Opportunities and Challenges in Vaccine Development

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**Disclosure**

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Ivan Chan is an employee of AbbVie Inc. and may own AbbVie stock.
What are vaccines?

- Biological products
- Use antigen or attenuated live virus to trigger immune responses for disease protection
- Administered as a single series with a potential booster dose
- Typically for prophylaxis, not treatment

Vaccine has been one of the 10 greatest public health achievements of 20th century
- Eradication of smallpox in 1980
- Elimination of Polio in the US in 1979 (WHO’s initiative to eradicate Polio from the world)
Benefits of Vaccines

• Direct benefit
  – Protection of individuals after vaccination
  – Usually measured in clinical trials
  – Risk benefit at individual level

• Indirect benefit
  – Herd immunity (protection of non-immune individuals) by reducing exposure and transmission in the community
  – Public health impact


Lauri E. Markowitz, Susan Hariri, Carol Lin, Eileen F. Dunne, Martin Steinau, Geraldine McQuillan, and Elizabeth R. Unger

Journal of Infectious Diseases, 2013

• Vaccine coverage ~34%
• Vaccine effectiveness ~82%
• Reduced overall prevalence by ~56%

Substantial protection from herd immunity (~ 43%)
Types of Immunity

Humoral (antibody-mediated) immunity
- B lymphocytes
- Plasma cells
- Immunoglobulins (IgG, IgM, IgA, IgD, IgE)
- Antibody titers increase to a plateau and then decline

Functions of Antibodies
- Neutralize viruses and bacterial toxins
- Bind antigen
- Prevent or clear first infection

Cell-mediated or T-cell immunity
- T lymphocytes
- Cytokines/interleukins

Functions of Cell-mediated immunity
- T lymphocytes (helper cells) stimulate B cells to produce antibodies
- T suppressor (regulatory) cells play an inhibitory role and control the level and quality of the immune response (CD4)
- Cytotoxic T-cells recognize and destroy infected cells (CD8)
Evaluation of New Vaccines - Safety

- Assess local (injection-site) and systemic adverse experiences
- Choice of safety parameters depend on type of disease, population, and route of administration
- Need a large database, particularly because of giving vaccines to healthy subjects
  - E.g., Rotavirus vaccines (RotaTeq and Rotarix), studied for intussusception with 60-75K subjects
- Need large-scale post licensure study for additional safety monitoring
Evaluation of New Vaccines - Efficacy

• Measure the relative reduction (RR) of disease incidence after vaccination compared with placebos (Chan, Wang and Heyse 2003)
  \[ VE = 1 - RR = 1 - \frac{P_V}{P_C} \]

• Require a high level of evidence and precision
  – Success typically requires showing efficacy greater than a non-zero (e.g. 20% - 50%) lower bound

• May need a very large study for diseases with low incidence rates
  – Event-driven design often used to guard against uncertain event rate (Chan and Bohidar 1998)
  Conditional on total events \( n = n_V + n_C \)
  \[ n_V \sim \text{binomial} \left( n, \frac{P_V}{P_V + P_C} \right) \]

• Need long-term data to assess duration of efficacy
  – When is a booster dose needed?
  – Historical controls may be used if concurrent controls are not available
Impact of VE Lower Bound Requirement on Sample Size

- Rapid increase of sample size when VE lower bound increases

- Examples assumes
  - 5/1000 incidence
  - 90% power
  - 60% true VE
  - One-sided 2.5% test
  - 1:1 randomization

- Real example: Herpes zoster vaccine efficacy trial (Oxman et al 2005) used a lower bound of .25 (N = ~38,500).

<table>
<thead>
<tr>
<th>VE Lower Bound</th>
<th>Total Number of Events</th>
<th>Total Sample Size</th>
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<tbody>
<tr>
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<td>28,500</td>
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<tr>
<td>.30</td>
<td>154</td>
<td>43,900</td>
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Evaluation of New Vaccines - Immunogenicity

• Important to understand biological responses
  – Antibody or T-cell responses
  – Valuable measure for early phase clinical studies

• Assess correlates of protection (CoP, “surrogate” endpoints) and immune markers
  – CoP is an immune marker statistically correlated with vaccine efficacy (predictive of vaccine efficacy) (Plotkin and Gilbert, CID 2012)
    ▪ CoP is *mechanistic* if immune response is a causal agent to protection
    ▪ CoP is *non-mechanistic* if immune response predicts vaccine efficacy but is not a causal agent to protection
  – Useful for bridging studies (new vs. old formulations) and combination vaccine studies
  – Key endpoint for assessing consistency of vaccine manufacturing process
  – Correlate of protection may also support approval of second-generation vaccines or follow-on vaccines
Assessing Correlates of Protection

• Titer-Specific Method (Siber et al, Vaccine 2007)
  – Model risk of disease as a step function of immune responses
  – Used to establish the immune correlate for licensure of Prevnar13

