

FDA's Role in COVID-19 Vaccine Development

Julia Tierney, JD

Chief of Staff

Food and Drug Administration

Center for Biologics Evaluation and Research

Overview



- Provide an overview of the vaccine development process
- Discuss FDA's role in the scientific and regulatory oversight
 - How FDA helps to ensure the quality, safety, and effectiveness of vaccines

FDA's Mission

The U.S. Food and Drug Administration's mission is to protect and promote the public health, both in the U.S. and globally, by ensuring the safety and effectiveness of the products we regulate.

FDA Regulates

- Human Drugs
- Biological Products
- Medical Devices
- Products that emit radiation
- Tobacco Products
- Veterinary Products
- Cosmetics
- Foods

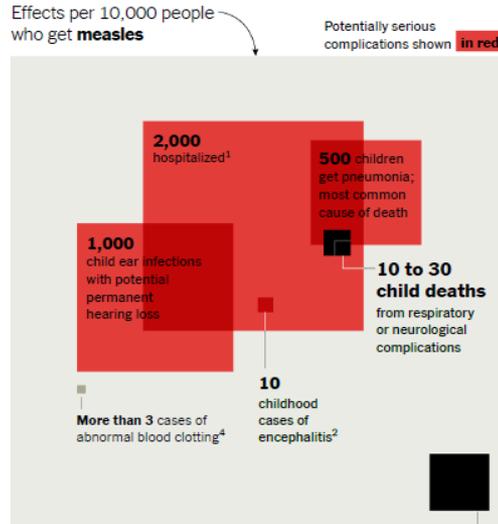
The Center for Biologics and Evaluation and Research (CBER) regulates vaccines at FDA.



Vaccine Development – FDA's Role

- Strain selection and reference standard production
- Lot release
- Evaluation of safety and efficacy
- Post-market surveillance
- Advancing vaccine technology
- Helping to ensure public confidence

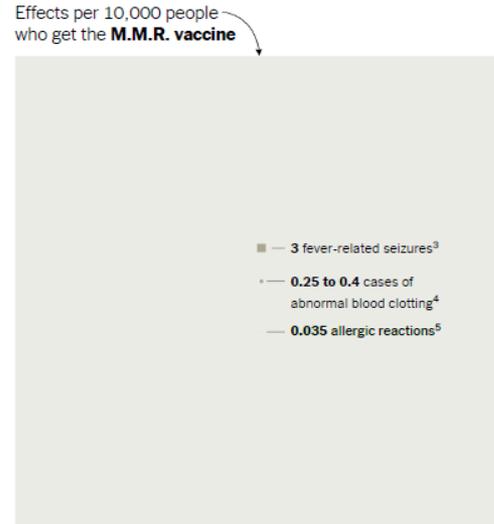
Importance of Public Confidence



146 deaths per 10,000 in the current measles outbreak in Samoa (as of Jan. 7: 83 deaths out of 5,697 cases since September)

1. The amount of overlap between hospitalizations and complications or deaths listed here is not known; this chart assumes that many serious complications from measles result in hospitalizations.

2. Encephalitis (swelling of the brain) can cause convulsions and leave the child deaf or with an intellectual disability.



No risk from M.M.R. vaccine: autism

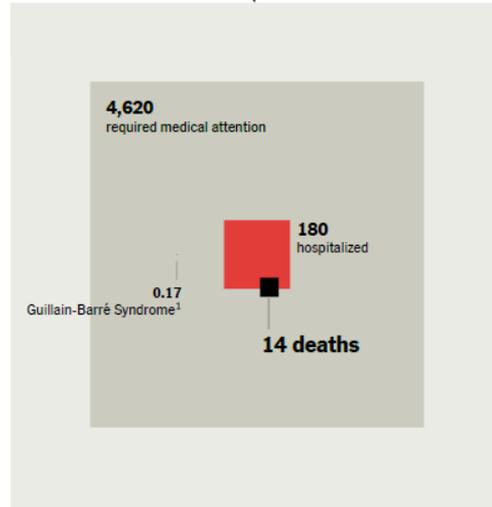
3. Child seizures may occur 72 hours to 14 days after vaccination, and are not associated with long-term effects. But these seizures also occur overall in 2 percent to 5 percent of all children 6 months to 5 years of age (200 to 500 seizures per 10,000 children).

