

P9185 - Project 5: Protocal design and analysis for COVID-19

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- Vaccine efficacy protocol
- Adverse effect analysis for Vaccine v.s. Control
- Survival analysis COVID contraction after vaccine shot

- Coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had devastating consequences globally.
- Control measures, such as the use of masks, have been variably implemented and have proved insufficient in impeding the spread of coronavirus disease 2019 (Covid-19), the disease caused by SARS-CoV-2.
- Vaccines are urgently needed to reduce the morbidity and mortality associated with Covid-19.

Vaccine efficacy protocol

- A pharmaceutical company therefore would like to conduct a phase III randomized (**1-to-1 ratio**), **stratified**, observer-blinded, placebo-controlled trial at **100 U.S. sites** to demonstrate the efficacy for their developing vaccine.

Define primary outcome

$$VE = 1 - \frac{p_1}{p_2}$$

- p_i : the number of new cases during 14-28 days over the total number at risk during 14-28 days in group i
- x_i cases in group i with n_i samples
- Goal: test the null hypothesis that the vaccine efficacy is 30% or less and provide 80% power to detect a 60% vaccine efficacy without planned interim analyses

Vaccine efficacy protocol – randomization procedure

- The study consists of **2 periods** :
 - vaccine period for 2 injections
 - follow up period:
 - second injection - 14 days: if the subjects have symptoms/being positive at this period, regard as not at risk and will not contribute to the efficacy calculation
 - 14-28 days: follow up period,

Vaccine efficacy protocol – randomization procedure

- collect study subjects with seronegative at baseline N_0
- take 2 covid shots
- collect status at day 14 after second shot
- remove those becoming positive during the 14 days
- Count new cases during 14-28 days

Vaccine efficacy protocol – randomization procedure

- Blinding and Randomization procedure
 - The primary blind codes are the group codes, and each vaccine number is the investigational vaccine or control vaccine corresponding to the research number, which is represented by different letters.
 - The secondary blind codes will uncover the final blind codes, i.e. the vaccine name represented by letters, and the low-dose, medium-dose and high-dose investigational vaccine or control vaccine.
 - Use random number generating process in R(?) to generate random codes
- A stratified block randomization method was used, with study site as the stratification factor and block size in each stratum of 15.

Vaccine efficacy protocol – analysis approach

- $H_0 : VE \leq 30\%, H_1 : VE > 30\%$
- parameters:
- Test stat:

$$Z_L = (\log \hat{R} - \log R_0) / \hat{\sigma} \sim N(0, 1)$$

* Rejection rule: [add]

Vaccine efficacy protocol – sample size calculation

$$N = (Z_{\alpha} + Z_{\beta})^2 \frac{q_1/kp_1 + q_2/(1-k)p_2}{(\log R_0 - \log R)^2}$$

p2	rho	lambda	n
0.01	0.000	0.000	13740.340
0.01	0.000	0.005	13809.387
0.01	0.000	0.010	13879.131
0.01	0.005	0.000	17106.723
0.01	0.005	0.005	17192.686
0.01	0.005	0.010	17279.518
0.01	0.010	0.000	20473.106
0.01	0.010	0.005	20575.986
0.01	0.010	0.010	20679.905
0.03	0.000	0.000	4527.468
0.03	0.000	0.005	4550.219
0.03	0.000	0.010	4573.200

Adverse effect analysis for Vaccine v.s. Control

Characteristic	control, N = 20,625 ¹	vaccine, N = 20,625 ¹	p-value ²
id	10,313 (5,157, 15,469)	60,313 (55,157, 65,469)	<0.001
sae	25 (0.1%)	37 (0.2%)	0.069
Unknown	611	2,051	
site	50 (25, 75)	50 (25, 75)	>0.9
sex			0.2
female	10,313 (50%)	10,190 (49%)	
male	10,312 (50%)	10,435 (51%)	
age	45 (38, 51)	45 (36, 53)	0.3
¹ Median (IQR); n (%)			
² Wilcoxon rank sum test; Pearson's Chi-squared test			

