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

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Outline

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

Background

- 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 12 months over the total number at risk during 12 months 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
    - 12 months: 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 12 months

Vaccine efficacy protocol – randomization procedure

- Blinding and Randomization procedure
  - The Phase III clinical trial will be conducted in multicenter, randomized, stratified, observer-blinded, and placebo-controlled design
  - There are 100 participating centers in the US
  - Eligible participants are those aged 16 years or older who tested seronegative for SARS-CoV-2 at the recruitment time
  - We stratify the participants by age and gender, and randomly assigned persons in each stratification in a 1:1 ratio to receive either two doses of vaccines or placebo
  - They will be monitored for 12 months by active surveillance of COVID-19.
  - The trial is observer-blinded to avoid introducing bias, i.e, the participants and those responsible for the evaluation are blinded to the treatment group

Vaccine efficacy protocol – analysis approach

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

$$Z = \frac{\phi_0 \hat{p}_2 - \hat{p}_1}{\sqrt{\frac{\tilde{p}_1(1-\tilde{p}_1)}{n_1} + \phi_0^2 \frac{\tilde{p}_2(1-\tilde{p}_2)}{n_2}}},$$

where $\phi_0 = 1 - \text{VE}_0, \hat{p}_1 = \frac{x_1}{n_1}, \hat{p}_2 = \frac{x_2}{n_2}$, and $\tilde{p}_1$ and $\tilde{p}_2$ are the maximum likelihood estimates under the null hypothesis, calculated by

$$\tilde{p}_1 = \phi_0 \tilde{p}_2, \qquad \tilde{p}_2 = \frac{-B - \sqrt{B^2 - 4AC}}{2A},$$

where

$$A = (n_1 + n_2)\phi_0, \qquad B = -(n_1\phi_0 + x_1 + n_2 + x_2\phi_0), \qquad C = x_1 + x_2,$$

and we reject the null hypothesis if $Z > Z_\alpha$, the upper α-th percentile of a standard normal distribution.

Vaccine efficacy protocol – sample size calculation

To detect a vaccine efficacy of $\mathrm{VE}_1 = 0.6$ (or vaccine event probability of $p_1 = 0.4p_2$) with $1 - \beta = 80\%$ power, we assume that $n_1 = n_2$, and the number of subjects needed will be determined by the following formula:

$$N = \frac{(Z_\alpha[\phi_0 p_2(1-\phi_0 p_2)/0.5 + \phi_0^2 p_2(1-p_2)/0.5]^{1/2} + Z_\beta[p_1(1-p_1)/0.5 + \phi_0^2 p_2(1-p_2)/0.5]^{1/2})^2}{(\phi_0 p_2 - p_1)^2}.$$

	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
0.00	18952	9400	6216	4624	3668	3032	2578	2236	1970
0.05	19950	9894	6544	4868	3862	3192	2712	2354	2074
0.10	21058	10444	6906	5138	4076	3368	2864	2484	2190
0.15	22296	11058	7312	5440	4316	3568	3032	2630	2318
0.20	23690	11750	7770	5780	4586	3790	3222	2794	2464

Table 1: Sample size calculation changing missing rate(row) and control prevalence(column)

