

Association between S antibody levels and immunological events (COVID-19 infection or vaccination) from nationwide community surveillance data in South Korea

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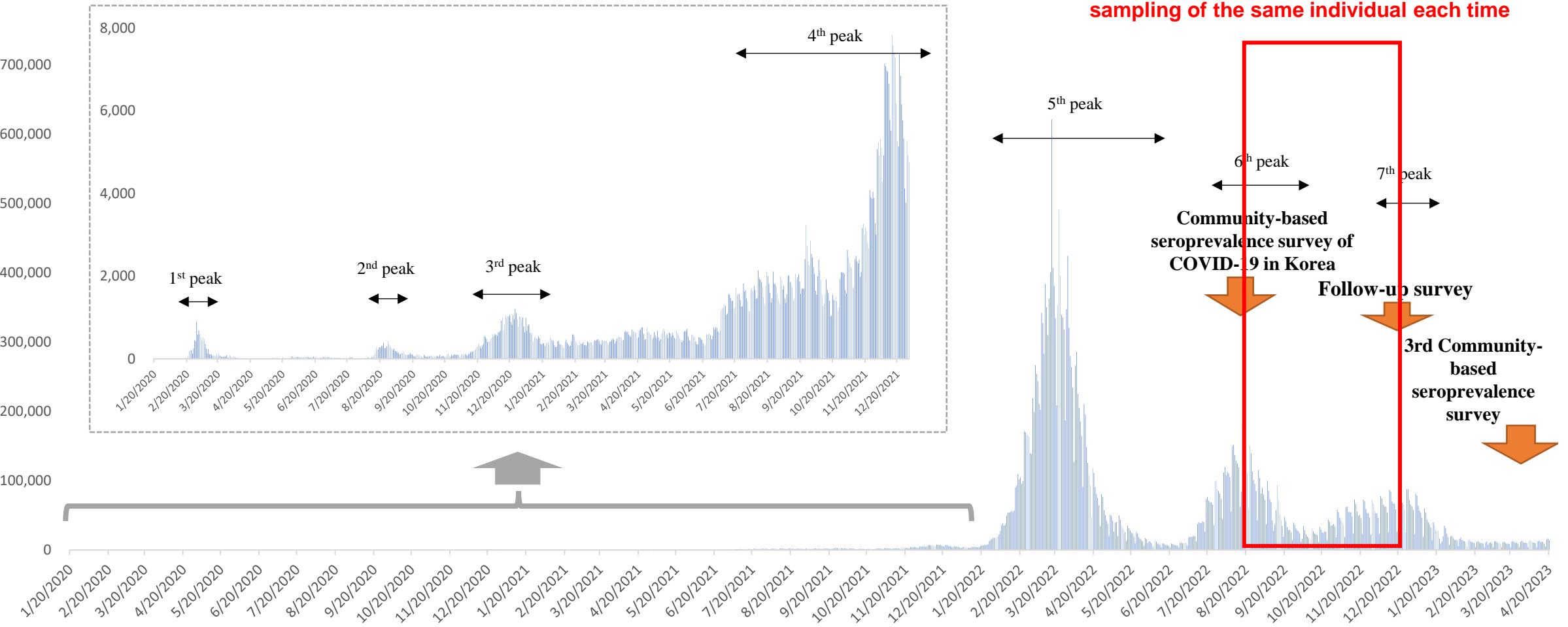
Background

- ❖ Previous studies identified that neutralizing antibody levels are highly predictive of immune protection from SARS-CoV-2 infection (Khoury DS et al, 2021) and the levels of antibody protection required to prevent COVID-19 (Feng S et al, 2021)
 - **Neutralizing Antibodies:** The S antibodies include neutralizing antibodies, which can directly interfere with the virus's ability to infect cells. Higher levels of S antibodies generally correlate with a stronger capacity to neutralize the virus and prevent infection.
 - **Vaccine Efficacy:** COVID-19 vaccine efficacy is linked to strong S antibody responses. Vaccines with higher S antibody titers are generally more effective in preventing or lessening COVID-19 severity.
 - **Duration of Protection:** Although S antibodies offer an initial defense, their levels may decrease over time, reducing protection. This has prompted booster shot recommendations to sustain immunity.
 - **Variants of Concern:** Variants with mutations in the S protein can lower antibody effectiveness, risking breakthrough infections in vaccinated people. Research continues to explore the protection correlation against various variants.
 - **Measurement and Interpretation:** Quantitative S antibody level assessments offer insights into immune status, but the protective threshold varies and isn't precisely defined for the population; it is challenging to assess risk trends based on cross-sectional surveys, and most existing longitudinal studies are hospital-based with relatively small sample sizes.

|| Objective

- ❖ Repeated Community-Based Antibody Surveys
 - 1) Aim 1: Examining the association between Spike (S) protein antibody levels and COVID-19 infection (Case control study design)
 - 2) Aim 2: Determine the change of S antibody level by infection or vaccination over time (Cohort study design)

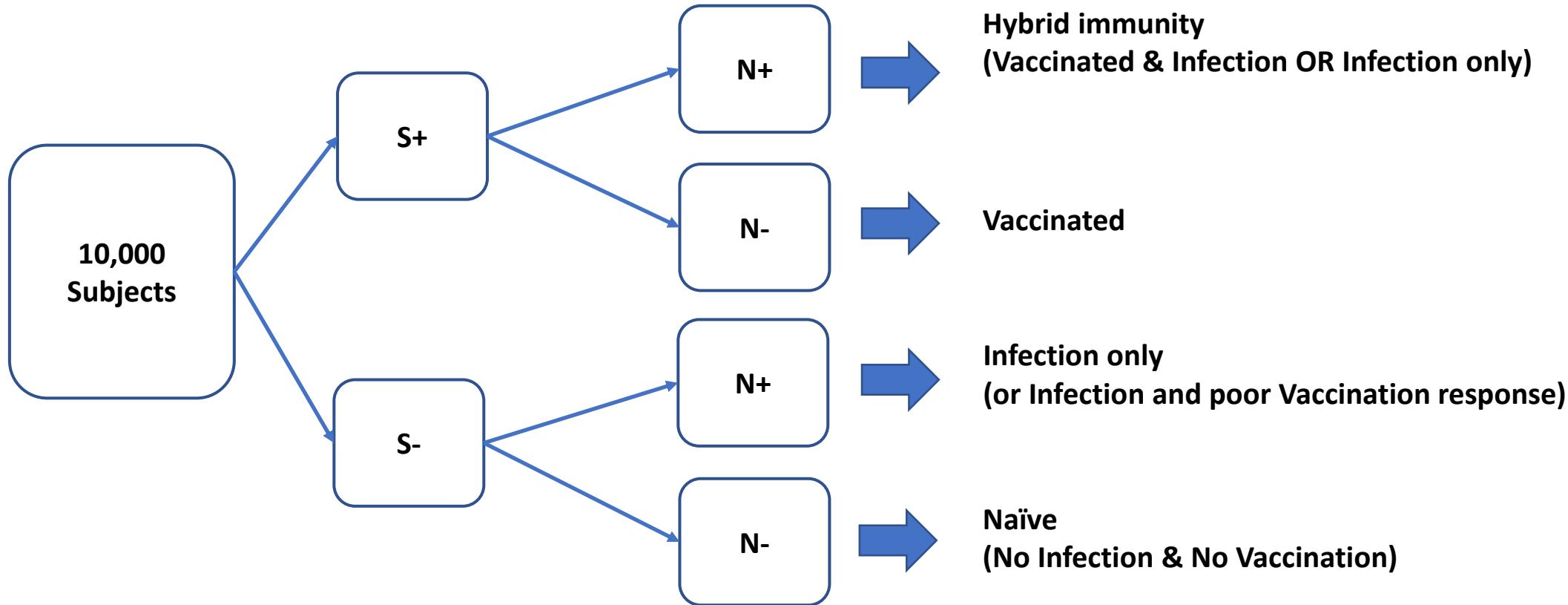
Epidemic curve of COVID-19 in Korea (2020.1.20.~2023.4.20.)



Method

- **Surveillance period:** August 2022 (1st survey) – December 2022 (2nd survey)
- **Surveillance area:** 258 public health centers and 113 private medical facilities from 259 cities/counties nationwide in South Korea
- **Surveillance subjects:** 10,000 individuals aged 5+ were randomly selected from 5,000 households.
- **Surveillance method:** Nationwide community-based surveillance. Surveyors conduct one-on-one interviews via tablets.

Population immunological status by S/N ab level



Study design

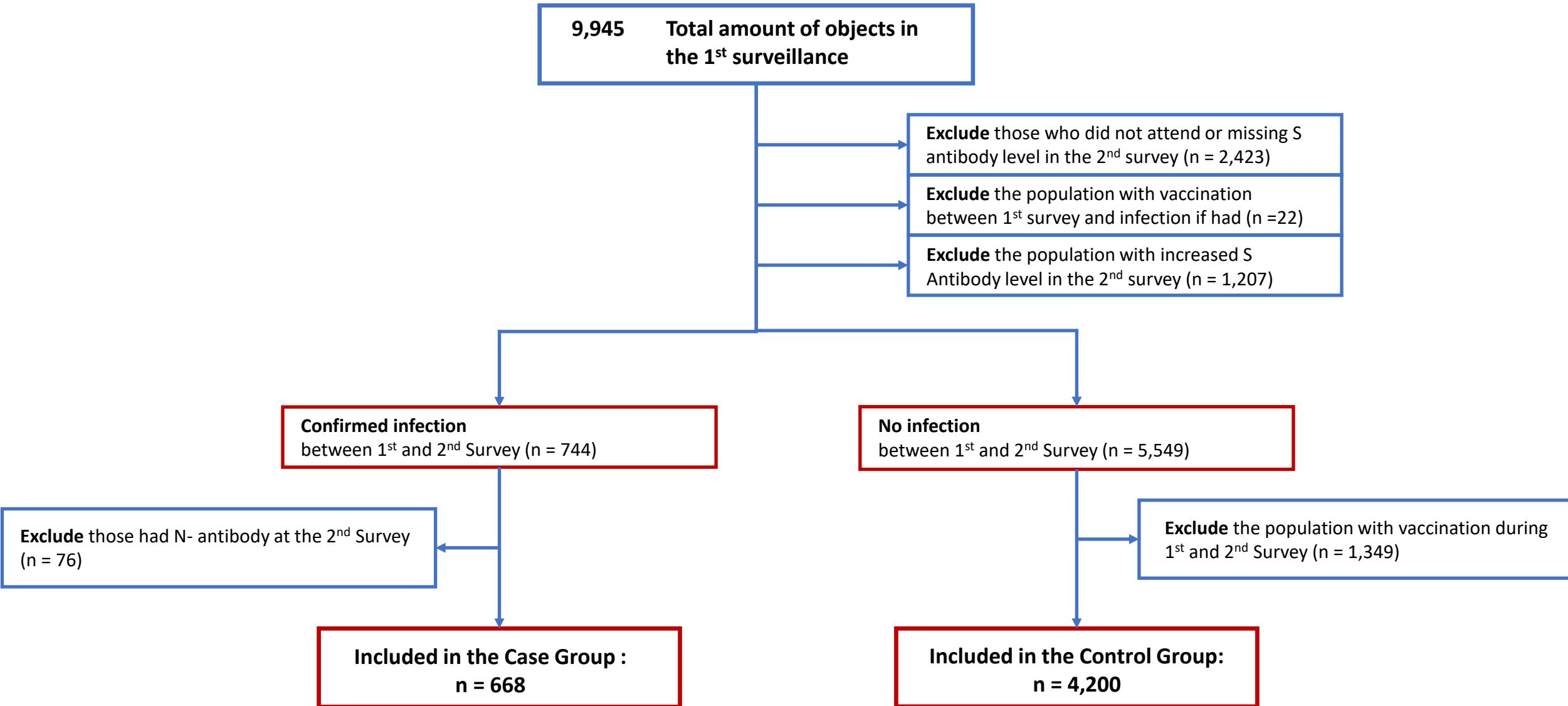
Aim 1: Nested case-control study design

- **Outcome measurement:** Confirmed infection between 1st and 2nd surveillance
- **Exposure measurement:** anti-Spike (S) antibody level
- **Statistical analysis:** Logistic regression, Statistical inference