4. Resolves within six months in 93 percent of cases. Rates of abnormal clotting (idiopathic thrombocytopenic purpura, or I.T.P.) after M.M.R. vaccination have been estimated at 1 case per 25,000 to 40,000 doses. Measles and rubella cause abnormal blood clotting at a far higher rate.

5. This translates to 1 to 2.5 reactions per 1 million doses. The lifetime risk of getting killed by lightning in the United States is as much as roughly four times greater: 1 in 210,106.

Importance of Public Confidence

Effects per 10,000 people who got **flu in 2017-18**



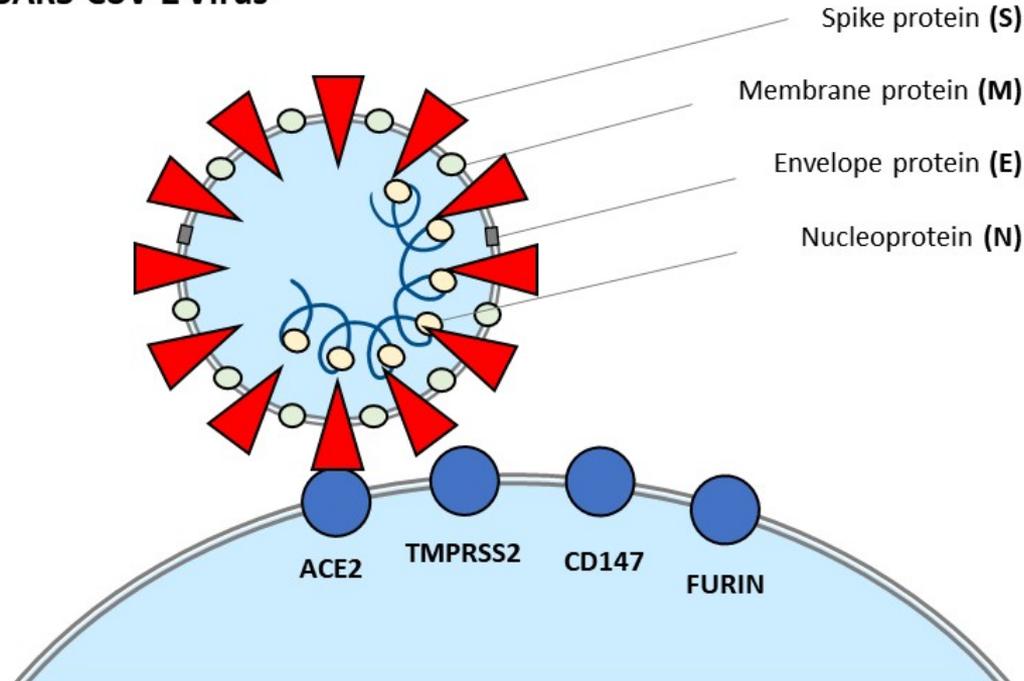
Effects per 10,000 people who get the **flu vaccine**



1. Guillain-Barré Syndrome is a rare disorder that causes the immune system to attack the body's nerves. Most people recover, but some effects — weakness, numbness — may persist. Guillain-Barré Syndrome is several times more likely to occur after a flu infection than after a flu vaccination. Rates for influenza infection based on a population of 13 million studied between 1993 and 2011.

SARS-CoV-2 Vaccine Targets

The SARS-CoV-2 Virus





Vaccine Approaches - Examples

- DNA
- RNA
- Protein Subunit
- Inactivated Virus
- Non-Replicating Viral Vector
- Replicating Viral Vector
- Live attenuated
- Virus-like particle

Vaccine Development

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](https://www.fda.gov/cber)

COVID-19 Vaccine Development

- FDA continues to provide rapid feedback and technical advice to sponsors and researchers regarding the data needed to support the manufacturing, clinical development, and approval or authorization of COVID-19 vaccines
- FDA continues to work collaboratively with federal partners such as CDC and NIH, as well as international regulatory counterparts, to help facilitate efficient development programs
- Vaccine development timelines shortened ***without compromising vaccine safety and efficacy standards***