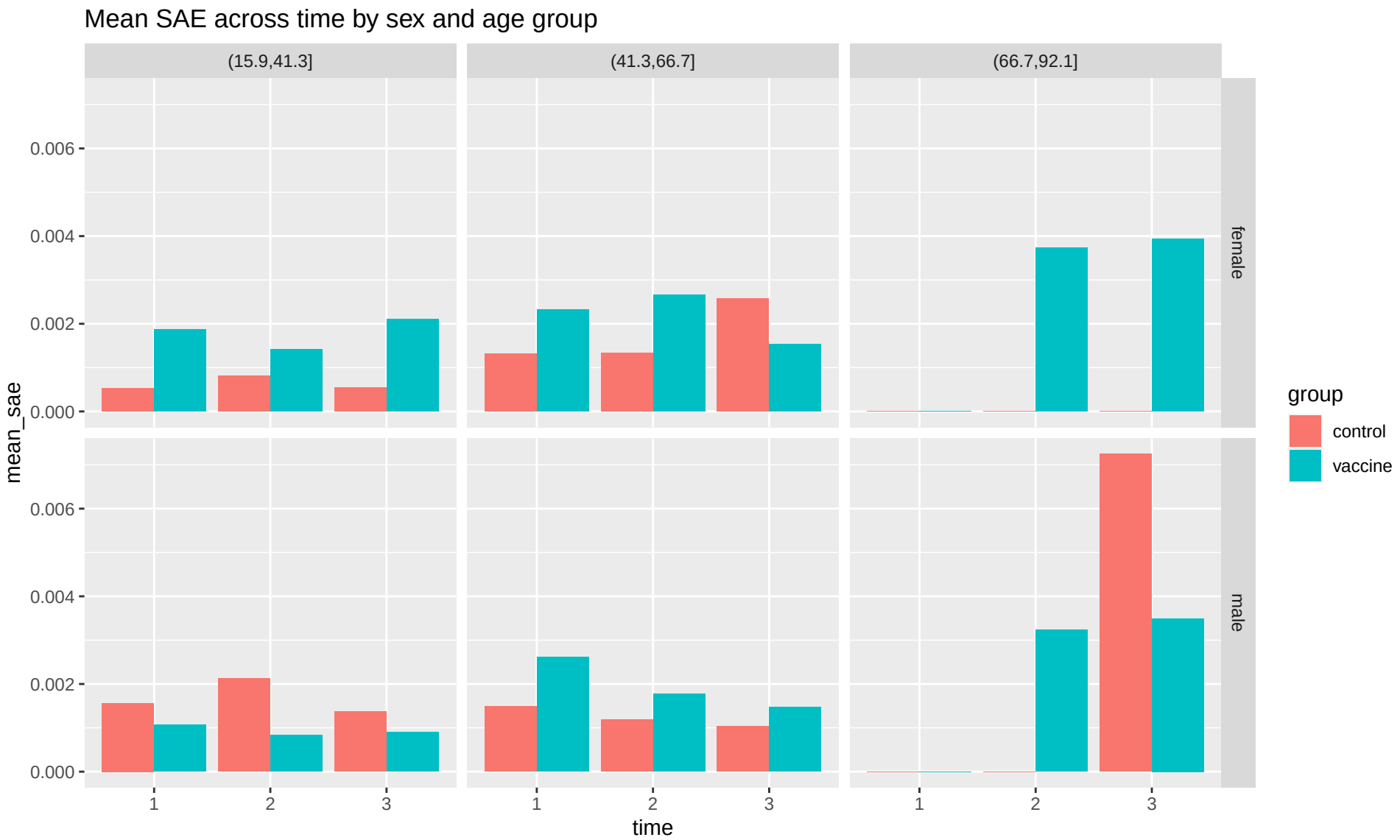
Adverse effect analysis for Vaccine v.s. Control

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



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 – missing pattern

GLM: missing_id ~ sae+sex+age+site+time

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-1.1853	0.0372	-31.83	0.0000
sae	0.0731	0.1917	0.38	0.7030
sexmale	-0.0046	0.0155	-0.30	0.7645
age	-0.0023	0.0007	-3.23	0.0013
site	-0.0003	0.0003	-1.02	0.3093
time2	-0.1826	0.0182	-10.01	0.0000
time3	-0.4402	0.0194	-22.71	0.0000

- Missing_id: =0 if no missing follow up, =1 if any missing follow up.
- Missing pattern is not related to the outcome;
- Assuming Missing at random and parameter separability;

Adverse effect analysis for Vaccine v.s. Control

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

- i for site, j for subject, k for time measure
- α_{0i} – site-level random intercept
- α_{1ij} – nested random intercept, $\alpha_{1ij} = \alpha_{1ik}$ if $I(\text{group} == \text{Vaccine})_{ij} = I(\text{group} == \text{Vaccine})_{ik}$

Adverse effect analysis for Vaccine v.s. Control

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-7.38	0.39	-19.08	0.00
time2	0.06	0.28	0.21	0.83
time3	0.19	0.27	0.70	0.48
sexmale	-0.10	0.15	-0.64	0.52
age	0.01	0.01	2.09	0.04
time1:groupvaccine	0.47	0.27	1.76	0.08
time2:groupvaccine	0.32	0.27	1.17	0.24
time3:groupvaccine	0.04	0.28	0.15	0.88

Table 3: Fixed effect estimation for adverse effect model

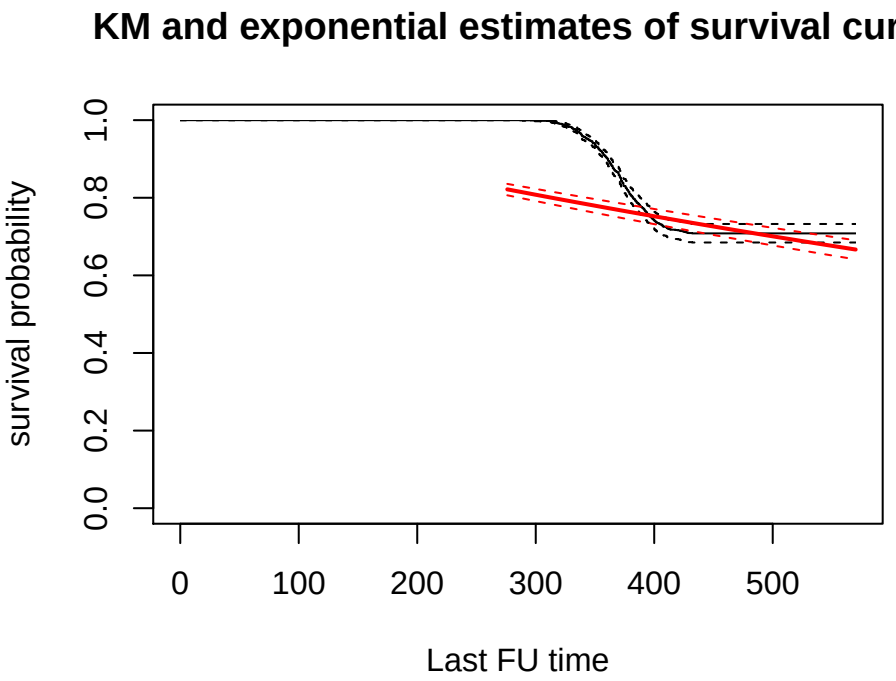
Adverse effect analysis – ANOVA for time effect