Aim 2: Cohort study design

- **Outcome measurement:** Immunological events (Infection and/or vaccination) between 1st and 2nd surveillance
- **Exposure measurement:** Hybrid immunity and vaccine-induced immunity
- **Statistical analysis:** Descriptive analysis

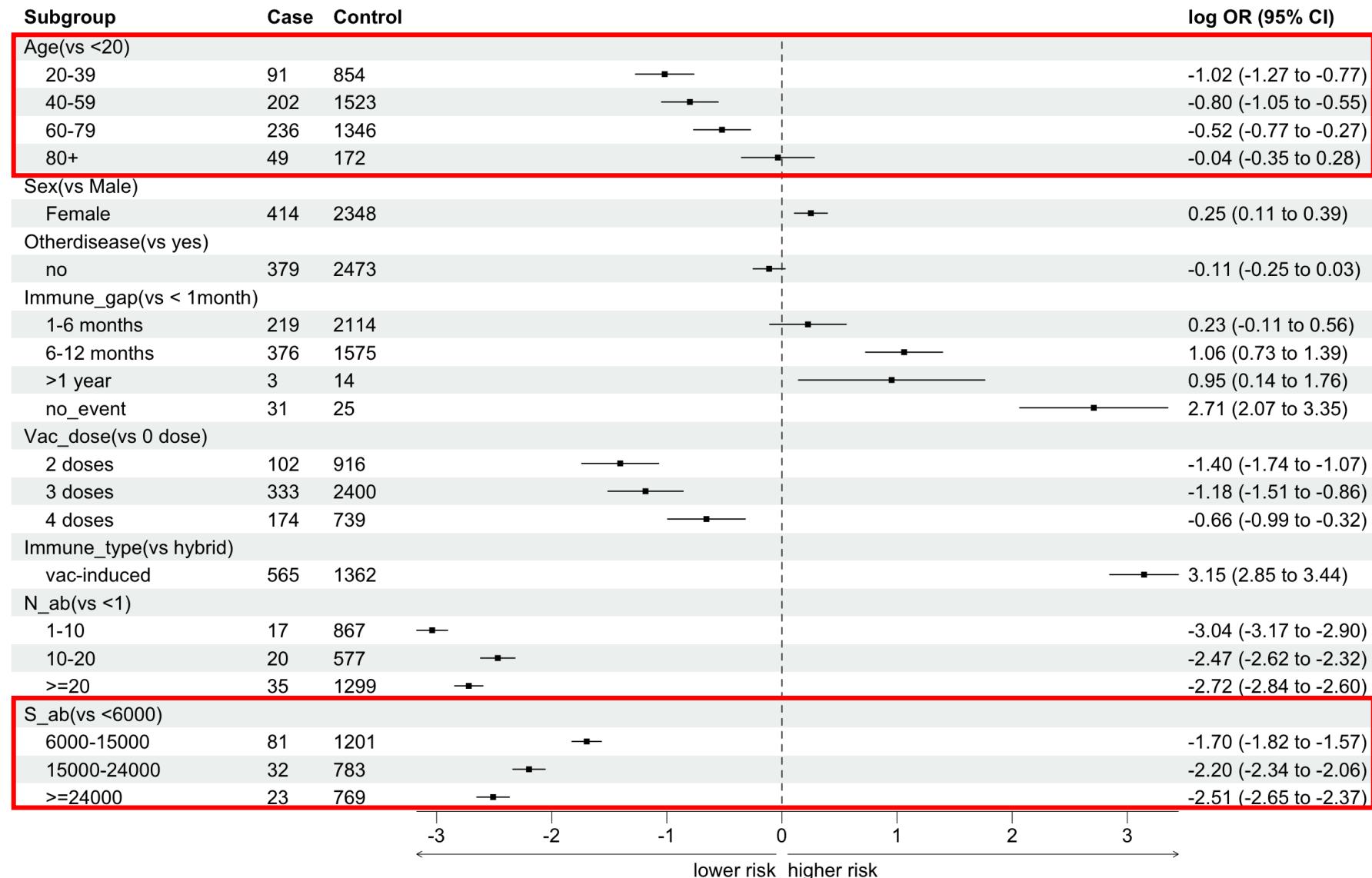
Case control study design



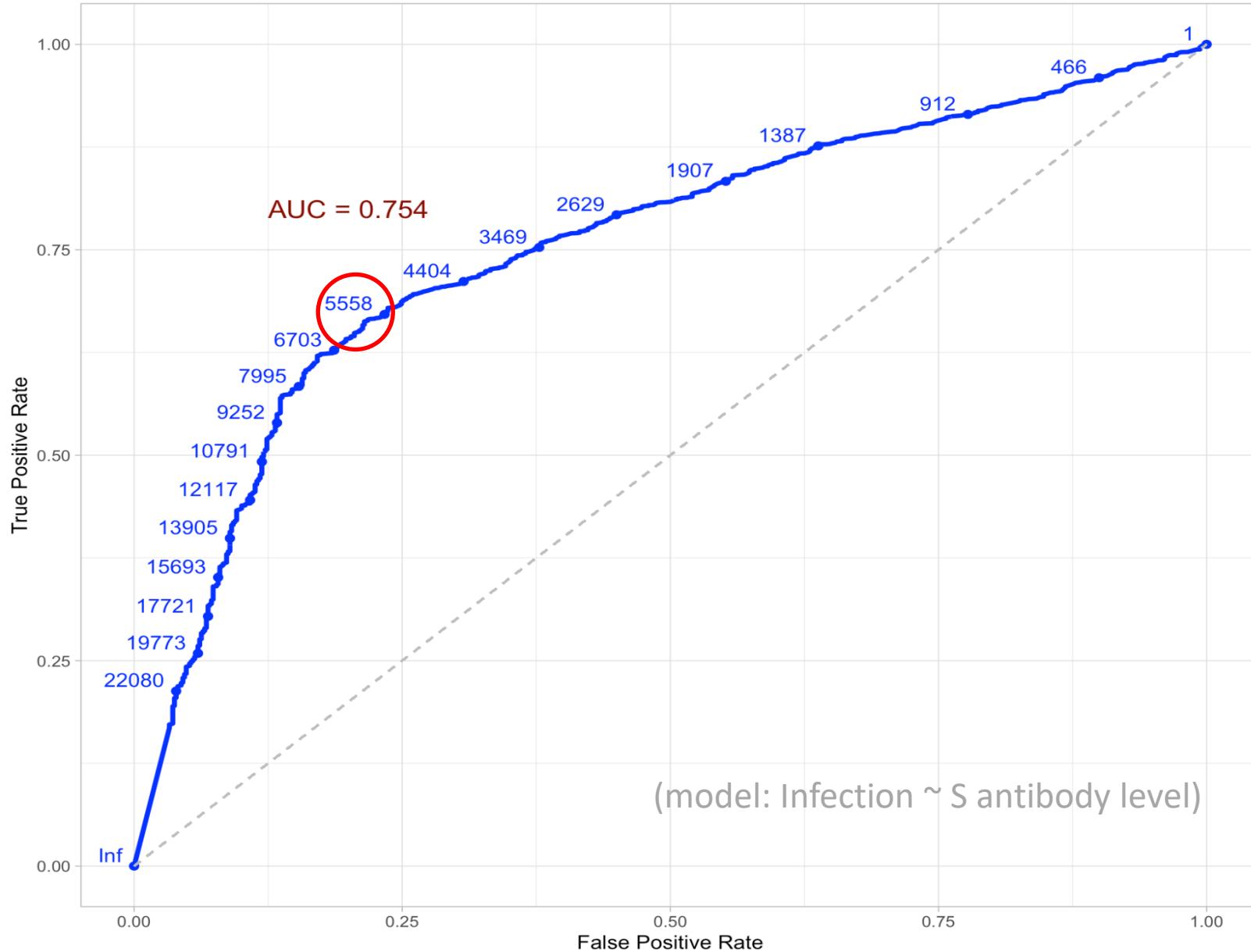
Summary table comparing case and control group characteristics

1st Surveillance - 2nd Surveillance Community-based Data						Chisq-test		
Characteristic	Group	TOTAL (PER)		Control (non-infec)	Case (infec)			
		4,868	-	4,200	-	668	-	P-value
Age	<20	395	8%	305	7%	90	13%	1.152e-12***
	20-39	945	19%	854	20%	91	14%	
	40-59	1,725	35%	1,523	36%	202	30%	
	60-79	1,582	32%	1,346	32%	236	35%	
	80+	221	5%	172	4%	49	7%	
Sex	male	2,106	43%	1,852	44%	254	38%	0.004**
	female	2,762	57%	2,348	56%	414	62%	
Underlying diseases	Yes	1,901	39%	1,623	39%	278	42%	0.2
	No	2,852	59%	2,473	59%	379	57%	
Time since most recent immunology	< 1 month	511	10%	472	11%	39	6%	2.2e-16***
	1-6 months	17	0%	14	0%	3	0%	
	6-12 months	2,333	48%	2,114	50%	219	33%	
	> 1 year	1,951	40%	1,575	38%	376	56%	
	no event	56	1%	25	1%	31	5%	
Vaccination	no vaccine	173	4%	119	3%	54	8%	2.2e-16***
	1 dose	31	1%	26	1%	5	1%	
	2 dose	1,018	21%	916	22%	102	15%	
	3 dose	2,733	56%	2,400	57%	333	50%	
	4 dose	913	19%	739	18%	174	26%	
Previous infection	yes	2,174	45%	2,117	50%	57	9%	2.2e-16***
	no	2,694	55%	2,083	50%	611	91%	
Immunology Type	hybrid-induced	2,678	55%	2,631	63%	47	7%	2.2e-16***
	vaccine-induced	1,927	40%	1,362	32%	565	85%	
	naïve	30	1%	1	0%	29	4%	
S Antibody level category	<6000	1,979	41%	1,447	34%	532	80%	2.2e-16***
	6000-15000	1,282	26%	1,201	29%	81	12%	
	15000-24000	815	17%	783	19%	32	5%	
	≥24000	792	16%	769	18%	23	3%	

