Introduction to Vaccines

Vaccine Research

Vaccine Development

Vaccines approved by FDA

Discovery of novel vaccine candidate

Test vaccine in animal models and humans

Vaccine Approval
AN ORIGINS STORY

Inoculation (variolation) from smallpox lesions (~900)

Inoculation introduced to the British court by Lady Montague in (1721)

Edward Jenner inoculates James Phipps with matter from cowpox lesions (1798)

Robert Koch and Louis Pasteur instrumental in establishing the germ theory of disease (mid to late 1800s)

Paul Ehrlich and Emil von Berhing (late 1800s)

Pathogens: Variola major and Variola minor

Disease: smallpox

Source: CDC

“A vaccine is a biological product that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen.”

• Protection: the individual will not develop the disease when exposed to the pathogen against which the vaccine has been administered.

The essential component of a vaccine is an antigen from the pathogen.

• Antigen: parts of the pathogen or killed whole organisms that can induce an immune response.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
</tr>
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<tbody>
<tr>
<td>Diphtheria</td>
<td>Corynebacterium diphtheriae</td>
</tr>
<tr>
<td>Polio (poliomyelitis)</td>
<td>poliovirus (Enterovirus C subtype)</td>
</tr>
<tr>
<td>Measles</td>
<td>Measles morbillivirus</td>
</tr>
</tbody>
</table>

**Exposure to pathogen**
- Viruses
- Bacteria
- Fungi
- Parasites

**Medical intervention**
- Vaccine intervention

**Vaccine intervention**

**Disease manifestation**

**Treatment course**
- Full recovery
- Recovery with side effects
- Death

**Outcome**

The years for each continent correspond to the year when the disease was eradicated there.

- **North America**: 1952
  - **Ecuador**: 1962
    - Last known case of variola major on the continent

- **South America**: 1971
  - **Brazil**: April 19, 1971
    - Last known case of variola minor on the continent

- **Africa**: 1977
  - **Somalia**: October 12, 1977
    - Last known case of variola minor in the world

- **Asia**: 1975
  - **Bangladesh**: October 16, 1975
    - Last known case of variola major in the world

- **Europe**: 1953

1950, North America
1953, Europe
1971, South America
1975, Asia
1977, Africa
1980, WHO declares the world free of smallpox

* Smallpox was never endemic (widespread) in Australia
BENEFITS OF VACCINES

- Reduce transmission rate in communities
- Reduce disease severity and long-term negative outcomes
- Reduce case-fatality rates among infected individuals
- Prevent emergence of more virulent and pathogenic strains
- Proven and safe means of building an effective immune response
VACCINE RESEARCH, DEVELOPMENT AND APPROVAL PROCESS

- Discovering novel vaccines
- Preclinical trials (testing in vitro (in cells) and in vivo (in animal models))
- Phase 1 clinical trials (testing in 20-100 healthy volunteers)
- Phase 2 clinical trials (testing involves 100s of people)
- Phase 3 clinical trials (testing in thousands of volunteers)
- Biologics License Application (BLA) (approval by the FDA for interstate distribution)
- Phase 4 clinical trials (testing and monitoring continues after licensure)

*Safety*
*Immunogenicity (inducing an immune response)*
*Protective efficacy (capacity to prevent disease)*

Gathering preliminary information

Testing on human subjects
- Adults
- Adolescents
- Children
- Infants
- Immunocompromised individuals
RESEARCH AND DISCOVERY STAGE

“A vaccine is a *biological product* that can be used to safely induce an immune response that confers *protection* against infection and/or *disease* on subsequent exposure to a *pathogen*.”

