COVID vaccines, the EUA process was a more rapid way to accomplish the same goal; this process was allowed because of the Public Health Emergency
- FDA and CDC worked closely together with the EUA process so that CDC could also evaluate the vaccines and make public health recommendations
- Both agencies follow up and collect further safety and efficacy information once the vaccines are used by the public