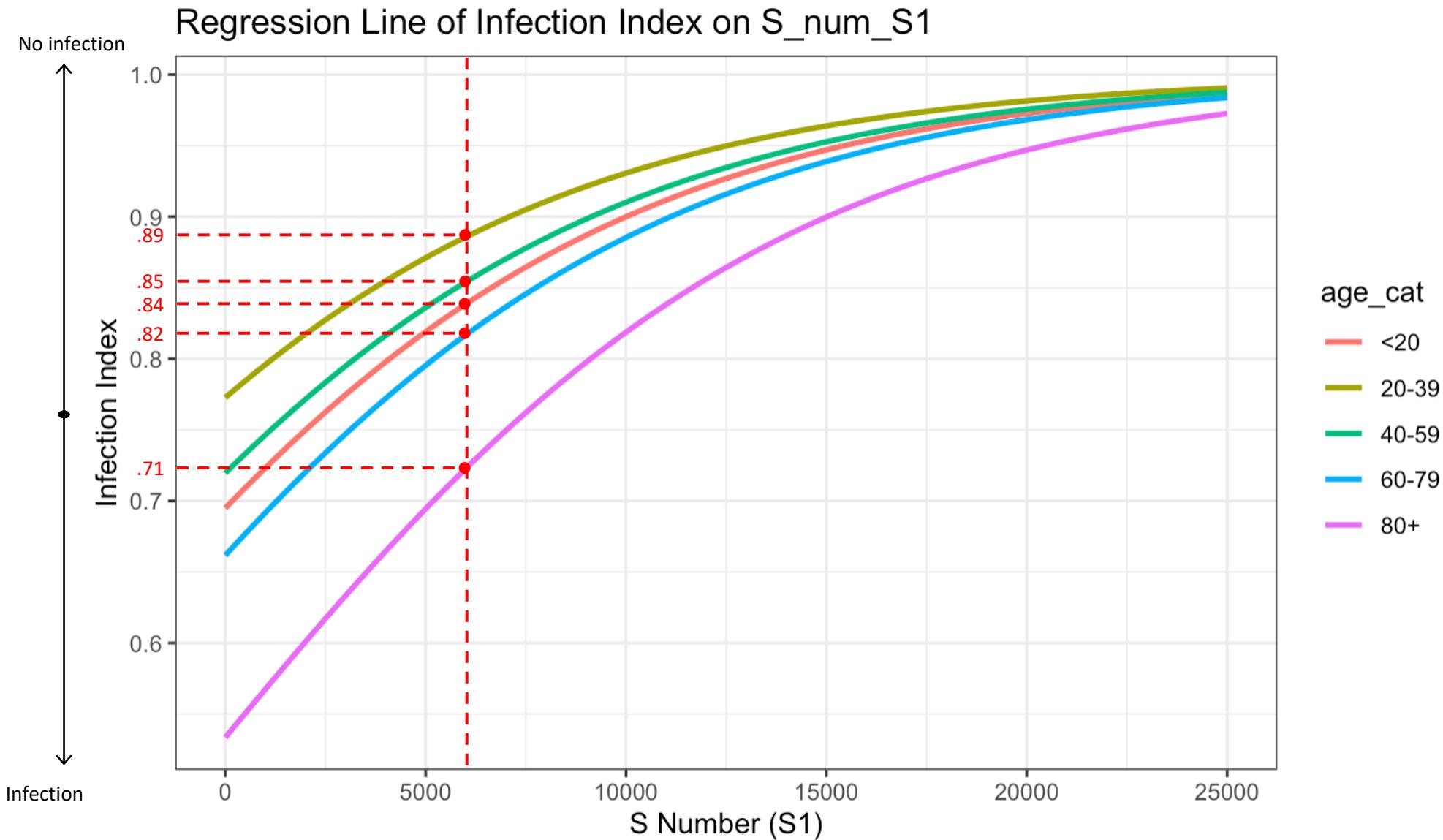
Forest plot showing infection risk odds ratios



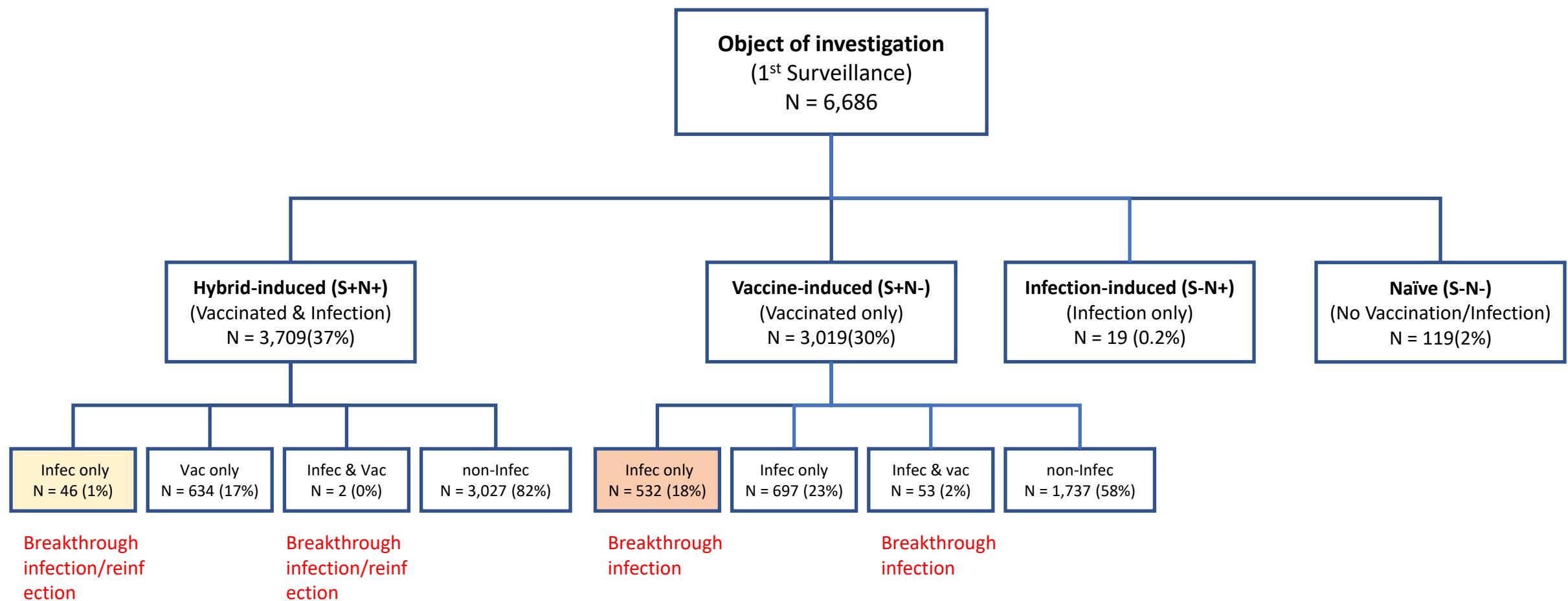
ROC Curve



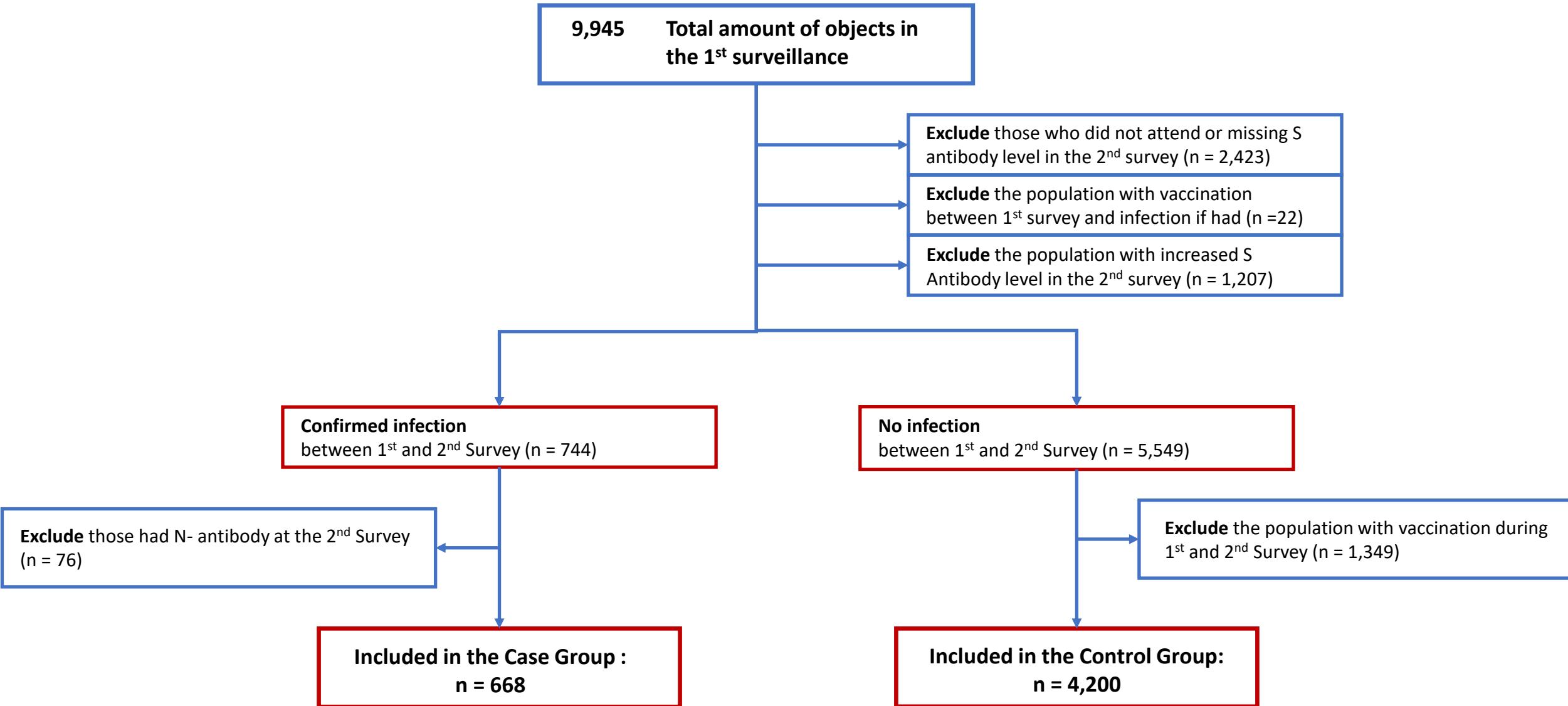
Logistic regression curve (model: Infection ~ S antibody level + Age)