1. Develop the vaccine candidate
2. Test vaccine in preclinical trials
RESEARCH AND DISCOVERY STAGE

1. DEVELOP VACCINE

“A vaccine is a biological product…”

Vaccines

- Live
  Chance of uncontrolled replication in compromised individuals
- Non-live (inactivated)
  No risk of uncontrolled replication in immunocompromised individual

RESEARCH AND DISCOVERY STAGE

2. TEST VACCINE IN PRECLINICAL TRIALS

1. **Confirm** expression of antigen
2. **Characterize** immune response
3. **Check** for any adverse effects

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PFIZER AND BIONTECH ANNOUNCE DATA FROM PRECLINICAL STUDIES OF MRNA-BASED VACCINE CANDIDATE AGAINST COVID-19

Wednesday, September 09, 2020 - 07:45am

- Immunization of non-human primates (rhesus macaques) with BNT162b2, a nucleoside-modified messenger RNA (modRNA) candidate that expresses the SARS-CoV-2 spike glycoprotein, resulted in strong anti-viral effects against an infectious SARS-CoV-2 challenge.
- BNT162b2 immunization prevented lung infection in 100% of the SARS-CoV-2 challenged rhesus macaques, with no viral RNA detected in the lower respiratory tract of immunized and challenged animals. The BNT162b2 vaccination also cleared the nose of detectable viral RNA in 100% of the SARS-CoV-2 challenged rhesus macaques within 3 days after the infection.
- The BNT162b2 vaccine candidate induced SARS-CoV-2 neutralizing antibodies in rhesus macaques, pseudovirus neutralizing antibodies in mice, and strong, antigen-specific CD4+ and CD8+ T cells in mice and macaques.


bioRxiv 2020.09.08.280818; doi: https://doi.org/10.1101/2020.09.08.280818
CLINICAL TRIALS

Discovering novel vaccines
- Testing vaccine candidates *in vitro* (in cells) and *in vivo* (in animal models)

Preclinical trials
- Testing in 20-100 healthy volunteers
- Testing involves 100s of people
- Testing in thousands of volunteers

Phase I/II trials
- Phase 1 clinical trials
- Phase 2 clinical trials

Phase II/III trials
- Phase 3 clinical trials

Phase 4 clinical trials
- Approval for interstate distribution
- Testing in vulnerable populations (sick)

Gathering preliminary information
Testing on human subjects

*Safety*
*Immunogenicity (inducing an immune response)*
*Protective efficacy (capacity to prevent disease)*
Limit bias: observer-blinded to prevent bias.
Thorough: any changes to the vaccine require that the trial be repeated.
Safe: volunteers are observed during the trial to monitor adverse reactions.
Nontoxic: abide by the FDA's guidance on toxicity measures.
Consistent: methods of data collection, analysis and reporting are standardized.
Establish immunogenicity: link between vaccine and immunity.

Clinical or Laboratory abnormalities:
- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Potentially life threatening

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFMA-40), 1401 Rockville Pike, Suite 280N, Rockville, MD 20852-1448, or by calling 1-800-855-4789 or 301-827-1100, or from the Internet at http://www.fda.gov/cber/_guide/lab.jpg.
For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-8070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2007
Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults


Abstract

In March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic. With rapidly accumulating numbers of cases and deaths reported globally, investigators were working to develop vaccines, monoclonal antibodies, and antiviral drugs to treat COVID-19. The researchers included in this study created a vaccine using the mRNA encoding the SARS-CoV-2 spike protein.

Table

<table>
<thead>
<tr>
<th>Row</th>
<th>Saved</th>
<th>Status</th>
<th>Study Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Recruiting</td>
<td>Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals</td>
</tr>
</tbody>
</table>

- SARS-CoV-2 Infection
- COVID-19
- Biological: BNT162b1
- Biological: BNT162b2
- Other: Placebo
- Biological: BNT162b2SA

Consortiuim:
- North Alabama Research Center, LLC
  Athens, Alabama, United States
- Birmingham Clinical Research Unit
  Birmingham, Alabama, United States
- Medical Affiliated Research Center
  Huntsville, Alabama, United States

IgG concentrations and SARS-CoV-2 neutralizing titers in sera increased with dose level and after a second dose. Geometric mean neutralizing titers reached 1.6-4.6-fold that of a panel of COVID-19 convalescent human sera, which were obtained at least 14 days after a positive SARS-CoV-2 PCR. These results support further evaluation of this mRNA vaccine candidate.
PHASE I: PROTECTIVE EFFICACY TRIALS

- Vaccine must have already been tested in preclinical trials
- Small number of healthy, immunocompetent volunteers
- Intended to investigate underlying immunological mechanisms (e.g., immunological memory and antibody production postvaccination)
- Gain experience with vaccine before testing in larger populations (e.g., mode of administration, injection site, etc.)
- May or may not be controlled

“The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.”

