A review of sample size calculation for Phase III clinical trials for COVID-19 vaccine

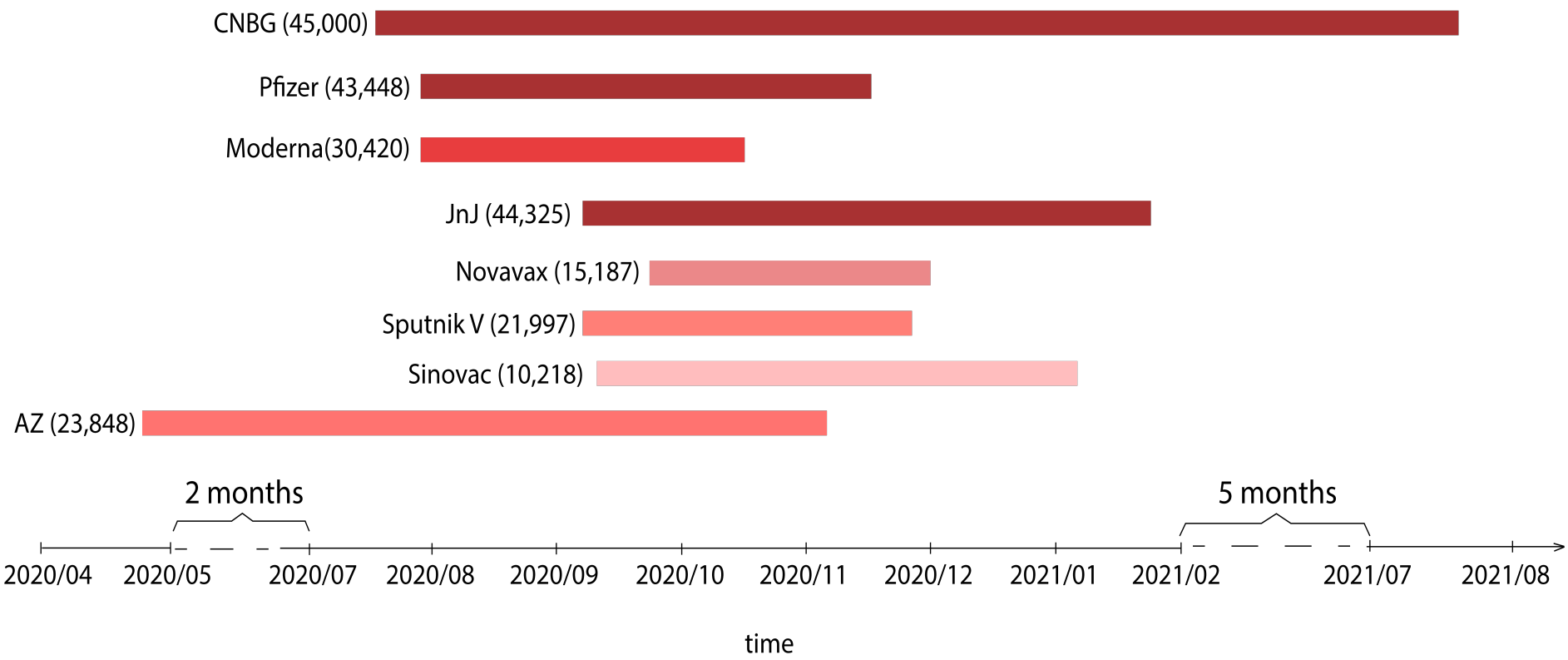
Zijian Chen

School of Statistics, East China Normal University
Department of Mathematics, University of Wisconsin - Madison

Outline

- Overview of eight trials
- Sample size calculation
- Summary

Overview of COVID-19 vaccine phase III trials



Primary endpoint

- The primary endpoint of Vaccine Efficacy (VE) is defined as

$$\mathrm{VE} = 1 - \mathrm{IRR},$$

where

$$\mathrm{IRR} = \frac{\text{incidence rate of vaccine group}}{\text{incidence rate of placebo group}}$$

- An effective vaccine means a decline in the incidence rate compared with the placebo group, equivalently a smaller IRR or a higher VE.