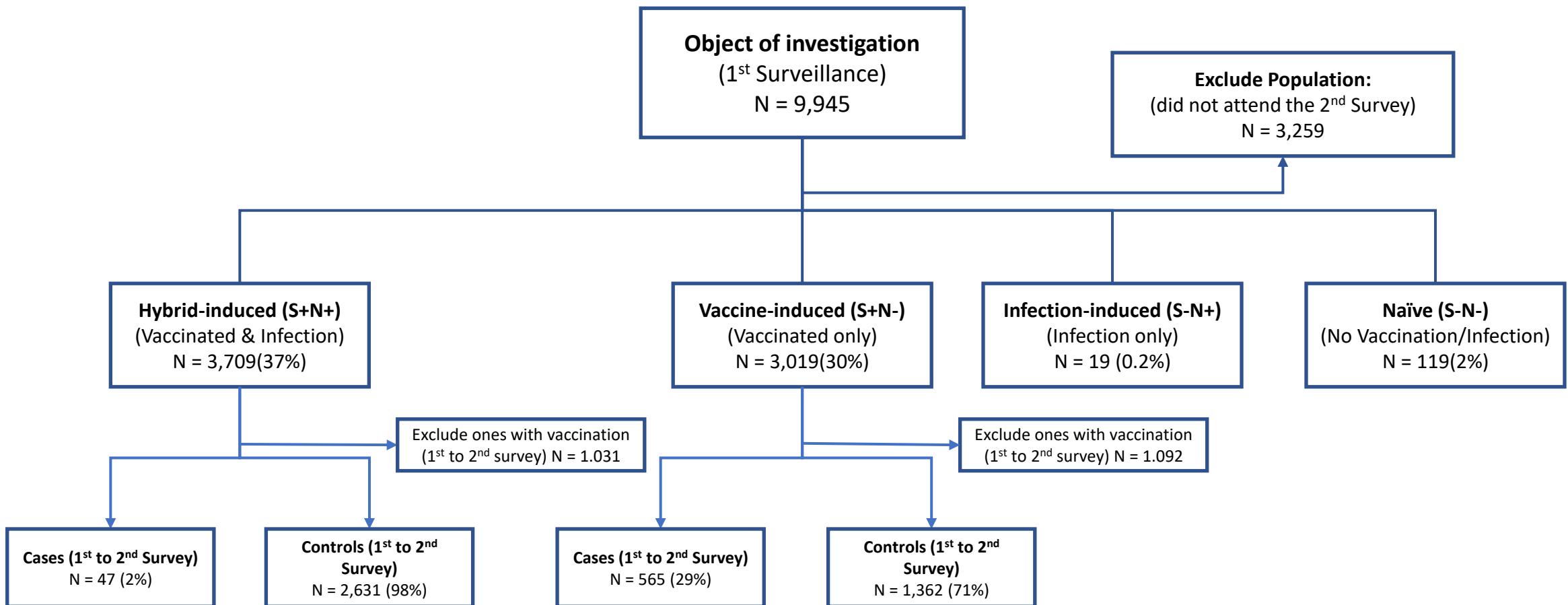
Cohort study design

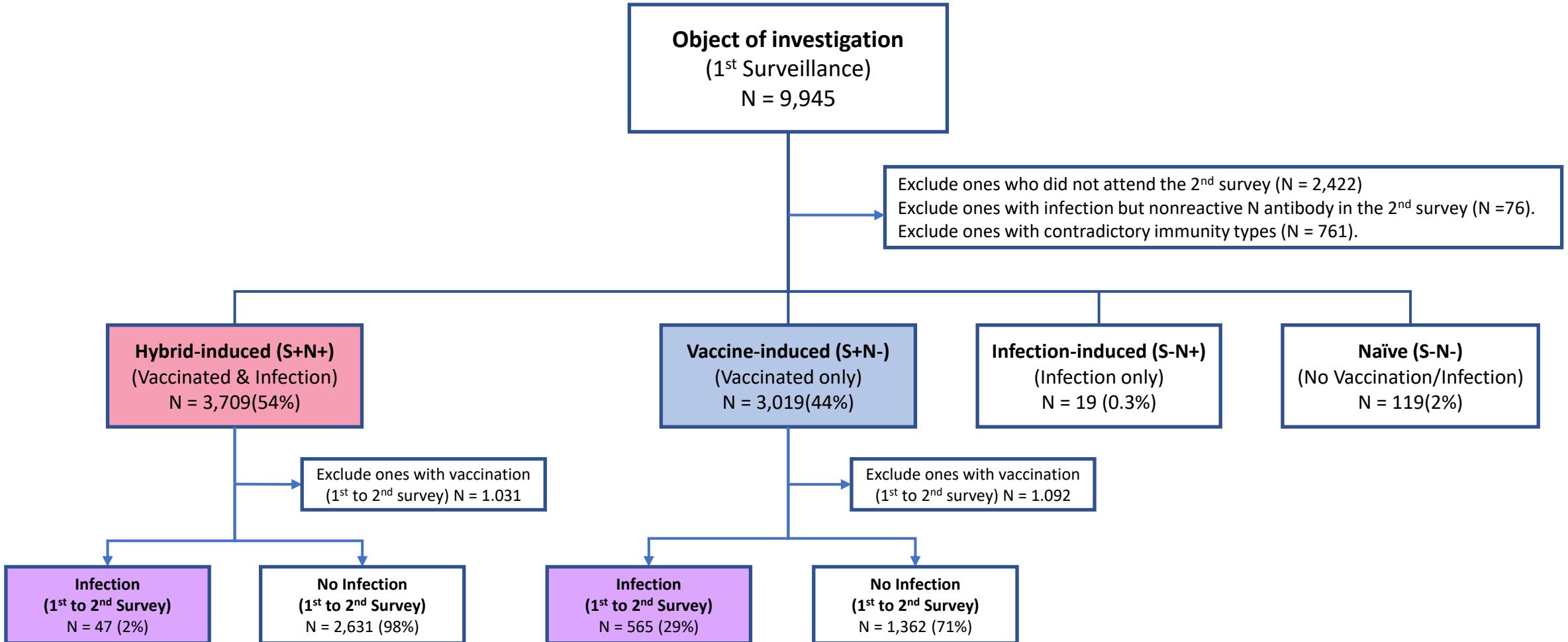


Case control study design



Cohort study design





Summary table of immunology population

			Hybrid-induced (S+N+ Vac&Infec)	Vaccine-induced (S+N- Vac&noInfec)	Chi-Squared test (hybrid v.s. vaccine)
		TOTAL (PER)	NUM (PER)	NUM (PER)	P-value
Total population		6,728 -	3,709 -	3,019 -	
Age	<20	371 5%	186 5%	108 4%	2.2e-16***
	20-39	1,084 16%	690 19%	394 13%	
	40-59	2,169 32%	1,320 36%	849 28%	
	60-79	2,706 39%	1,350 36%	1,356 45%	
	80+	475 7%	163 4%	312 10%	
Sex	male	3,080 45%	1,621 44%	1,391 46%	0.03**
	female	3,716 54%	2,088 56%	1,628 54%	
Underlying diseases	Yes	3,187 46%	1,558 42%	1,584 52%	2.2e-16***
	No	3,431 50%	2,057 55%	1,374 46%	
Time since most recent immunology	< 1 month	686 10%	436 12%	246 8%	2.2e-16***
	1-6 months	3423 50%	2407 65%	1016 34%	
	6-12 months	2603 38%	863 23%	1740 58%	
	> 1 year	20 0%	3 0%	17 1%	
	no event	0 0%	0 0%	0 0%	
Vaccination	no vaccine	134 2%	0 0%	0 0%	2.2e-16***
	1 dose	37 1%	24 1%	13 0%	
	2 dose	1161 17%	793 21%	368 12%	
	3 dose	3645 53%	2127 57%	1518 50%	
	4 dose	1865 27%	765 21%	1100 36%	
1st-2nd events	infec	608 9%	46 1%	532 18%	2.2e-16***
	vac	1331 19%	634 17%	697 23%	
	infec-vac	55 1%	2 0%	53 2%	
	no event	4764 69%	3027 82%	1737 58%	

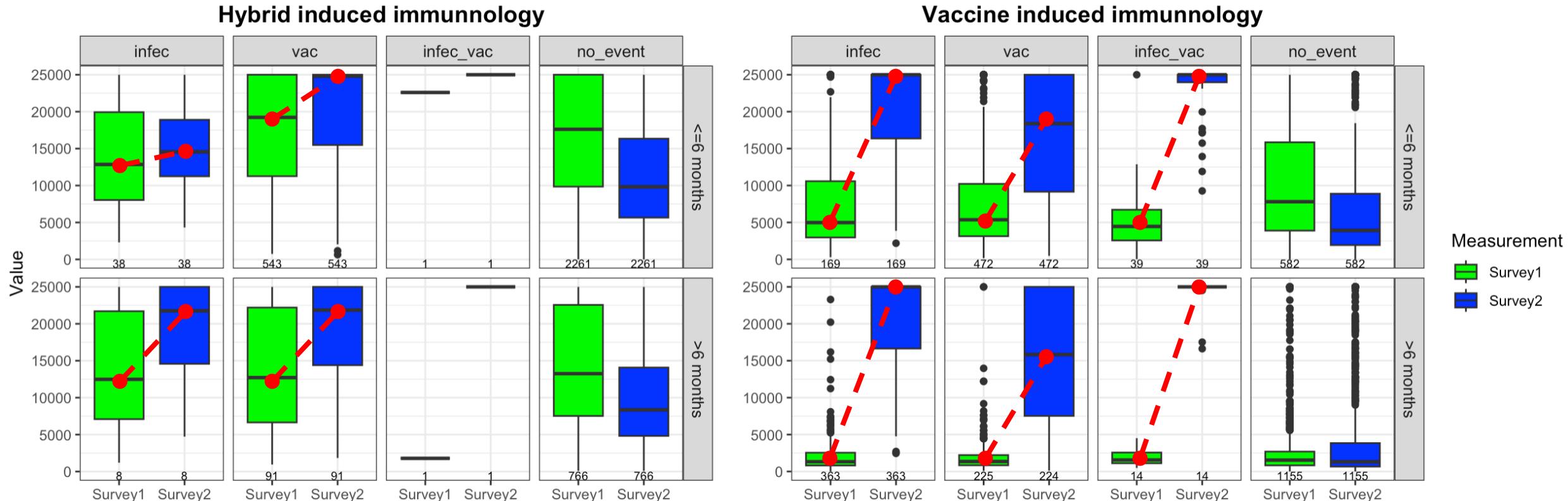
Linear regression of the change of S Antibody level

Variables	Unadjusted Analysis			Adjusted Analysis		
	Beta	95% CI	p-value	Beta	95% CI	p-value
(Intercept)	-833.6	[-1883,215.9]	0.119	-265.3	[-1043.6,513]	0.504
ImmuneType(Hybrid-induced)						
Vaccine-induced	1713.7	[1322.3,2105]	< 2e-16 ***	1709.1	[1318.9,2099.3]	< 2e-16 ***
Naïve	1752.6	[-2058.7,5563.8]	0.367	1559.2	[-2240,5358.4]	0.421
Event(None)						
Infection	14424.8	[13868.1,14981.6]	< 2e-16 ***	14418.0	[13861.8,14974.2]	< 2e-16 ***
Vaccination	9364.6	[8960.4,9768.7]	< 2e-16 ***	9321.7	[8920.4,9723.1]	< 2e-16 ***
Infection&Vaccination	17961.4	[16331,19591.8]	< 2e-16 ***	17923.4	[16294.6,19552.1]	< 2e-16 ***
TimeSinceLatestImmunology	8.6	[6.5,10.8]	4.05e-15 ***	8.9	[6.8,11.1]	3.13e-16 ***
Previous S ab level	0.6	[0.6,0.6]	< 2e-16 ***	0.6	[0.6,0.6]	< 2e-16 ***
Age	2.6	[-8.1,13.3]	0.63	-3.3	[-12.3,5.6]	0.465
Gender(Male)						
Female	23.8	[-275.3,322.9]	0.876			
Edu(PrimaryScholl)						
Middle/High School	59.2	[-392.3,510.7]	0.797			
Postsecondary	326.6	[-174.2,827.4]	0.201			
Otherdisease(Yes)						
No	231.3	[-120.3,582.9]	0.197			

Adjusted: $2^{nd} \text{Sab level} = \beta_0^* + \beta_1^* * \text{ImmuneType} + \beta_2^* * \text{Event} + \beta_3^* * \text{TimeSinceLatestImmune} + \beta_4^* * 1^{st} \text{Sab level} + \beta_5^* * \text{Age} + \epsilon^*$

*The F statistic for the hypothesis is 1.21 with df = 4, the p value is .30 and the reduced model is accepted