Clinical Trials – Key Considerations

Efficacy Considerations

- Development programs should pursue traditional approval based on direct evidence of vaccine safety and efficacy in protecting humans from SARS-CoV-2 infection or disease
- Primary efficacy endpoint point estimate for placebo-controlled efficacy trials should be at least 50%
 - Lower bound of appropriately alpha adjusted confidence interval around the primary efficacy endpoint point estimate should be $> 30\%$
 - Applies to interim and final efficacy analyses
- Late phase studies should also include interim analyses to assess risk of enhanced disease and fertility

Clinical Trials – Key Considerations

Safety Considerations

- General safety evaluation including the size of the safety data base should be in the same range as for other preventive vaccines
- Subject follow up should be long enough to evaluate safety, duration of immune response and risk of disease enhancement as antibody titers wane
- FDA anticipates that adequately powered efficacy trials for COVID-19 vaccines will be of sufficient size to provide an acceptable safety database

Clinical Trials – Key Considerations

Clinical Trial Diversity



- Early phase studies should first enroll healthy adults
- Late phase clinical trials to demonstrate vaccine efficacy will likely need to enroll many thousands of participants
 - Include those with medical comorbidities
- FDA encourages enrollment of diverse populations most affected in all phases of vaccine clinical development including racial and ethnic minorities
- Recommendations provided include data to support enrollment of:
 - Elderly individuals and individuals with medical comorbidities
 - Pregnant women and women of childbearing potential not avoiding pregnancy
 - Pediatric populations

COVID-19 Vaccine Authorization or Approval

- FDA will only approve or authorize a COVID-19 vaccine that has met the agency's rigorous and science-based standards for *quality, safety, and effectiveness*
- Decisions will be made by FDA's scientific and medical experts following an evaluation of the totality of the evidence
- Sponsors will decide when and whether to submit under one of two pathways:
 - Emergency Use Authorization (EUA – “Authorization”)
 - Biologics License Application (BLA – “Approval” or “Licensure”)

Vaccines and Related Biological Products Advisory Committee (VRBPAC)



- FDA recognizes that transparency is an important element in public confidence in any approved or authorized COVID-19 and we are committed to being as transparent as possible regarding the decision-making
- FDA's VRBPAC consists of external experts who provide non-binding recommendations to FDA related to data concerning the safety and effectiveness of vaccines and other biological products
- VRBPAC Meeting scheduled for October 22, 2020 to discuss, in general, the development, authorization, and/or licensure of COVID-19 vaccines
- FDA expects to convene an open session of FDA's VRBPAC prior to the issuance of any EUA or BLA for a COVID-19 vaccine to discuss the safety and effectiveness data supporting a specific vaccine

Approval of COVID-19 Vaccines

- Standard for approval of a BLA is that the vaccine is safe, pure, and potent, or *safe and effective*
- *Guidance on Development and Licensure of Vaccines to Prevent COVID-19*
 - Consistency of Manufacturing
 - Need for manufacturing process and controls including appropriate scale up
 - Need for inspected facilities to produce vaccines under GMP
 - Evaluation of Safety
 - Potential risk for vaccine induced enhancement of disease
 - Need for adequate safety evaluation of vaccine that will be widely deployed
 - Evaluation of Efficacy
 - Need for clinical disease endpoint efficacy study
 - Prespecified success criteria needed to ensure success of effective vaccine and rejection of ineffective vaccine

Emergency Use Authorization of COVID-19 Vaccines

- Emergency Use Authorization (EUA) is a mechanism during an emergency to facilitate the availability of unapproved products that diagnose, treat, or prevent serious or life-threatening diseases caused by a threat agent when there are no adequate, approved, and available alternatives
- In order to issue an EUA for a vaccine, FDA must find, among other things, that the product may be effective preventing such a disease, and that the product's known and potential benefits, when used to prevent such disease, exceed its known and potential risks
 - Benefit-risk assessment for a vaccine that will potentially be administered to millions of people, including healthy individuals, will be very different than for COVID-19 therapeutics
- For a vaccine for which there is adequate manufacturing information, issuance of an EUA may be appropriate once studies have demonstrated the safety and effectiveness of the vaccine but before the manufacturer has submitted and/or FDA has completed its formal review of the BLA

Safety Surveillance for COVID-19 Vaccines

- After approval of a BLA or issuance of an EUA by FDA, the safety of COVID-19 vaccines will be closely monitored using various existing surveillance systems
- In certain cases, FDA may require the manufacturer to conduct post-marketing studies to further assess known or potential serious risks.



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