Testing hypothesis

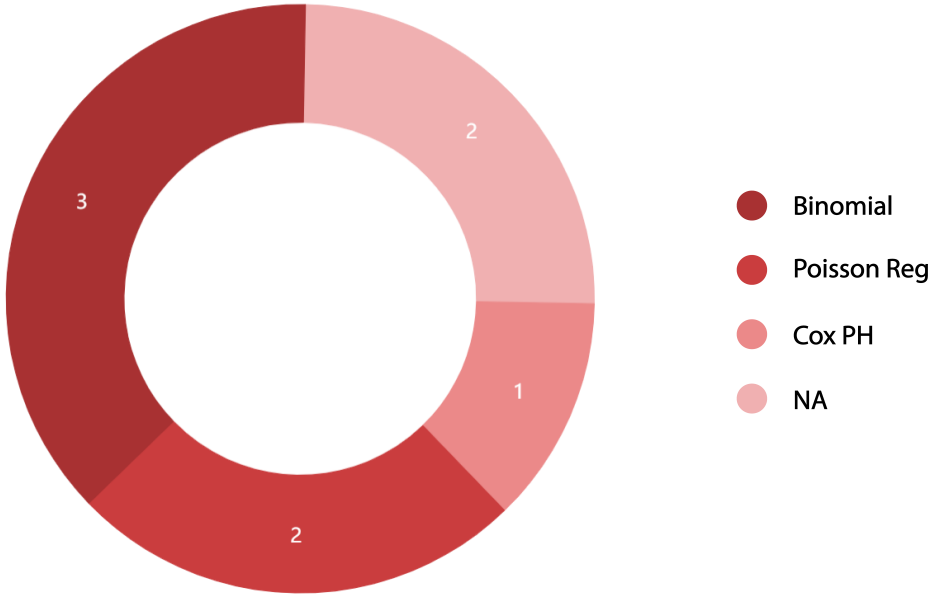
- According to WHO (2020),
  - The lower limit of 95% CI of VE should exceed 30%
  - The point estimate for VE should be at least 50%
- That is to test

$$H_0 : \mathrm{VE} = 0.3 \quad \text{vs} \quad H_1 : \mathrm{VE} \geq 0.5$$

- The main task is to find proper statistical model for VE (or a monotone transformation of VE).

Models

- Overview of the statistical models for VE (or equivalently, IRR) for the eight approved vaccines



- The modeling details of Sputnik V (Logunov et al., 21, Lancet) and Sinovac (Tanriover et al., 21, Lancet) (marked as NA) are not reported.

Notation

n_c	sample size of the placebo group
n_v	sample size of the vaccine group
	$k = n_c/n_v, \quad N = n_c + n_v$
p_c	incidence rate of the placebo group
p_v	incidence rate of the vaccine group
	$\mathrm{IRR} = p_v/p_c$
T	total number of events observed in the study
Y	number of events observed in the vaccine group

Model 1: Binomial

- Used by Sinopharm (Kaabi et al., 21, JAMA), J&J (Sadoff et al., 21, NEJM) and Pfizer (Polack et al., 20, NEJM).
- When the disease incidence rate is extremely low, the numbers of cases in the vaccine groups and the control groups approximately have the Poisson distribution (Chow et al., 08). Consequently, model

$$Y \sim \text{Binom}(T, \theta)$$

where

$$\theta = \frac{n_v p_v}{n_c p_c + n_v p_v} = \frac{1 - \text{VE}}{k + 1 - \text{VE}}$$

- Equivalent to test one-sample Binomial proportion

$$H_0 : \theta = \theta_0 = \frac{1 - \text{VE}_0}{1 - \text{VE}_0 + k} \quad \text{vs} \quad H_1 : \theta = \theta_1 = \frac{1 - \text{VE}_1}{1 - \text{VE}_1 + k}$$

Model 1: Binomial (Cont'd)

- Target event numbers (T and Y) can be solve from

$$\begin{cases} \sum_{a=0}^{Y} \binom{T}{a} \theta_0^a (1-\theta_0^{T-a}) = \alpha \\ \sum_{a=0}^{Y} \binom{T}{a} \theta_1^a (1-\theta_1^{T-a}) = 1-\beta \end{cases}$$

- To get the sample size n_v (or n_c), use

$$T = k n_v p_c + n_v p_v \quad \Rightarrow \quad n_v = \frac{T}{(k+1-\mathrm{VE}_1)p_c},\ n_c = k n_v$$

- Example (Pfizer):
  - $\mathrm{VE}_0 = 0.2$, $\mathrm{VE}_1 = 0.7$, $k = 1$. ($\theta_0 = 0.44$, $\theta_1 = 0.23$)
  - We get $T = 53$ (as reported).
  - Assuming $p_c = 0.017$ and 20% drop-out, we get $N = 2,998$.

Model 2: Modified Poisson Regression (Zou, 2004, Am. J. Epi.)

- Used by AstraZeneca (Voysey et al., 21, Lancet) and Novavax (Heath et al., 21, NEJM)
- The Poisson regression Model:

$$\log \pi(x_i) = \alpha + \beta x_i + \text{covariates}$$

where x_i is a binary exposure with value 1 if exposed and 0 otherwise. $\pi(x_i)$ can be the expected number of diagnosed patients.