Box plot comparing S antibody level by latest immunology events



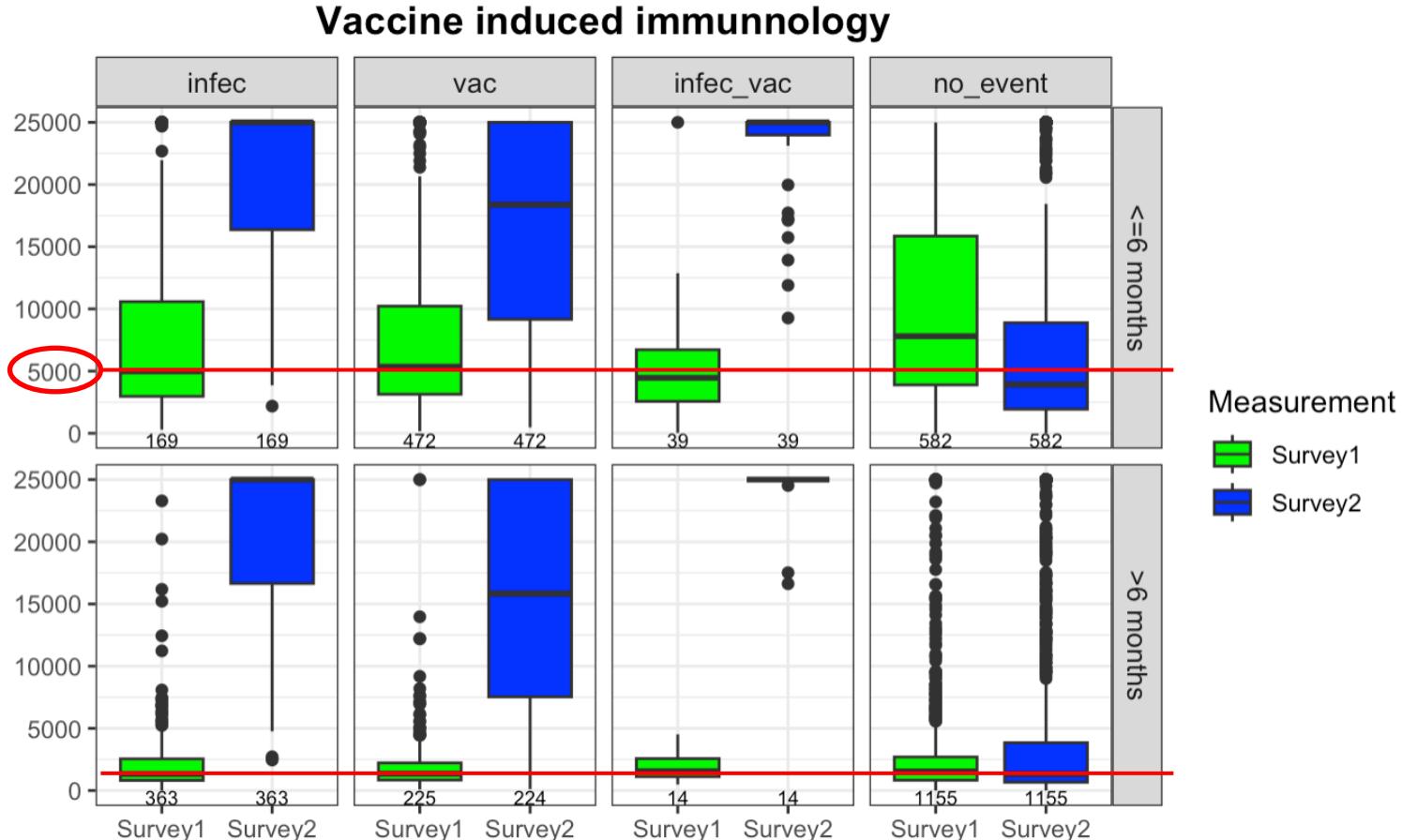
- The vaccine-induced population had a bigger boost in their S antibody levels than hybrid-induced ones, no matter if they were vaccinated, infected, or both.

Summary table quantifying S antibody level changes between 1st and 2nd surveillance

Immunology	Vac Gap	Events	Population	1st Surveillance		2nd Surveillance		PER Comparison (/times)
					Median Range		Median Range	
TOTAL	-	-	6,728	8985 [2737, 10081]		10150 [3940, 21141]		13%
Vaccine induced population	All Time	infection	532	2069 [993,4522]		25000 [16544,25000]		1109% 61.7
		vaccination	697	3695 [1673,8103]		17333 [8983,25000]		369% 11.3
		infection & vaccination	53	3198 [1953,5027]		25000 [24524,25000]		682% -
		no event	1,737	2352 [1073,6284]		1923 [843,6570]		-18% 0.4
	<6 month	infection	169	4978 [2967,10582]		25000 [16368,25000]		402% 30.3
		vaccination	472	5361 [3137,10221]		18376 [9158,25000]		243% 8.4
		infection & vaccination	39	4458 [2566,6720]		25000 [23978,25000]		461% -
		no event	582	7808 [3891,15852]		3918 [1931,8886]		-50% 1.1
	>6 months	infection	363	1326 [816,2547]		25000 [16648,25000]		1785% 24.0
		vaccination	225	1355 [842,2223]		15837 [7531,25000]		1069% 14.9
		infection & vaccination	14	1562 [1116,2568]		25000 [25000,25000]		1501% -
		no event	1,155	1539 [830,2698]		1317 [664,3842]		-14% 0.4

- According to the summary table, the increase rate for the vaccine-induced group, regardless of the type of immunological events, is at least eight times higher than that observed in the hybrid-induced group.

Box plot comparing S antibody level by latest immunology events



- The longer the gap since the last immunological event, the lower the initial level of S antibodies. Additionally, the greater the boost—regardless of whether it's due to infection, vaccination, or both—indicating that after such events, the depleted S antibody levels recover rapidly.

Summary table quantifying S antibody level changes between 1st and 2nd surveillance

Immunology	Immune gap	Events	Population	1st Surveillance		2nd Surveillance		PER	PER Comparison (/times)
				#REF!	Median Range	Median Range	PER		
TOTAL	-	-	#REF!	8985 [2737, 10081]		10150 [3940, 21141]		13%	-
Vaccine induced population	All Time	infection	532	2069 [993,4522]		25000 [16544,25000]		1109%	
		vaccination	697	3695 [1673,8103]		17333 [8983,25000]		369%	
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		no event	1,737	2352 [1073,6284]		1923 [843,6570]		18%	
	<6 month	infection	169	4978 [2967,10582]		25000 [16368,25000]		402%	reference
		vaccination	472	5361 [3137,10221]		18376 [9158,25000]		243%	reference
		infection & vaccination	39	4458 [2566,6720]		25000 [23978,25000]		461%	reference
		no event	582	7808 [3891,15852]		3918 [1931,8886]		-50%	reference
	>6 months	infection	363	1326 [816,2547]		25000 [16648,25000]		1785%	4.4
		vaccination	225	1355 [842,2223]		15837 [7531,25000]		1069%	4.4
		infection & vaccination	14	1562 [1116,2568]		25000 [25000,25000]		1501%	3.3
		no event	1,155	1539 [830,2698]		1317 [664,3842]		-14%	0.3

- According to the summary table, the increase rate for over 6 months , regardless of the type of immunological events, is at least eight times higher than that observed in the hybrid-induced group.

Discussion

➤ Case control study design:

- Population Spike (S) antibody level threshold can guide appropriate vaccination interval by age group.
- Age presents a clear correlation with COVID-19 infection risk, indicating that the age 80+ groups face the highest risk than younger groups (89% versus 71%)

➤ Cohort study design:

- Overall, the hybrid-induced population had a lower likelihood of infection, associated with higher Spike (S) antibody levels.
- The Spike (S) antibody level four months post-exposure is primarily influenced by immune type, subsequent immunological events, the time elapsed since the most recent immunological event, and the current Spike antibody level. Among these factors, **the current Spike antibody level and subsequent immunological events** are the most dominant, accounting for the majority of the variance in the model.
- Compared to the hybrid-induced population, the naive and vaccine-only induced populations respond more effectively to an additional vaccine, achieving a significantly faster increase in Spike antibody levels.

Discussion

➤ Limitations:

- The surveillance data was not collected through a scientifically randomized design; therefore, the validity of comparisons and analyses may be completely compromised.
- From a logical standpoint, it's possible that individuals exhibiting both S and N antibodies have been exposed solely through infection. However, given their minimal representation in the sample, the cohort study has categorized them as hybrid-induced for the purposes of analysis.

➤ Implications:

- If the survey had been conducted in the early stages of the COVID-19 pandemic, we would be able to analyze the effectiveness of vaccines against various variants of the virus, not just Omicron.
- More frequent continuous surveillance data allows us to better quantify the protective efficacy of infection and vaccination by measuring the levels of S antibodies.

Reference

- [1] <https://ourworldindata.org/covid-vaccinations>
- [2] Amjadi, M. F., & O'Connell, S. E. (2021). Specific COVID-19 symptoms correlate with high antibody levels against SARS-CoV-2. *AAI*.
- [3] Imai, K., Kitagawa, Y., Tabata, S., Kubota, K., Nagura-Ikeda, M., Matsuoka, M., Miyoshi, K., Sakai, J., & all authors. (2021). Antibody response patterns in COVID-19 patients with different levels of disease severity in Japan. *Journal of Medical Virology*.
- [4] Goldblatt, D., Fiore-Gartland, A., Johnson, M., Hunt, A., Bengt, C., Zavadska, D., Snipe, H. D., Brown, J. S., Workman, L., Zar, H. J., Montefiori, D., Shen, X., Dull, P., Plotkin, S., Siber, G., & Ambrosino, D. (2021). Towards a population-based threshold of protection for COVID-19 vaccines. *Vaccine*.

Appendix

More Reference (relationship between S and N antibody levels)

- [1] <https://ourworldindata.org/covid-vaccinations>
- [2] Amjadi, M. F., & O'Connell, S. E. (2021). Specific COVID-19 symptoms correlate with high antibody levels against SARS-CoV-2. *AAI*.
- [3] Imai, K., Kitagawa, Y., Tabata, S., Kubota, K., Nagura-Ikeda, M., Matsuoka, M., Miyoshi, K., Sakai, J., & all authors. (2021). Antibody response patterns in COVID-19 patients with different levels of disease severity in Japan. *Journal of Medical Virology*.
- [4] Goldblatt, D., Fiore-Gartland, A., Johnson, M., Hunt, A., Bengt, C., Zavadská, D., Snipe, H. D., Brown, J. S., Workman, L., Zar, H. J., Montefiori, D., Shen, X., Dull, P., Plotkin, S., Siber, G., & Ambrosino, D. (2021). Towards a population-based threshold of protection for COVID-19 vaccines. *Vaccine*.

Model Comparison

Baseline model: $infec = \beta_0 + \beta_1 * Sab_{level} + \epsilon$

model1: $infec = \beta_0 + \beta_1 * Sab_{level} + \beta_2 * age + \epsilon$

model2: $infec = \beta_0 + \beta_1 * Sab_{level} + \beta_2 * sex + \epsilon$

model3: $infec = \beta_0 + \beta_1 * Sab_{level} + \beta_2 * immune\ type + \epsilon$

model4: $infec = \beta_0 + \beta_1 * Sab_{level} + \beta_2 * latest\ immune\ gap + \epsilon$

Analysis of Deviance Table

Model 1: Fail ~ S_num_S1

Model 2: Fail ~ S_num_S1 + age

Model 3: Fail ~ S_num_S1 + sex

Model 4: Fail ~ S_num_S1 + induced_index

Model 5: Fail ~ S_num_S1 + latest_immunology_cat

Resid. Df Resid. Dev Df Deviance Pr(>Chi)

1 1644 2111.3

2 1643 2111.2 1 0.0666 0.79634

3 1643 2111.3 0 -0.0666

4 1642 2107.8 1 3.4706 0.06247 .

