Opportunities and Challenges in Vaccine Development

Ivan S.F. Chan, Ph.D.
AbbVie

National Institute of Statistical Sciences (NISS)-Merck Virtual Meet-up in Vaccine Development

September 16, 2020

Disclosure & Acknowledgement

Disclosure

The support of this presentation was provided by AbbVie. AbbVie participated in the review and approval of the content.

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

Reduction in Human Papillomavirus (HPV) Prevalence Among Young Women Following HPV Vaccine Introduction in the United States, National Health and Nutrition Examination Surveys, 2003–2010

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)

$$VE = 1 - RR = 1 - P_V/P_C$$

- 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 $n = n_v + n_c$

$n_v \sim$ binomial $(n, P_v/(P_v + P_c))$

- 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).

VE Lower Bound	Total Number of Events	Total Sample Size
0	56	16,300
.10	74	20,800
.20	100	28,500
.30	154	43,900

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

FDA Guidance on Approval of Vaccines to Prevent COVID-19

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

Acceleration of Vaccine Development in Outbreaks and Pandemics

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

Acceleration of Vaccine Development in Outbreaks and Pandemics

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

1. Chan, I.S.F. and Bohidar, N.R. (1998) 'Exact power and sample size for vaccine efficacy studies,' Communications in Statistics, Theory and Methods, 27, 1305-1322.

2. Chan, I.S.F., Wang, W.W. and Heyse, J.F. (2003) 'Vaccine clinical trials,' Encyclopedia of Biopharmaceutical Statistics, 2nd Edition, Marcel Dekker, NY, 1005-1022.

3. Chen YJ, Gesser R, and Luxembourg A (2015). A Seamless Phase IIB/III Adaptive Outcome Trial: Design Rationale and Implementation Challenges, Clin Trials, 12(1):84–90.

4. FDA Guidance for Industry (2020). Development and licensure of vaccines to prevent COVID-19.

5. Gilbert, PS., Hudgens, M (2008). Evaluating candidate principal surrogate endpoints. Biometrics, 64, 1146-1154.

6. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, Carroll MW, Dean NE, Diatta I, Doumbia M, Draguez B, Duraffour S, Enwere G, Grais R, Gunther S, Gsell PS, Hossmann S, Watle SV, Konde MK, Keita S, Kone S, Kuisma E, Levine MM, Mandal S, Mauget T, Norheim G, Riveros X, Soumah A, Trelle S, Vicari AS, Kieny MP, Rottingen JA, Kieny MP. (2015) Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial. The Lancet, 389, 505-518.

7. Heyse JF and Chan ISF. (2016) 'Review of statistical innovations in trials supporting vaccine clinical development,' Statistics in Biopharmaceutical Research, 8, 128-142.

8. Heyse JF, Kuter B, Dallas MJ, Heaton P. (2008) Evaluating the safety of a rotavirus vaccine: the REST of the story. Clinical Trials, 5:131–139.

Key References

9. Lauri E. Markowitz, Susan Hariri, Carol Lin, Eileen F. Dunne, Martin Steinau, Geraldine McQuillan, and Elizabeth R. Unger (2013) Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. Journal of Infectious Diseases, 208 (3): 385-93.

10. Li, S., Parnes, M., Chan, I.S.F. (2013) 'Determining the cutoff based on a continuous variable to define two populations with application to vaccines,' Journal of Biopharmaceutical Statistics, 23, 662-680.

11. Oxman, M.N., Levin, M.J., Johnson, G.R., Schmader, K.E., Straus, S.E., Gelb, L.D., Arbeit, R.D., Simberkoff, M.S., Gershon, A.A., Davis, L.E., Weinberg, A., Boardman, K.D., Williams, H.M., Zhang, J.H., Peduzzi, P.N., Beisel, C.E., Morrison, V.A., Guatelli, J.C., Brooks, P.A., Kauffman, C.A., Pachucki, C.T., Neuzil, K.M., Betts, R.F., Wright, P.F., Griffin, M.R., Brunell, P., Soto, N.E., Marques, A.R., Keay, S.K., Goodman, R.P., Cotton, D.J., Gnann, J.W., Loutit, J., Holodniy, M., Keitel, W.A., Crawford, G.E., Yeh, S.S.Y., Lobo, Z., Toney, J.F., Greenberg, R.N., Keller, P.M., Harbecke, R., Hayward, A.R., Irwin, M.R., Kyriakides, T.C., Chan, C.Y., Chan, I.S.F., Wang, W.W.B., Annunziato, P.W., and Silber, J.L. (2005) 'A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults", *New England Journal of Medicine*, 352, 2271-2284.

12. Prentice R.L. (1989) Surrogate endpoints in clinical trials: definition and operational criteria. *Statistics in Medicine*, 8:431-440.

13. Siber G.R. (1997). Methods for estimating serological correlates of protection. Developments in Biological Standardization 89, 283-296.

14. Siber, G.R., Chang, I., Baker, S., Fernsten, P., O'Brien, K.L., Santosham, M., Klugman, K.P., Madhi, S.A., Paradiso, P., Kohberger, R. (2007). Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. *Vaccine* 25, 3816-3826.

15. Su, Li, Zhao and Chan (2018). Population-enrichment adaptive design strategy for an event-driven vaccine efficacy trial. Statistics in Biosciences, 10(2), 357-370.