FDA
PHASE I: FIRST TRIALS IN HUMANS

Phase I

- Objectives:
  - Establish safety: symptoms associated with immune response such as fever, swelling, etc.
  - Collect data on immune response
  - Administration protocol
    - Delivery method
    - Dose

- Test group
  - Size: A small group of 20-100 of naïve and immunocompetent human subjects
  - Age group: first trials in humans, target population

Phase I: Pfizer–BioNTech mRNA vaccine

- Objectives:
  - Establish safety: primary event was pain at injection site
  - Immune response: neutralizing antibodies observed in sera
  - Administration protocol
    - Delivery method: 10, 20, 30 or 100 µg into the deltoid (arm)
    - 2 doses at 21-day intervals

- Test Group:
  - Size
    - 13 groups of 15 participants (total 195)
    - 12 received vaccine and 3 received placebo
  - Age group: 18-55 and 65-85
PHASE II: TESTING IN A TARGET POPULATION

- Safety and immunogenicity
- Larger number of participants, typically in the 100s of people
- Intended to extract as much information about the vaccine as possible (dose, vaccine schedule, vaccine composition, age-specific responses, duration of immune response, reactions to the vaccine)
- Continue gaining experience with vaccine before testing in larger populations
- Control and vaccine groups
- Clinical evaluators, laboratory staff and participants themselves are unaware about who is in the control or vaccine groups until trial has been completed.
PHASE II: TESTING IN A TARGET POPULATION

Phase II

- Objectives:
  - Optimize vaccine use and delivery conditions
  - Optimal dose
  - Plan for phase 3 trials

- Test group
  - Size: A small group of 50-500 of naïve and immunocompetent human subjects
  - Age group: Vaccine target population

Phase I/II: Pfizer BioNTech (mRNA)

- Objectives:
  - Optimize vaccine use and delivery conditions
  - Optimal dose test: 10, 30 or 100 µg, 1 or 2 doses 21 days apart
  - Also tested single doses of 100 µg
  - Prepare for Phase II/III trials

- Test group
  - Size: 76 participants
  - Age group: 19-54 years
PHASE I/II: INITIAL SAFETY TRIALS AND TARGET POPULATIONS

PFIZER AND BIONTECH SHARE POSITIVE EARLY DATA ON LEAD MRNA VACCINE CANDIDATE BNT162B2 AGAINST COVID-19

Thursday, August 20, 2020 - 08:00pm

- In a Phase 1 study in the U.S., at 7 days after a second dose of 30μg, BNT162b2 elicited SARS-CoV-2-neutralizing geometric mean titers (GMTs) in younger adults (18-55 years of age) that were 3.8 times the GMT of a panel of 38 sera of SARS-CoV-2 convalescent patients, and in older adults (65-85 years of age) the vaccine candidate elicited a neutralizing GMT 1.6 times the GMT of the same panel, demonstrating strong immunogenicity in younger and older adults.
- The companies previously announced that BNT162b2-vaccinated human participants displayed a favorable breadth of epitopes recognized in T cell responses specific to the SARS-CoV-2 spike antigen, and that BNT162b2 demonstrated concurrent induction of high magnitude CD4+ and CD8+ T cell responses against the receptor binding domain (RBD) and against the remainder of the spike glycoprotein.
- Across all populations, BNT162b2 administration was well tolerated with mild to moderate fever in fewer than 20% of the participants.
- These results informed the selection of the BNT162b2 candidate for the pivotal Phase 2/3 global study in up to 30,000 participants that started in July 2020, which has to date enrolled more than 11,000 participants, including in areas with significant SARS-CoV-2 transmission.
- Assuming clinical success, Pfizer and BioNTech are on track to seek regulatory review of BNT162b2 as early as October 2020 and, if regulatory authorization or approval is obtained, currently plan to supply up to 100 million doses worldwide by the end of 2020 and approximately 1.3 billion doses by the end of 2021.
PHASE III: PROTECTIVE EFFICACY TRIALS