5 1641 2104.2 1 3.6019 0.05771 .

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Model Comparison

Baseline model: $infec = \beta_0 + \beta_1 * Sab_{level} + \epsilon$

model5: $infec = \beta_0 + \beta_1 * Sab_{level} + \beta_2 * immune\ type + \beta_3 * latest\ immune\ gap + \epsilon$

Analysis of Deviance Table

```
Model 1: Fail ~ S_num_S1
Model 2: Fail ~ S_num_S1 + latest_immunology_cat + induced_index
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1       1644     2111.3
2       1640     2100.5  4   10.728   0.0298 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

model6: $infec = \beta_0 + \beta_1 * Sab_{level} + \beta_2 * immune\ type + \beta_3 * latest\ immune\ gap + \beta_4 * age + \epsilon$

model7: $infec = \beta_0 + \beta_1 * Sab_{level} + \beta_2 * immune\ type + \beta_3 * latest\ immune\ gap + \beta_4 * sex + \epsilon$

full model: $infec = \beta_0 + \beta_1 * Sab_{level} + \beta_2 * immune\ type + \beta_3 * latest\ immune\ gap + \beta_4 * age + \beta_5 * sex + \epsilon$

Analysis of Deviance Table

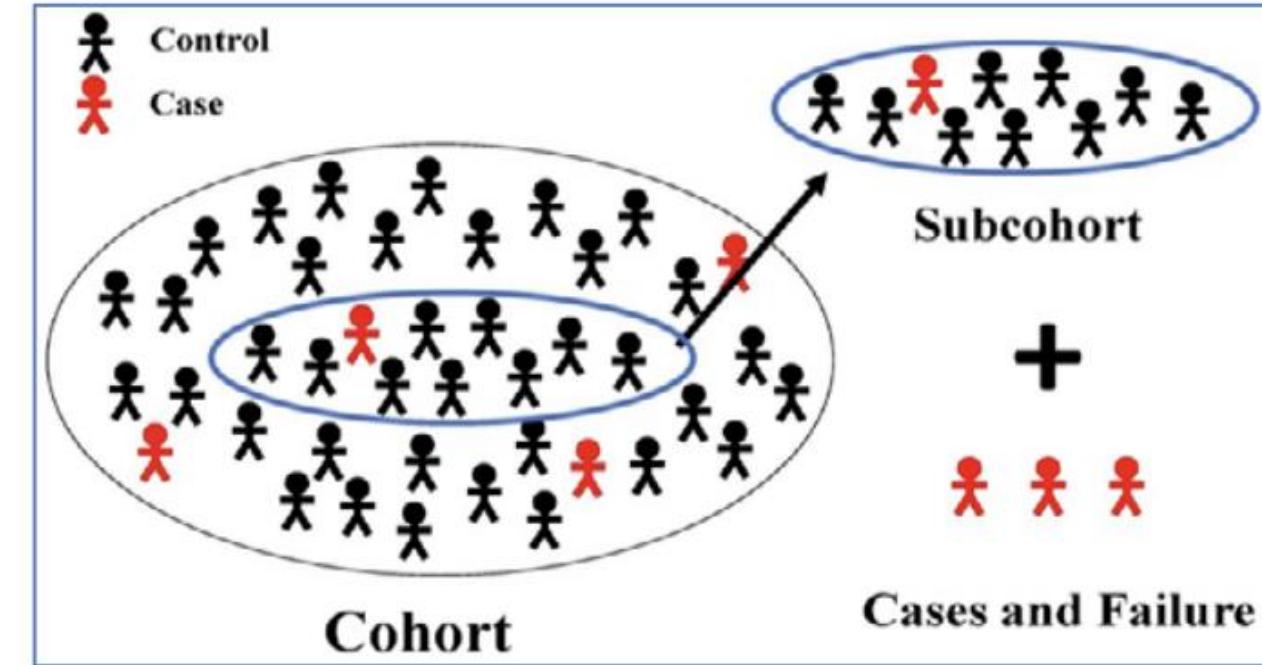
```
Model 1: Fail ~ S_num_S1 + latest_immunology_cat + induced_index
Model 2: Fail ~ S_num_S1 + latest_immunology_cat + induced_index + age
Model 3: Fail ~ S_num_S1 + latest_immunology_cat + induced_index + sex
Model 4: Fail ~ S_num_S1 + latest_immunology_cat + induced_index + sex +
  age
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1       1640     2100.5
2       1639     2100.5  1  0.00102352   0.9745
3       1639     2100.5  0  0.00008305
4       1638     2100.5  1  0.00105615   0.9741
```

Methodology

Nested Case-control Study (NCC)

Unbalanced case-control data refer to a situation in epidemiological and medical research where the number of cases does not match the number of controls.

To maximize statistical efficiency and minimize bias, for each case, a subset of controls is selected from the same cohort. Controls are often matched to cases on various factors like age, gender, or other characteristics to ensure comparability.



{Epi} in R, by B. Carstensen and M. Plummer, Mar 30, 2024

Raw Case-control cohort

	<20	20-39	40-59	60-79	80+
case	69	87	200	236	49
control	227	820	1477	1305	165

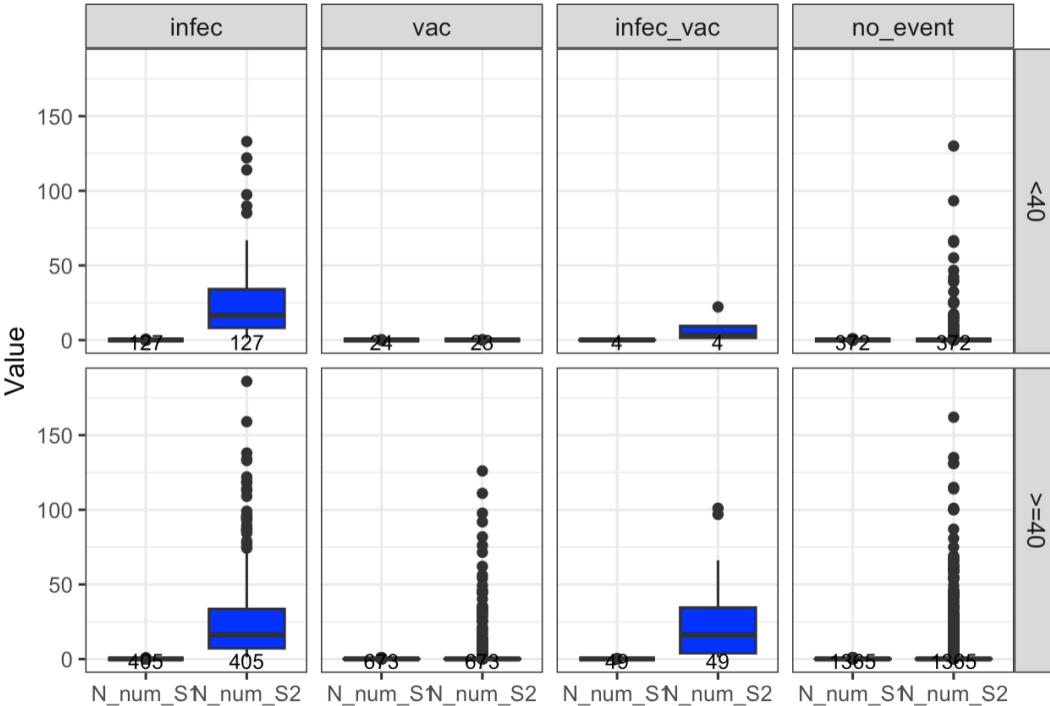


Nested Case-control design cohort

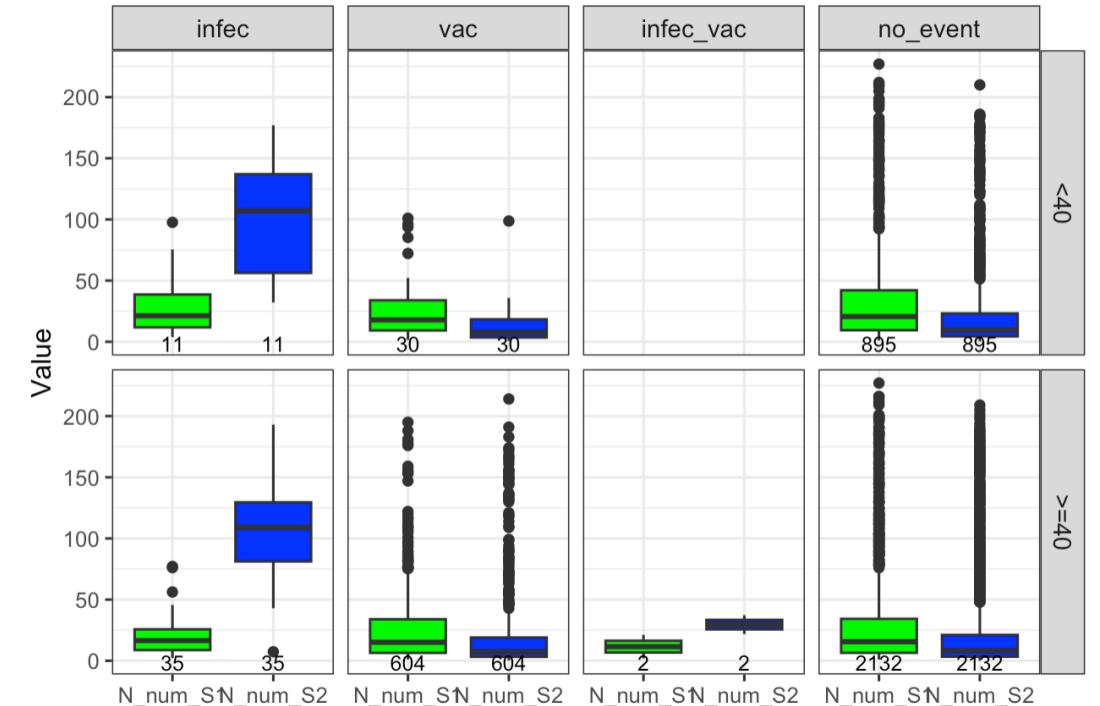
	<20	20-39	40-59	60-79	80+
case	69	86	199	235	48
control	137	172	397	469	96

Figure 2: Box plots for N antibody level grouped by Age and later events

Vaccine induced vaccination



Hybrid induced vaccination



Measurement

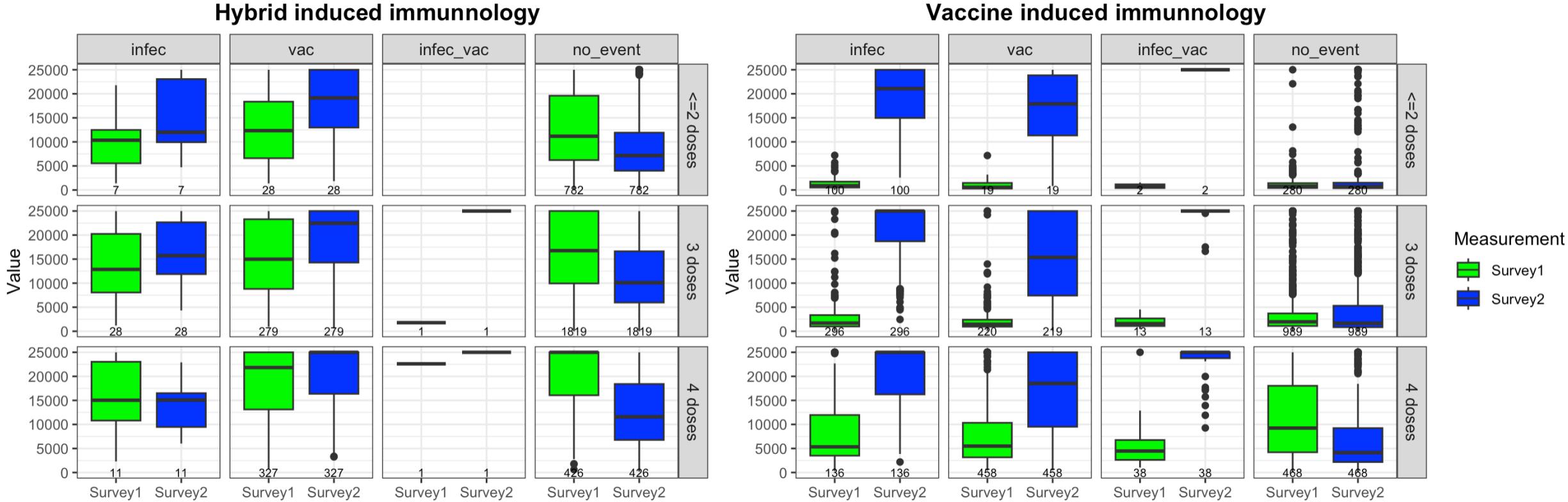
- █ N_num_S1
- █ N_num_S2

- The trends in N antibody levels are not well-defined, as these antibodies are typically produced only in response to an infection.

Table 3: Quantification table for the difference of N antibody level from 1st to 2nd Surveillance

Immunology	Age	Events	Population	1st Surveillance		2nd Surveillance		PER
				Median	Range	Median	Range	
TOTAL	-	-	6,728	5.16	[0.08, 19.13]	4.52	[0.08, 16.00]	-12.32%
Vaccine induced	TOTAL	TOTAL	3,019	0.08	-	0.07	[0.07, 5.32]	-12.5%
	<40	infection	127	0.08	-	16.70	[8.19, 34.15]	20775.0%
		vaccination	24	0.08	-	0.07	-	-12.5%
		infection & vaccination	4	0.09	[0.08, 0.10]	3.37	[1.48, 9.45]	3864.7%
		no event	372	0.08	-	0.07	-	-12.5%
	>=40	infection	405	0.08	-	16.50	[7.19, 33.60]	20525.0%
		vaccination	673	0.08	-	0.07	-	-12.5%
		infection & vaccination	49	0.08	-	16.30	[3.93, 34.50]	20275.0%
		no event	1,365	0.08	-	0.07	-	-12.5%
Hybrid induced	TOTAL	TOTAL	3,709	16.60	[7.14, 36.30]	8.61	[3.61, 22.20]	-48.1%
	<40	infection	11	21.20	[11.80, 38.65]	107.00	[56.25, 137.00]	404.7%
		vaccination	30	17.85	[9.23, 33.93]	7.72	[3.48, 18.38]	-56.8%
		infection & vaccination	-	-	-	-	-	-
		no event	895	30.60	[9.45, 42.10]	9.71	[4.38, 23.15]	-68.3%
	>=40	infection	35	16.50	[8.74, 25.70]	8.74	[81.20, 129.50]	-47.1%
		vaccination	604	15.10	[6.45, 33.93]	6.45	[3.23, 19.00]	-57.3%
		infection & vaccination	2	11.53	[6.70, 16.37]	29.55	[25.68, 33.43]	156.3%
		no event	2,132	15.60	[6.49, 34.25]	6.49	[3.35, 21.13]	-58.4%

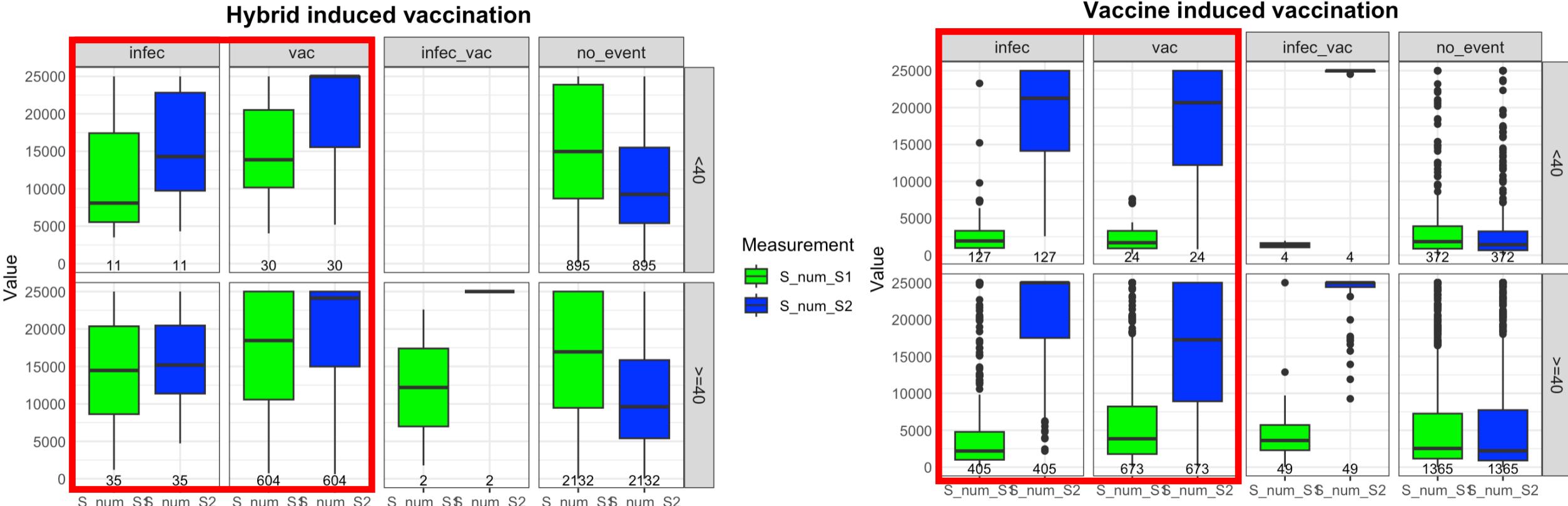
Box plot comparing S antibody level changes between 1st and 2nd surveillance



Summary table quantifying S antibody level changes between 1st and 2nd surveillance