Adverse effect analysis for Vaccine v.s. Control

Table 2: Missing Data Pattern

	time1	time2	time3	
30342	1	1	1	0
4552	1	1	0	1
3089	1	0	1	1
605	1	0	0	2
1933	0	1	1	1
385	0	1	0	2
288	0	0	1	2
56	0	0	0	3
	2662	4038	5598	12298

Adverse effect analysis for Vaccine v.s. Control

$$\begin{aligned} \text{logit}\left(\frac{\pi_{ijk}}{1 - \pi_{ijk}}\right) = & \beta_0 \\ & + \beta_1 I(\text{time} == 2)_{ijk} + \beta_1 I(\text{time} == 3)_{ijk} \\ & + \beta_3 I(\text{time} == 1)_{ijk} \times I(\text{group} == \text{Vaccine})_{ij} \\ & + \beta_4 I(\text{time} == 2)_{ijk} \times I(\text{group} == \text{Vaccine})_{ij} \\ & + \beta_5 I(\text{time} == 3)_{ijk} \times I(\text{group} == \text{Vaccine})_{ij} \\ & + \beta_6 I(\text{sex} == \text{male})_{ij} \\ & + \beta_7 \text{age}_{ij} \\ & + \alpha_{0i} + \alpha_{0ij} + \epsilon_{ijk} \end{aligned}$$

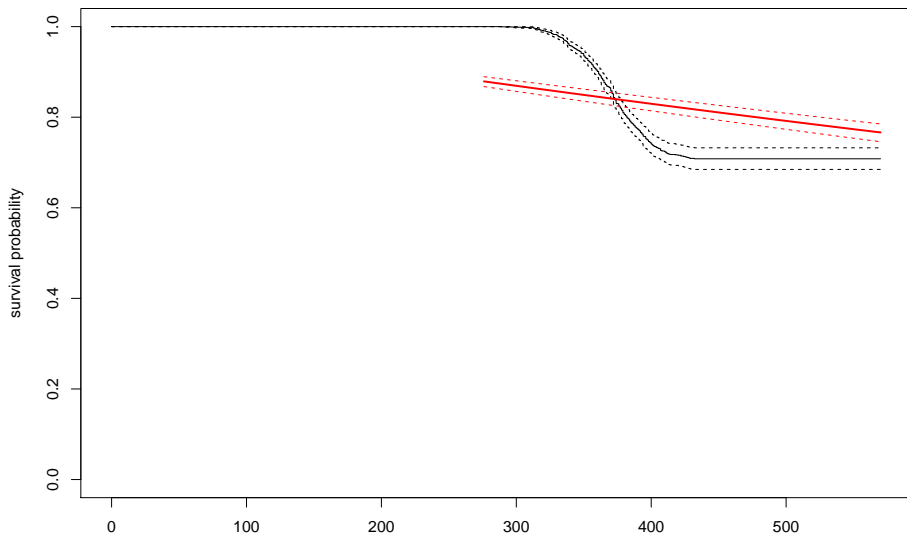
- i for site, j for subject, k for time measure

Adverse effect analysis for Vaccine v.s. Control

```
##
## \begin{table}
## \begin{center}
## \begin{tabular}{l c c c}
## \hline
## & mod_mis1 & mod_mis0 & mod_all \\
## \hline
## (Intercept) & & $-17.44^{\{***\}}$ & $-7.34^{\{***\}}$ & 
## & $(3.14)$ & $(0.42)$ & 
## time2 & & $4.95^{\{**\}}$ & $-0.30$ & 
## & $(1.53)$ & $(0.32)$ & 
## time3 & & $2.64$ & $0.16$ & 
## & $(2.19)$ & $(0.28)$ & 
## sexmale & & $-0.27$ & $-0.06$ & 
## & $(1.19)$ & $(0.17)$ & 
## age & & $0.01$ & $0.02^{\{*\}}$ & 
## & $(0.05)$ & $(0.01)$ & 
```

Survival analysis COVID contraction after vaccine shot

KM and exponential estimates of survival curve



Survival analysis COVID contraction after vaccine shot

Survival analysis COVID contraction after vaccine shot

Conclusion and discussion