• Logistic regression and statistical modeling
  – Assess the relationship between immune response and disease risk (Chan et al 2002)
  – Determine protective level of immune responses based on minimizing misclassification rate or maximizing correlation (Li, Parnes and Chan 2013)
  – Require both immune responses and survival data on all subjects

• Prentice criteria for surrogate endpoint validation (Prentice 1989)
  – Proportion of treatment effect explained

• Causal inference (Gilbert and Hudgen 2008)
  – Herpes zoster vaccine study - Miao et al 2013; Gilbert et al 2014
Variability/Stability of Vaccines

• Vaccines are biological products that have more variability in than chemical compound
  – Need to demonstrate consistency of manufacturing
  – May require lot consistency clinical study

• Many vaccines contains attenuated live viruses and will lose potency over time
  – E.g., chickenpox vaccine, zoster vaccine

• Need to establish a range of potency for manufacturing and product shelf-life
  – Study safety at the high potency
  – Establish efficacy at near-expiry potencies
Regulatory Pathway for Demonstration of Vaccine Effectiveness

Traditional approval pathway
- Provide direct evidence of effectiveness via efficacy trials

Accelerated approval pathway
- Effectiveness demonstrated using a surrogate endpoint (or immunological marker) that is reasonably likely to predict clinical benefit
- Requires post-licensure studies to confirm clinical benefit

Animal rule approval pathway
- Effectiveness demonstrated in animal models, with reasonable likelihood of predicting human clinical benefits
- Only used when both traditional and accelerated approval pathways cannot be achieved
**Efficacy**
- Randomized, placebo-controlled trial
- Demonstrate an observed efficacy ≥50% with a lower bound >30%
- Well powered with type I error control for multiple endpoints and interim analyses
- An efficacy trial evaluating multiple vaccine candidates against a single placebo may be acceptable (platform trial)
- If a COVID-19 vaccine is proven to be safe and effective, that vaccine could serve as the control treatment to evaluate efficacy of the new vaccine candidate using noninferiority study design

**Safety**
- Requirements similar to other preventive vaccines
- Pre-licensure safety database ≥3000 individuals
- Solicited local and systemic adverse events (AE) for at least 7 days post each vaccination
- Unsolicited AEs for at least 21-28 days post each vaccination
- AE of special interest is vaccine-associated enhanced respiratory disease (ERD)
Opportunities to Accelerate Vaccine Development

• Advancement of genomics to understand the disease
• Use of immune marker and correlate of protection to guide smart R&D
  – Approval of Prevnar 13 and many combination vaccines based on immune correlates
  – Predicting vaccine protection at end-expiry dose (Chan et al 2002)
• Innovative clinical trial design and development strategy (Heyse and Chan 2016)
  – Novel endpoint to capture efficacy in both disease incidence and severity in herpes zoster vaccine (Oxman et al 2005)
  – Sequential likelihood ratio method for safety monitoring for rotavirus vaccine (Heyse et al 2008)
  – Adaptive designs such as seamless phase II/III design for HPV vaccine (Chen et al 2015), population enrichment for an event-driven vaccine trial (Su et al 2018)
  – Platform trial/master protocol
• Private-public partnership
Ebola vaccine (Ervebo) Development

- Developed during Ebola outbreaks in Africa
- International private-public partnership (Merck, NewLink, NIH, CDC, US Department of Defense, WHO, Welcome Trust, Public Health Agency of Canada, others)
- Phase I study initiated Oct 2014
- Phase III dose selected Jan 2015 based on immune responses
- Phase III study was a randomized cluster (ring) vaccine study of 3537 contacts and contacts of contacts of individuals with confirmed Ebola (Henao-Restrepo et al 2017)
  - Immediate vs 21-day delayed vaccination
- Vaccine (Ervebo) approved in Dec 2019
COVID-19 Vaccine Development

- SARS-COV-2 genome sequence identified Jan 2020
- First COVID-19 vaccine (mRNA) trial initiated Mar 2020, Phase III started Jul 2020
- Three vaccine programs currently in phase III development in the US
  - N=30,000 participants for each study, randomized, placebo controlled
  - Power at 90% for a true vaccine efficacy of 60%
  - The success criterion is an observed efficacy of ≥50% with a lower bound >30%
- Tremendous collaboration between industry and government to shorten the development timeline
  - potentially 12 to 18 months instead of years
Summary

• Vaccines are important medical products that have great public health benefits

• Vaccine development poses special challenges due to the biological variability
  – Important to assess immune correlate of protection
  – Need to understand the durability of protection
  – Large study may be required to meet a high bar of success

• Opportunities exist for acceleration of vaccine development
  – Innovative study designs and endpoints
  – Leveraging immune markers and correlates of protection
  – Private-public partnership
Key References


Key References