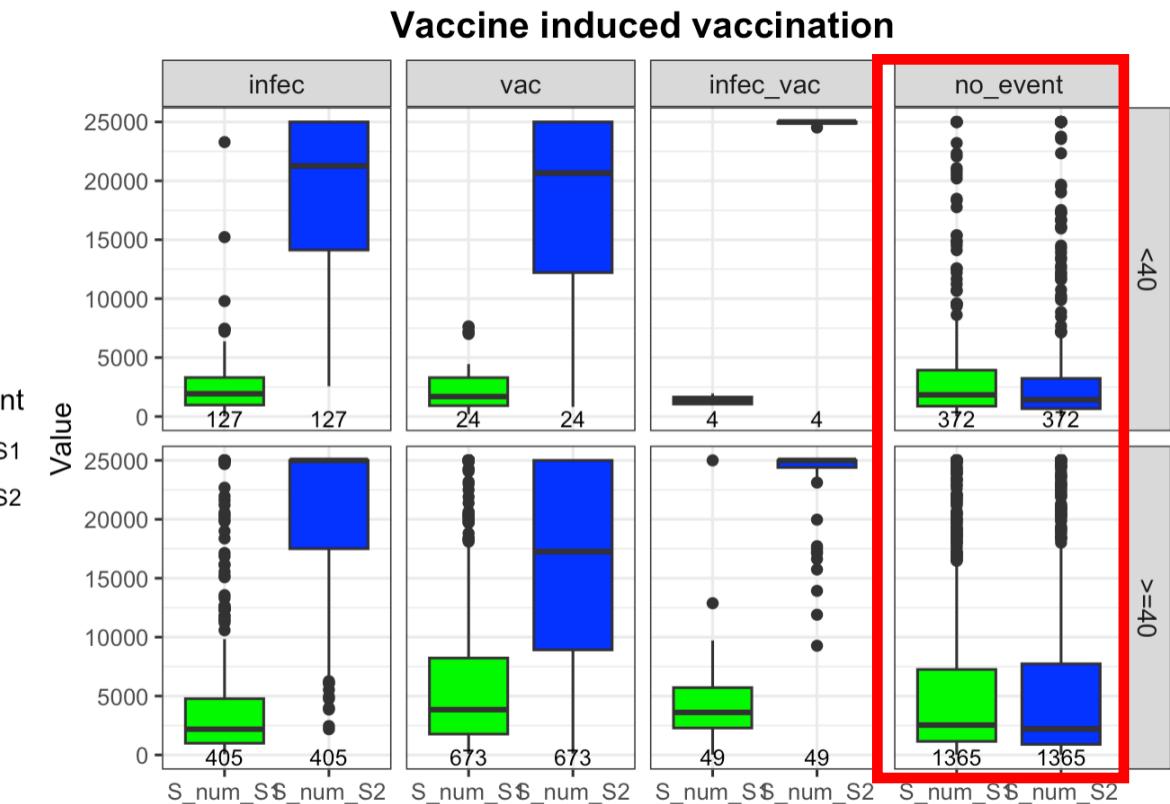
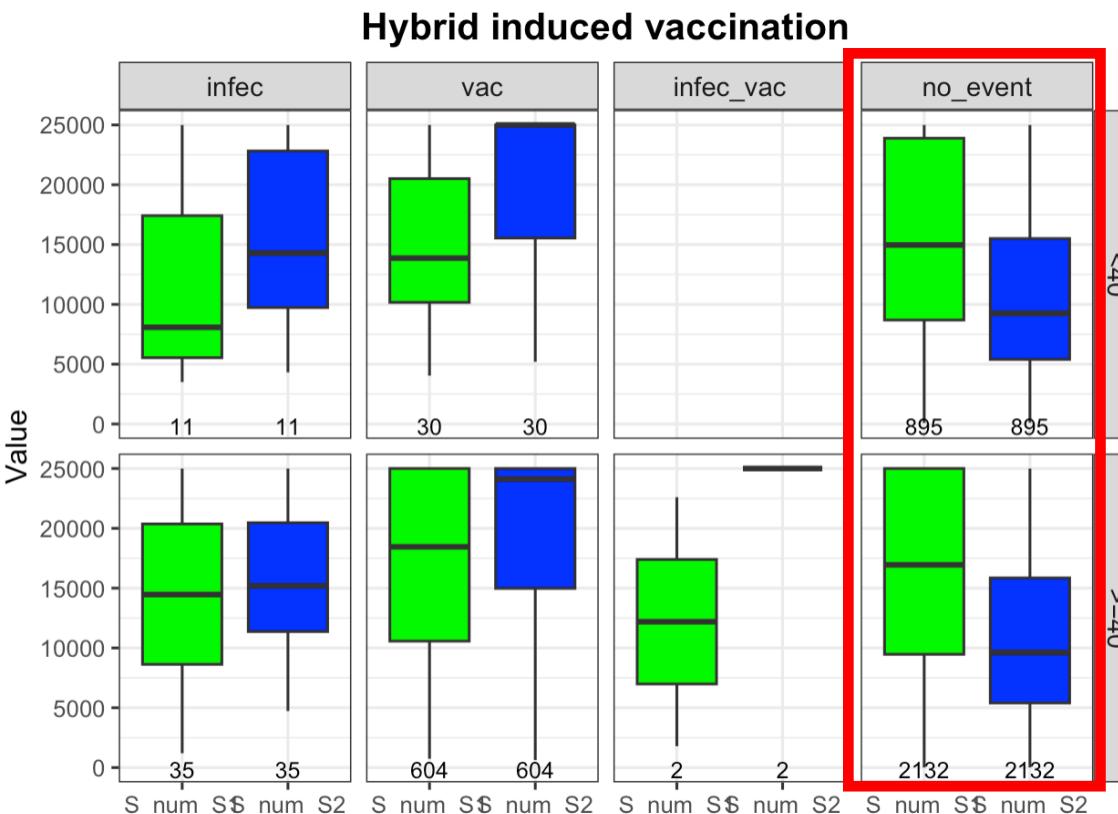
Immunology	Age	Events	Population	1st Surveillance		2nd Surveillance	
				Median	Range	Median	Range
TOTAL	-	-	6,728	8985 [2737, 10081]		10150 [3940, 21141]	13%
Vaccine induced population	All doses	infection	532	2069 [993,4522]		25000 [16544,25000]	1109%
		vaccination	697	3695 [1673,8103]		17333 [8983,25000]	369%
		infection & vaccination	53	3198 [1953,5027]		25000 [24524,25000]	682%
		no event	1,737	2352 [1073,6284]		1923 [843,6570]	-18%
	<=2 doses	infection	100	871 [505,1726]		21082 [14969,25000]	2322%
		vaccination	19	560 [288,1462]		17893 [11336,23846]	3095%
		infection & vaccination	2	784 [405,1163]		25000 [25000,25000]	3088%
		no event	280	790 [408,1415]		692 [377,1501]	-12%
	3 doses	infection	296	1704 [996,3354]		25000 [18710,25000]	1367%
		vaccination	220	1449 [950,2402]		15358 [7414,25000]	960%
		infection & vaccination	13	1582 [1082,2660]		25000 [25000,25000]	1480%
		no event	989	1959 [1092,3702]		1656 [837,5298]	-15%
	4 doses	infection	136	5336 [3506,11956]		25000 [16248,25000]	369%
		vaccination	458	5484 [3156,10333]		18521 [9514,25000]	238%
		infection & vaccination	38	4468 [2620,6750]		25000 [23768,25000]	460%
		no event	468	9237 [4211,18032]		4129 [2179,9233]	-55%
Hybrid induced population	All doses	infection	46	12827 [8038,20484]		15133 [11249,21662]	18%
		vaccination	634	18231 [10465,25000]		24179 [15048,25000]	33%
		infection & vaccination	2	12193 [6990,17396]		25000 [25000,25000]	105%
		no event	3,027	16392 [9177,25000]		9507 [5402,15690]	-42%
	<=2 doses	infection	7	10339 [5546,12481]		12005 [9934,23061]	16%
		vaccination	28	12337 [6608,18357]		19141 [12986,25000]	55%
		infection & vaccination	-	--		--	-
		no event	782	11184 [6215,19598]		7167 [4000,11918]	-36%
	3 doses	infection	28	12857 [8068,20242]		15717 [11879,22655]	22%
		vaccination	279	14981 [8806,23293]		22459 [14286,25000]	50%
		infection & vaccination	1	1786 [1786,1786]		25000 [25000,25000]	1300%
		no event	1,819	16756 [9952,25000]		10093 [5973,16626]	-40%
	4 doses	infection	11	15030 [10803,23027]		15071 [9472,16500]	0%
		vaccination	327	21834 [13120,25000]		25000 [16367,25000]	15%
		infection & vaccination	1	22600 [22600,22600]		25000 [25000,25000]	11%
		no event	426	25000 [16069,25000]		11590 [6777,18406]	-54%

Box plot comparing S antibody level changes between 1st and 2nd surveillance



- The vaccine-induced population had a bigger boost in their S antibody levels than hybrid-induced ones, no matter if they were vaccinated, infected, or both.

Box plot comparing S antibody level changes between 1st and 2nd surveillance



- If no events occur, the rate of decrease in S antibody levels in the vaccine-induced population is lower compared to the hybrid-induced group.

Summary table quantifying S antibody level changes between 1st and 2nd surveillance

Immunology	Age	Events	Population	1st Surveillance		2nd Surveillance		PER Comparison (/times)
					Median Range		Median Range	
TOTAL	-	-	6,728	8985 [2737, 10081]		10150 [3940, 21141]	13%	-
Vaccine induced population	All Age	infection	532	2069 [993, 4522]		25000 [16544, 25000]	1108%	61.6
		vaccination	697	3695 [1673, 8103]		17333 [8983, 25000]	369%	11.3
		infection & vaccination	53	3198 [1953, 5027]		25000 [24524, 25000]	682%	6.5
		no event	1,737	2352 [1073, 6284]		1923 [843, 6750]	-18%	0.4
	<40	infection	127	1932 [975, 3056]		21272 [14127, 25000]	1001%	13.0
		vaccination	24	1692 [919, 3297]		20670 [12212, 25000]	1122%	14.0
		infection & vaccination	4	1312 [1058, 1645]		25000 [24881, 25000]	1805%	-
		no event	372	1839 [875, 3928]		1421 [665, 3232]	-23%	0.6
	>=40	infection	405	2188 [997, 4774]		25000 [17503, 25000]	1043%	207.2
		vaccination	673	3847 [1773, 8222]		17261 [8920, 25000]	349%	11.4
		infection & vaccination	49	3610 [2290, 5713]		25000 [24397, 25000]	593%	5.6
		no event	1,365	2534 [1153, 7256]		2207 [899, 7736]	-13%	0.3
Hybrid induced population	All Age	infection	46	12827 [8039, 20485]		15133 [11249, 21662]	18%	reference
		vaccination	634	18231 [10465, 25000]		24179 [15048, 25000]	33%	reference
		infection & vaccination	2	12193 [6989, 17397]		25000 -	105%	reference
		no event	3,027	16392 [9177, 25000]		9507 [5402, 15690]	-42%	reference