- Study **protective efficacy**
  - “The primary purpose of a phase III trial is to assess the protective efficacy of the vaccine in the target population.”
  - Monitor vaccinated and unvaccinated participants for disease incidence over various periods of time to determine protection levels
- 1000-150,000 participants (determined by incidence of disease)
- Randomized, double-blind control trial: participants randomly allocated to placebo or vaccine groups or groups that receive nothing
- Mimic “field” conditions
- Large trials that may last up to several years
- Sufficient data allows for application of license with the FDA
Vaccine efficacy refers to how the vaccine performs in ideal conditions - controlled clinical trials.

Vaccine effectiveness refers to how the vaccine performs in the wider populations.

Vaccine efficacy is calculated in clinical trials by comparing disease rates between two groups: those who received a placebo and those who received the vaccine.

If a vaccine has an efficacy of 80 percent:

- It does not mean that the vaccine will only work 80% of the time.
- It does mean that in a vaccinated population, 80% fewer people will contract the disease when they come in contact with the virus.

PHASE III: TESTING IN A TARGET POPULATION

Phase III

- **Objectives:**
  - Protective efficacy
    - Define clinical trial endpoint

- **Test group**
  - Size: 1,000 – 150,0000
  - Age group: Vaccine target population
  - Vaccine locations

Phase III: Pfizer–BioNTech mRNA vaccine

- **Objectives:**
  - Protective efficacy
    - COVID-19 disease symptoms as outlined by the FDA and laboratory tests
    - Dosage: placebo or 30 µg of vaccine, 21 days apart

- **Test group**
  - Size
    - 43,548 participants
  - 21,720 received vaccine, 21,728 received placebo
  - Age group: 16 years old or older
  - Vaccine locations:
    - Multi-site (United States, Brazil, Argentina, South Africa, Germany, and Turkey)

PHASE III: TESTING IN A TARGET POPULATION

“The safety profile of BNT162b2 (vaccine) was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache.”

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.

<table>
<thead>
<tr>
<th>Efficacy End Point</th>
<th>BNT162b2</th>
<th>Placebo</th>
<th>Vaccine Efficacy, % (95% Credible Interval)‡</th>
<th>Posterior Probability (Vaccine Efficacy &gt;30%) §</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Surveillance Time (n) †</td>
<td>No. of Cases</td>
<td>Surveillance Time (n) †</td>
</tr>
<tr>
<td>Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection</td>
<td>(N=18,198)</td>
<td>8</td>
<td>2.214 (17,411)</td>
<td>162</td>
</tr>
<tr>
<td>Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection</td>
<td>(N=19,965)</td>
<td>9</td>
<td>2.332 (18,559)</td>
<td>169</td>
</tr>
</tbody>
</table>

"The Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce… A BLA is submitted to any person or entity who is engaged in manufacture.

Requirements for a BLA
- Applicant information
- Product/Manufacturing information
- Pre-clinical studies
- Clinical studies
- Labeling

BLA for Pfizer BioNTech vaccine approved by FDA on August 23, 2021 under the label Comirnaty.