- When applied to binomial data, the error for the estimated relative risk (RR) will be overestimated. This can be rectified by

$$\mathbb{V}\text{ar}(\log \widehat{\text{RR}}) = \frac{b}{an_v} + \frac{d}{cn_c}$$

Model 2: Modified Poisson Regression (Cont'd)

- Test statistic:

$$Z = \frac{\log \widehat{\mathrm{RR}} - \log \mathrm{RR}_0}{\mathbb{V}\mathrm{ar}(\log \widehat{\mathrm{RR}})} \quad \sim N(0,1)$$

- The power is approximated by

$$\Phi\left(z_{\alpha/2} + \frac{\log \mathrm{RR}_1 - \log \mathrm{RR}_0}{\mathbb{V}\mathrm{ar}(\log \widehat{\mathrm{RR}})} \right)$$

Model 2: Modified Poisson Regression (Cont'd)

- Solving

$$z_{\alpha/2} + \frac{\log \mathrm{RR}_1 - \log \mathrm{RR}_0}{\sqrt{1/n_v}\sqrt{(1-p_v)/kp_v + (1-p_c)/p_c}} = z_{1-\beta}$$

  we have the sample size

$$n_v = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{(\log \mathrm{RR}_1 - \log \mathrm{RR}_0)^2}\left(\frac{1-p_v}{kp_v} + \frac{1-p_c}{p_c}\right), \quad n_c = kn_v$$

- Example (AZ):
  - $\mathrm{RR}_1 = 0.4$, $\mathrm{RR}_0 = 0.7$, $p_c = 0.008$, $\alpha = 0.05$, $\beta = 0.1$
  - Total sample size $N = 22,213$.
  - The actual model includes covariates (e.g., age, follow-up time) in variance estimator (which amplifies the sample size).

Model 3: Cox Proportion Hazard

- Used by Moderna (Baden et al., 21, NEJM)
- Lachin and Foulkes (86, BCS):

$$N = \frac{w^2}{\{\log(p_c/p_v)\}^2}$$

where

$$w = \frac{z_{1-\frac{\alpha}{2}}}{\sqrt{(X_1 p_c + X_2 p_v) X_1 X_2}} + z_{1-\beta}\sqrt{\frac{X_1 p_c + X_2 p_v}{X_1 p_c X_2 p_v}}$$

and $X_1 = k/(k+1)$, $X_2 = 1/(k+1)$.

- Example (Moderna): [note: this is the single-stage result]
  - $\alpha = 0.05$, $\beta = 0.1$, $X_1 = X_2 = 0.5$, $p_c = 0.0075$, $p_v = 0.7 p_c$
  - Assuming 2% drop-out and 15% unevaluable, we have $N = 29,250$.

Sample size adjustment

- interim analysis methods overview:

	CNBG	J&J	Pfizer	Novavax	Moderna	AZ
method	g-seq	SPRT	Bayesian g-seq	g-seq	g-seq	g-seq
% of events	1/3, 2/3	weekly	38%, 56%, 73%	50%	35%, 70%	50%
sample size adjusted	NA	NA	NA	NA	YES	NO

Sample size adjustments based on group sequential designs:

$$N = R_B(K, \alpha, \beta) N_{\text{fix}},$$

where $R_B(K, \alpha, \beta)$ is the ratio of the maximum sample size of the group sequential test to the fixed sample size based on the O'Brien and Fleming's test.

- The estimation of sample size should meet the criteria of other endpoints (such as immunogenicity). (Kaabi et al., 21, JAMA)

Summary

- A general procedure to calculate the sample size in a Phase III trial:
  - Determine the primary endpoint (usually VE) and its expected value.
  - Choose a model for statistical inference.
  - Knowledge/assumption about the incidence rate in control group (use VE to calculate the incidence rate in vaccine group)
  - Based on the fixed sample size, make proper adjustment by interim analysis.
- As the incidence rate is low in vaccine trial, a Poisson model is preferred than the usual log-rank or Cox PH model.

References

[1] Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. *JAMA*. 2021;326(1):35-45.

[2] Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med.* 2020; 383(27): 2603-15.

[3] Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2020;384(5):403-16.

[4] Jerald Sadoff, M.D., Glenda Gray, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med*. 2021; 384:2187-2201.

References

[5] Heath PT, Galiza EP, Baxter DN, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *N Engl J Med*. 2021; 385:1172-1183

[6] Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *The Lancet*. 2021;397(10275):671-681.

[7] Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet* 2021;397:99-111.

[8] Tanriover MD, Doanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *The Lancet*. 2021;398(10296):213-22.

References

[9] World Health Organization. An international randomised trial of candidate vaccines against COVID-19. https://www.who.int/ publications-detail-redirect/an-international-randomised-trial-of-candidate-vaccines-against-covid-19. Accessed Sep 21, 2021.

[10] Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159:702-706.

[11] Chow, S.C., Shao, J., and Wang, H. 2008. Sample Size Calculations in Clinical Research, Second Edition. Chapman & Hall/CRC. Boca Raton, Florida.

[12] Lachin JM and Foulkes MA, Evaluation of Sample Size and Power for Analyses of Survival with Allowance for Nonuniform Patient Entry, Losses to Follow-Up, Noncompliance, and Stratification. *Biometrics*. 1986;42: 507-519.

Acknowledgements

- Mingyue Han, Guoli Jiang, Wenning Zhao, Fangyuan Rao, Tianyue Yuan, Qichang Wan, Tao Yang, Houtian Yi, Xingrong Xie, Xintong Zhai, Sheng Fang, Shiyun Zhou, Ziming Zhong, Ziang Zeng, Zihao Dong, Yuchen Xie, Lei Qian, Yuqing Yu, Yunhao Jiao.
- Prof Jin Xu