Vaccine Basics for COVID Vaccine Reporting

Tara Haelle
@tarahaelle
AHCJ Medical studies core topic leader
Independent science journalist and author
Stages of vaccine development

- Exploratory research
- Preclinical research and formulation development
- Clinical Trials
- Regulatory review and approval/licensure/recommendations
- Manufacturing and distribution
- Quality control and safety surveillance
Vaccine terminology

- Adverse events – any unpleasant thing that happens after receiving a vaccine, related/causal or not
- Antigen – what the immune system recognizes on the pathogen as being foreign (“enemy uniform”)
- Adjuvant – substance added to a vaccine to enhance the immune response
- Correlate of protection – measure of how much antibodies/immune response is needed to prevent infection
- Efficacy – how well the vaccine performs in clinical trials
- Immune enhancement – vaccine causes later infection to be worse
- Infection vs. disease – replication vs. symptoms
- Messenger RNA – carries instructions from DNA to ribosomes (protein factories)
- Neutralizing antibodies – antibodies that successfully eliminate the virus
- Spike – the protein many are targeting as an antigen on coronavirus
- Sterilizing immunity – cannot ever get the disease again (rare)
Exploratory and preclinical research

- Identify characteristics of the pathogen
- Understand immune response
- Determine vaccine target (antigen) and approach (type)
- Identify appropriate animal models
- Design and test in animal models
Clinical Development and Licensure

■ Clinical Trials
  - *Phase I* – safety, efficacy, different dosing (*n*=20-100)
  - *Phase II* – side effects/safety, immune response (*n*=200+)
    - *Phase III* – safety, efficacy (*n*=10,000+)

■ FDA approval (regulatory review)

■ CDC’s Advisory Committee on Immunization Practices (ACIP)
  - *Recommendations*: ages, populations, schedule (*number of doses, boosters, timing*)
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
Typical vaccine advancement

■ From 2006-2015:
■ Phase I:
  - 66% of vaccines move on
  - 16% ultimately approved
■ Phase II:
  - 33% of vaccines move on
  - 24% ultimately approved
■ Phase III: 74% approved

■ Source: Clinical Development Success Rates 2006-2015, Bio (research trade association)
Manufacturing and distribution

- Physical infrastructure (factories) and reagents/ingredients/supplies
- Supply Chains and Cold Chains
- Prioritization of recipient populations
- Processes for administration to different populations
  - Most infrastructure is set up for child immunizations, not adult.
  - In the US, flu vaccine infrastructure may suffice. (?)
  - Administration schedule (boosters, etc.)
- Safety surveillance (Quality control)
  - Vaccine Adverse Event Reporting System (VAERS)
  - Vaccine Safety Datalink (VSD)
  - Post-Licensure Rapid Immunization Safety Monitoring (PRISM)
  - Clinical Immunization Safety Assessment Project (CISA)
How a vaccine’s safety continues to be monitored

FDA and CDC closely monitor vaccine safety after the public begins using the vaccine. The purpose of monitoring is to watch for adverse events (possible side effects). Monitoring a vaccine after it is licensed helps ensure that possible risks associated with the vaccine are identified.

Vaccine Adverse Event Reporting System (VAERS)
VAERS collects and analyzes reports of adverse events that happen after vaccination. Anyone can submit a report, including parents, patients and healthcare professionals.

Vaccine Safety Datalink (VSD) and Post-Licensure Rapid Immunization Safety Monitoring (PRISM)
Two networks of healthcare organizations across the U.S.
- **VSD** can analyze healthcare information from over 24 million people.
- **PRISM** can analyze healthcare information from over 190 million people.
Scientists use these systems to actively monitor vaccine safety.

Clinical Immunization Safety Assessment Project (CISA)
CISA is a collaboration between CDC and 7 medical research centers.
- Vaccine safety experts assist U.S. healthcare providers with complex vaccine safety questions about their patients.
- CISA conducts clinical research studies to better understand vaccine safety and identify prevention strategies for adverse events following immunization.

Vaccine recommendations may change if safety monitoring reveals new information on vaccine risks (like if scientists detect a new serious side effect).