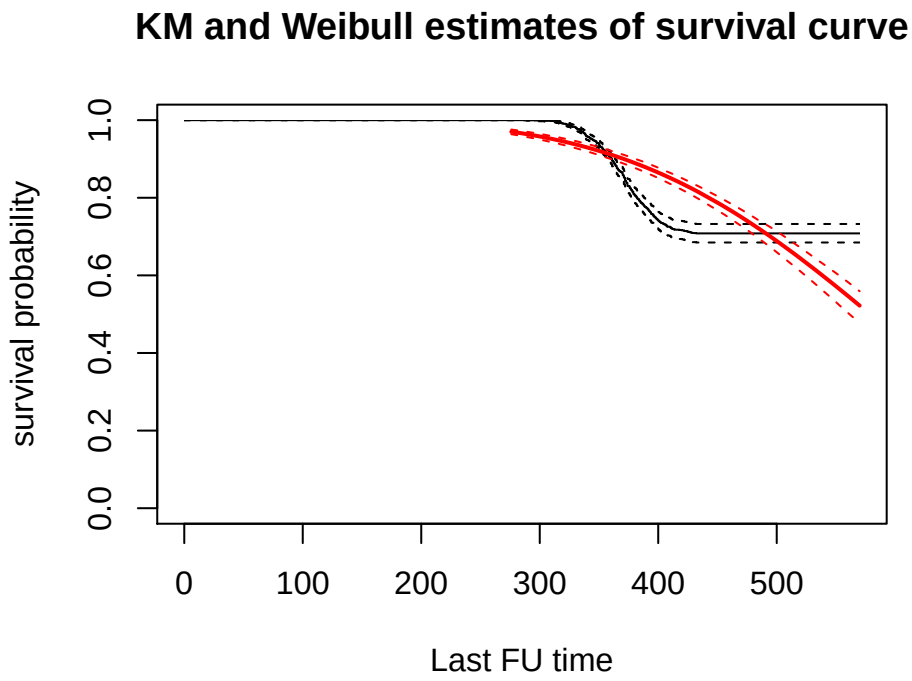
	Chisq	Df	Pr(>Chisq)
time	0.12	2	0.9399
sex	0.41	1	0.5206
age	4.36	1	0.0368
time:group	4.28	3	0.2329

Table 4: Deviance test for adverse effect model

- From the Deviance test using Wald chisquare test statistics, we have $T_{interaction} = 4.28 > \chi^2_{0.05,3}$, P value > 0.05
- There is no siginificant difference between odds of having SAE in the vaccine group and control group at any of the three assessment time points.

Survival analysis COVID contraction after vaccine shot





	time	n.risk	n.event	surv	std.err	lower	upper
1	360.00	1399.00	177.00	0.90	0.01	0.89	0.92

Table 5: Survival Rate at 12 Month

Survival analysis COVID contraction after vaccine shot

	par_fitting	est	lcl	ucl
1	Exponential	974.17	892.32	1075.15
2	Weibull	974.17	892.71	1068.79
3	K-M			

Table 6: Estimated Median Survival Time

- The survival rate didn't drop to 50% at the end of the study.
- Flat tail of the survival curv, both exponential and Weibull distribution can't fit the trend well.
- Not interpretable parametric model fitting for both median and mean survival time.

Conclusion and discussion

- A pharmaceutical company therefore would like to conduct a phase III randomized (**1-to-1 ratio**), **stratified**, observer-blinded, placebo-controlled trial is designed with sample size calculation changing missing rate and control prevalence.
- No siginificant difference between odds of having SAE in the vaccine group and control group at any of the three assessment time points.
- The survival rate didn't drop to 50% at the end of the study. No interpretable estimation of mean and median survival time.

Resource

Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial | Global Health | JAMA | JAMA Network. (n.d.). Retrieved May 2, 2022, from https://jamanetwork.com/journals/jama/fullarticle/2780562

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