1. Deferred pediatric Study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age.
   - Final Protocol Submission: October 7, 2020
   - Study Completion: May 31, 2023
   - Final Report Submission: October 31, 2023

2. Deferred pediatric Study C4591007 to evaluate the safety and effectiveness of COMIRNATY in infants and children 6 months to <12 years of age.
   - Final Protocol Submission: February 8, 2021
   - Study Completion: November 30, 2023
   - Final Report Submission: May 31, 2024

3. Deferred pediatric Study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age.
   - Final Protocol Submission: January 31, 2022
   - Study Completion: July 31, 2024
   - Final Report Submission: October 31, 2024

BLA APPROVAL
August 23, 2021

Submitted and received on
under the provisions of section 351 of the Public Health Service Act (PHS Act) for

https://www.fda.gov/media/151710/download
PHASE IV: CLINICAL TRIALS

- Postlicensure surveillance, i.e., monitoring continues following FDA approval
  - Safety
  - Vaccine effectiveness
  - Population level effects
- More focused on epidemiological studies
- Trials can be on-going for some substudies
  - Trials are still on-going for groups of ages 12 and under for the Pfizer–BioNTech vaccine

https://www.pfizer.com/science/clinical-trials/children
HEALTH AND HUMAN SERVICES ORGANIZATIONAL STRUCTURE

Secretary
Deputy Secretary
Chief of Staff

Centers for Disease Control and Prevention (CDC)

Food and Drug Administration (FDA)

Advisory Committee on Immunization Practices (ACIP)

- **15 voting members** selected by DHHS (experts in vaccinology, immunology, pediatrics, internal medicine, infectious diseases, virology, family medicine, preventative medicine, a consumer representative)

- **30 non-voting representatives** from professional organizations (American Academy of Pediatrics, American Academy of Family Physicians, American College of Nurse Midwives, American College of Obstetricians and Gynecologists, American College of Physicians)

[https://www.cdc.gov/vaccines/acip/committee/role-vaccine-recommendations.html](https://www.cdc.gov/vaccines/acip/committee/role-vaccine-recommendations.html)
WHAT HAPPENS WHEN NATIONAL AND GLOBAL HEALTH EMERGENCIES OCCUR?
EMERGENCY USE AUTHORIZATION (EUA)

Emergency Use Authorization of Medical Products and Related Authorities

Guidance for Industry and Other Stakeholders

A. EUA DECLARATION JUSTIFICATION

1. Determinations to Support

Before FDA may issue an EUA, the HHS must be justified the authorization (section 564 of the FD&C Act, an “EUA declaration”).

DATES:

1. A determination by the Secretary that there is a public health emergency, or a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV).

2. A determination by the Secretary of Defense that there is a military emergency, or a significant potential for a military emergency, involving a heightened risk of attack with a CBRN agent(s);

3. A determination by the Secretary of HHS that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves a CBRN agent or agents, or a disease or condition that may be attributable to such agent(s);
EMERGENCY USE AUTHORIZATION (EUA)

Emergency Use Authorization (EUA) “allows FDA to help strengthen the nation’s public health protections against chemical, biological, radiological and nuclear (CBRN) threats including infectious diseases by facilitating the availability and use of medical counter measures (MCMs) needed during public health emergencies.”
FACTORS THAT AFFECT SPEED OF VACCINE APPROVAL

- Adequate number of participants in Phase I/II/III trials
- Single or multicenter trials
- Cost
  - The CARES (Coronavirus Aid, Relief, and Economy Security) Act was used to fund vaccine research
    - Johnson & Johnson
    - AstraZeneca
    - Moderna
    - Novavax
- Collaboration across the globe
- Emergency Use Authorizations (EUA)
  - Use of Pfizer–BioNTech vaccine for ages 16 and above
  - Comirnaty is currently approved under an EUA for administration to 12–15-year-olds
    - Based on Phase III trials with 2,260 adolescents, with vaccine efficacy of 95%.
    - Comirnaty is still investigating the vaccine for children ages 12 and under.

CONCLUSION

- Vaccines are biological products that confer protection against symptomatic disease.
- Before authorization for use by the FDA, vaccines undergo rigorous safety, immunogenicity and protective efficacy tests in Phase I, Phase II and Phase III clinical trials.
- Vaccines are studied and monitored closely by the FDA, the ACIP and vaccine manufacturers even after licensure and approval for use.
- Emergency Authorization Use (EUA) can be declared by the Secretary of HHS during a public health crisis or a potential public health crisis to increase the speed with which vaccines are authorized by the FDA.