For more information, visit https://www.cdc.gov/vaccinesafety
Vaccine Types (increasing complexity)

- Live attenuated vaccine — whole pathogen, weakened
- Inactivated vaccine — whole pathogen, dead/deactivated
- Toxoid vaccine — whole toxin, defanged
- Subunit vaccine — pieces of pathogen (proteins)
- Conjugate vaccine — weak antigen + strong antigen (protein)
- Recombinant vaccine — cell (yeast, bacteria) contains DNA that encodes protein from pathogen
- Nucleic acid vaccines (DNA/mRNA) — DNA plasmid or messenger RNA that encodes pathogen protein (for body cells to encode)
- Viral vector vaccines — recombinant technology places DNA/mRNA into replicating or non-replicating virus, acting as vector
<table>
<thead>
<tr>
<th>Virus</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrovirus</td>
<td>Long-term gene expression</td>
<td>Generation of replication-competent virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential for tumorigenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infects dividing cells only</td>
</tr>
<tr>
<td>Lentivirus</td>
<td>Long-term gene expression</td>
<td>Generation of replication-competent virus</td>
</tr>
<tr>
<td></td>
<td>Infects non-dividing and dividing cells</td>
<td>Potential for tumorigenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinia virus</td>
<td>High immunogenicity</td>
<td>Pre-existing immunity</td>
</tr>
<tr>
<td></td>
<td>Safety: used as a smallpox vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High titer production</td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>High immunogenicity</td>
<td>Pre-existing immunity</td>
</tr>
<tr>
<td></td>
<td>Safety: used in many clinic trails</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High titer production</td>
<td></td>
</tr>
<tr>
<td>Adeno-associated virus</td>
<td>Long-term gene expression</td>
<td>Low titer production</td>
</tr>
<tr>
<td></td>
<td>Non-pathogenic virus</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Induces a unique CTL response</td>
<td>Pre-existing immunity</td>
</tr>
<tr>
<td></td>
<td>Protects against SIV infection in an animal model</td>
<td>Risk of pathogenesis in specific individuals</td>
</tr>
<tr>
<td>Sendai virus</td>
<td>High immunogenicity</td>
<td>Pre-existing immunity</td>
</tr>
</tbody>
</table>
Tracking vaccines in development

- More than 100 (no single number to pin down)
- Various COVID vaccine trackers, some with/without therapeutics
- Biocentury (combines with therapeutics; downloadable and sortable)
- **Biorender: https://biorender.com/covid-vaccine-tracker
- STAT curated, updated list: https://www.statnews.com/feature/coronavirus/drugs-vaccines-tracker/#vaccines
Vaccines in clinical development

- Moderna – mRNA vaccine; skipped animal trials; US-based; proprietary info; curb your enthusiasm ;)
- Bottazzi and Hotez
- Most common: inactivated, DNA, RNA, viral vector, subunit

- 'Operation Warp Speed’
  - 14 vaccine candidates → 8 candidates → ?? 3-5?
Ways to fast-track vaccine development

- Build the factories in advance (Bill Gates is building seven)
- Skip animal testing (as Moderna did)
- Combine trial phases (phase I/II, II/III)
- Human challenge studies

- All involve risk
Find the right experts

- Think of the 6 stages of vaccine development: where is their expertise?
  - Virology, preclinical work, clinical trials, licensure/recommendation, safety, efficacy, post-licensure safety surveillance, post-licensure effectiveness

- Specialize in bacteria or viruses? In respiratory disease or other body systems?

- Familiarity with regulatory environment for your audience

- National or international focus?

- Ask for suggestions

- Look at references in papers published on coronavirus vaccines (SARS, MERS, COVID)
Questions to ask researchers

- What type of vaccine is this? How does it work? Why did you choose this approach?
- What antigens does it target? Why did you choose those?
- What animal model(s) are you using? Why?
- How will it be administered? (oral, nasal, intramuscular, intradermal, subcutaneous)
- What are your endpoints for each trial? How will you test immune response?
- Who is in your population? Why did you choose them?
- Are you using an adjuvant? Which one? How did you choose that one?
- What type of immunity should it induce?
- Do you have any concerns about immune enhancement?
- What are the most likely side effects you’re anticipating?
- What’s your timeline, both pipedream and realistic?
- What are the challenges of your particular vaccine?
- What infrastructure and distribution processes might your vaccine require?
- Do you anticipate boosters or seasonal shots being needed?
Common pitfalls in reporting on vaccines

- Leaving out context
- Including too much context
- Efficacy vs. effectiveness
- Pay attention to the population: Who is it tested in? Who will get it?
- Curb your enthusiasm
- Adverse events vs. side effects
- False balance re: vaccine hesitancy
- Not reporting thoroughly on safety