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

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Outline

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

Backgroud

- 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 protocal

- 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 protocal – 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 protocal – 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 protocal – 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 protocal – 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 protocal – 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

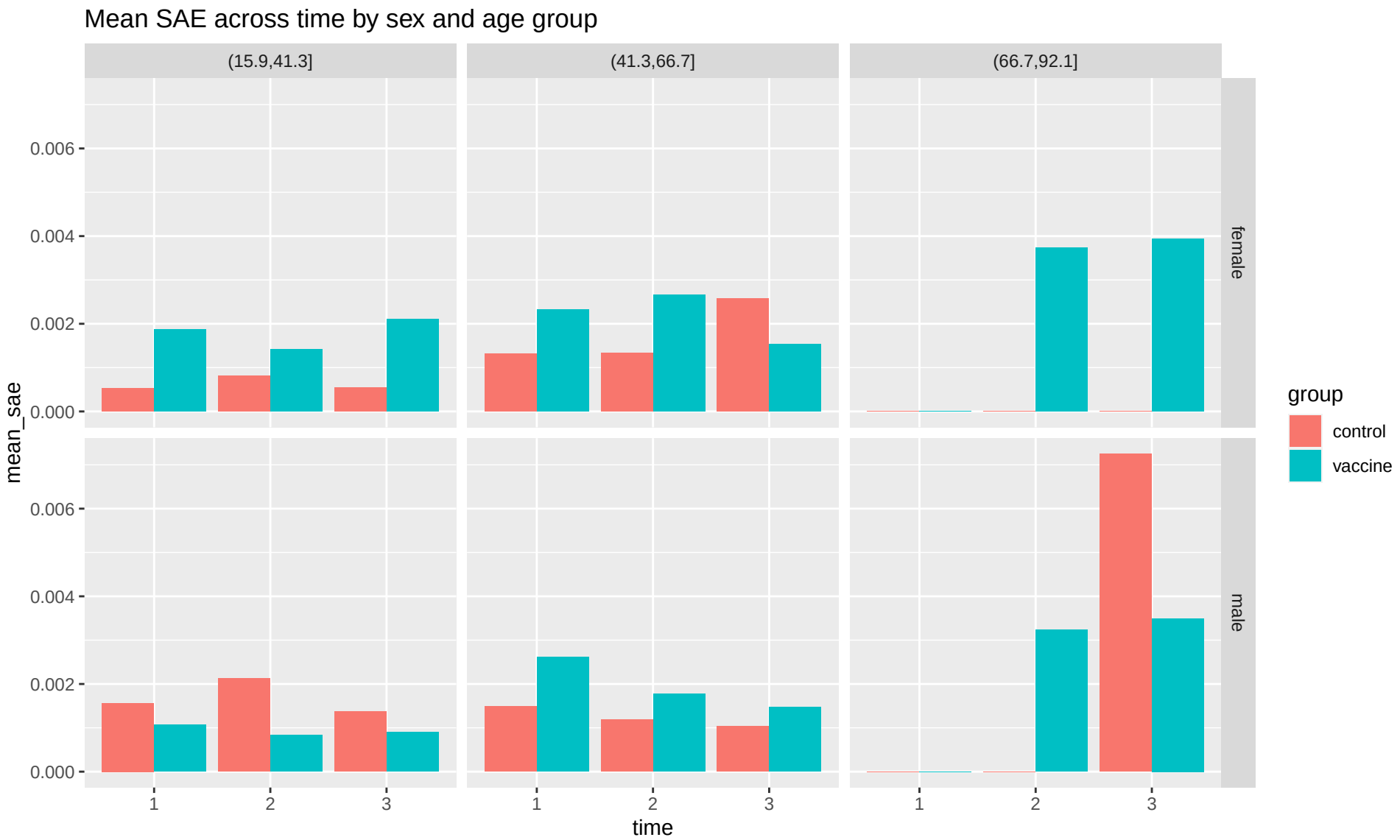
Adverse effect analysis for Vaccine v.s. Control

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



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 pattern is not related to the outcome;
- Assuming Missing at random and parameter separability;

Adverse effect analysis for Vaccine v.s. Control

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

- 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

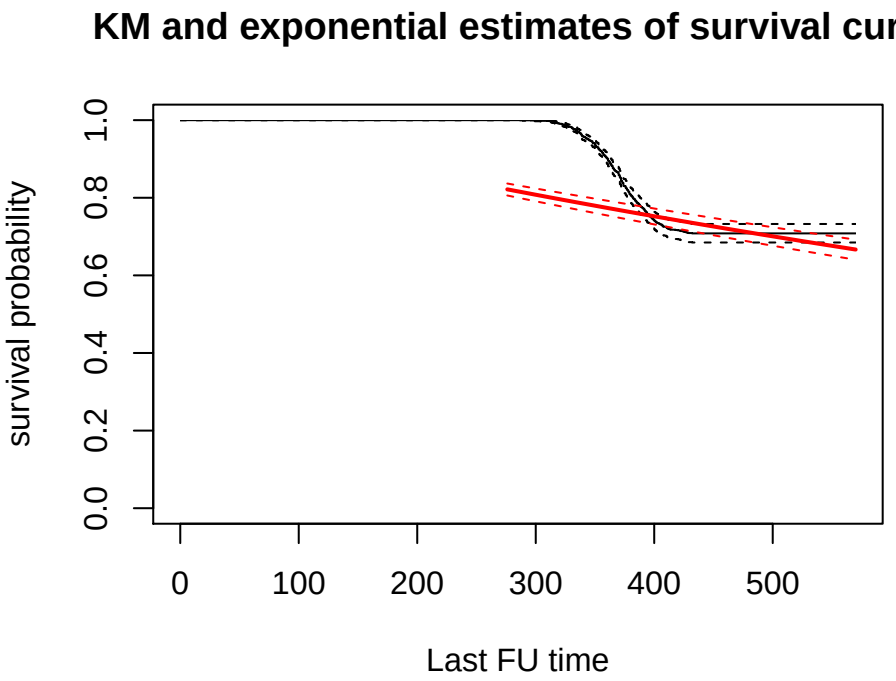
	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-7.38	0.39	-19.08	0.00
time2	0.06	0.28	0.21	0.83
time3	0.19	0.27	0.70	0.48
sexmale	-0.10	0.15	-0.64	0.52
age	0.01	0.01	2.09	0.04
time1:groupvaccine	0.47	0.27	1.76	0.08
time2:groupvaccine	0.32	0.27	1.17	0.24
time3:groupvaccine	0.04	0.28	0.15	0.88

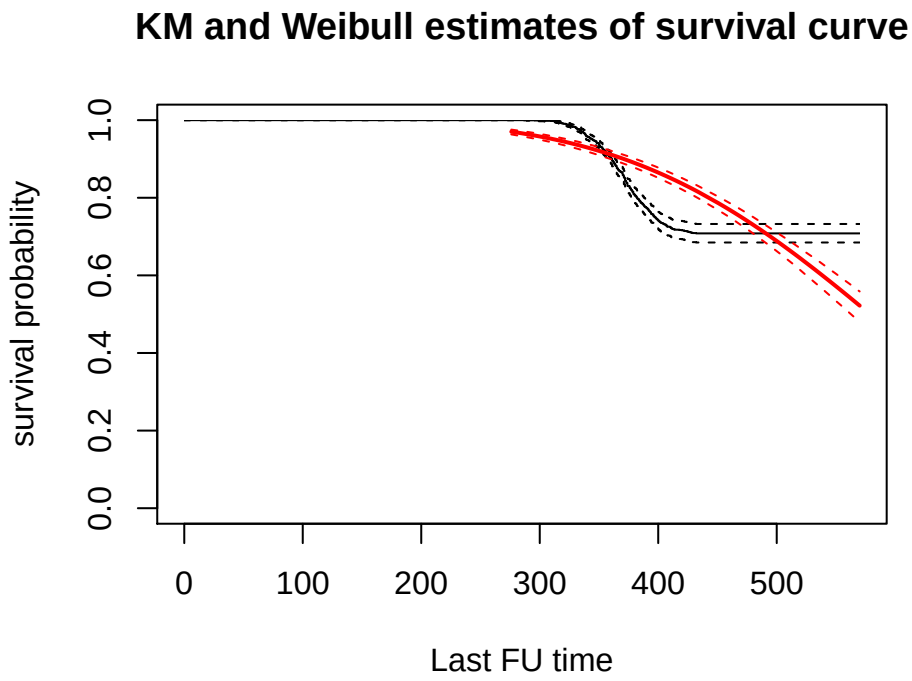
Adverse effect analysis – ANOVA for time effect

	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

- 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 3: 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 4: 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.

Survival analysis COVID contraction after vaccine shot

Conclusion and discussion