	<40	infection	11	8082 [5546, 17416]		14287 [9736, 22825]	77%	reference
		vaccination	30	13867 [10167, 20514]		25000 [15549, 25000]	80%	reference
		infection & vaccination	-	- - -		- - -	-	reference
		no event	895	14961 [8695, 23892]		9253 [5403, 15506]	-38%	reference
	>=40	infection	35	14466 [8632, 20363]		15194 [11372, 20467]	5%	reference
		vaccination	604	18456 [10571, 25000]		24122 [14980, 25000]	31%	reference
		infection & vaccination	2	12193 [6990, 17397]		25000 -	105%	reference
		no event	2,132	16946 [9617, 25000]		9618 [5401, 15852]	-43%	reference

- The increase in S antibody levels among the **vaccine-induced population** is at least **6 times** greater than that of the **hybrid-induced population**, regardless of whether they have undergone infection, vaccination, or both.

Summary table quantifying S antibody level changes between 1st and 2nd surveillance

Immunology	Age	Events	Population	1st Surveillance		2nd Surveillance			
				Median	Range	Median	Range		
TOTAL	-	-	6,728	8985	[2737, 10081]	10150	[3940, 21141]	13%	-
Vaccine induced population	All Age	infection	532	2069	[993, 4522]	25000	[16544, 25000]	1108%	61.6
		vaccination	697	3695	[1673, 8103]	17333	[8983, 25000]	369%	11.3
		infection & vaccination	53	3198	[1953, 5027]	25000	[24524, 25000]	682%	6.5
		no event	1,737	2352	[1073, 6284]	1923	[843, 6750]	-18%	0.4
	<40	infection	127	1932	[975, 3056]	21272	[14127, 25000]	1001%	13.0
		vaccination	24	1692	[919, 3297]	20670	[12212, 25000]	1122%	14.0
		infection & vaccination	4	1312	[1058, 1645]	25000	[24881, 25000]	1805%	-
		no event	372	1839	[875, 3928]	1421	[665, 3232]	-23%	0.6
	>=40	infection	405	2188	[997, 4774]	25000	[17503, 25000]	1043%	207.2
		vaccination	673	3847	[1773, 8222]	17261	[8920, 25000]	349%	11.4
		infection & vaccination	49	3610	[2290, 5713]	25000	[24397, 25000]	593%	5.6
		no event	1,365	2534	[1153, 7256]	2207	[899, 7736]	-13%	0.3
Hybrid induced population	All Age	infection	46	12827	[8039, 20485]	15133	[11249, 21662]	18%	reference
		vaccination	634	18231	[10465, 25000]	24179	[15048, 25000]	33%	reference
		infection & vaccination	2	12193	[6989, 17397]	25000	-	105%	reference
		no event	3,027	16392	[9177, 25000]	9507	[5402, 15690]	-42%	reference
	<40	infection	11	8082	[5546, 17416]	14287	[9736, 22825]	77%	reference
		vaccination	30	13867	[10167, 20514]	25000	[15549, 25000]	80%	reference
		infection & vaccination	-	-	-	-	-	-	reference
		no event	895	14961	[8695, 23892]	9253	[5403, 15506]	-38%	reference
	>=40	infection	35	14466	[8632, 20363]	15194	[11372, 20467]	5%	reference
		vaccination	604	18456	[10571, 25000]	24122	[14980, 25000]	31%	reference
		infection & vaccination	2	12193	[6990, 17397]	25000	-	105%	reference
		no event	2,132	16946	[9617, 25000]	9618	[5401, 15852]	-43%	reference

- If no events occurred, the rate of decline in S antibody levels for the **vaccine-induced population** is only half that observed in the **hybrid-induced population**.

Summary table quantifying S antibody level changes between 1st and 2nd surveillance

Immunology	Age	Events	Population	1st Surveillance		2nd Surveillance		PER Comparison (/times)
				Median	Range	Median	Range	
TOTAL	-	-	6,728	8985	[2737, 10081]	10150	[3940, 21141]	13%
Vaccine induced population	All Age	infection	532	2069	[993, 4522]	25000	[16544, 25000]	1108%
		vaccination	697	3695	[1673, 8103]	17333	[8983, 25000]	369%
		infection & vaccination	53	3198	[1953, 5027]	25000	[24524, 25000]	682%
		no event	1,737	2352	[1073, 6284]	1923	[843, 6750]	-18%
	<40	infection	127	1932	[975, 3056]	21272	[14127, 25000]	1001%
		vaccination	24	1692	[919, 3297]	20670	[12212, 25000]	1122%
		infection & vaccination	4	1312	[1058, 1645]	25000	[24881, 25000]	1805%
		no event	372	1839	[875, 3928]	1421	[665, 3232]	-23%
	>=40	infection	405	2188	[997, 4774]	25000	[17503, 25000]	1043%
		vaccination	673	3847	[1773, 8222]	17261	[8920, 25000]	349%
		infection & vaccination	49	3610	[2290, 5713]	25000	[24397, 25000]	593%
		no event	1,365	2534	[1153, 7256]	2207	[899, 7736]	-13%
Hybrid induced population	All Age	infection	46	12827	[8039, 20485]	15133	[11249, 21662]	18%
		vaccination	634	18231	[10465, 25000]	24179	[15048, 25000]	33%
		infection & vaccination	2	12193	[6989, 17397]	25000	-	105%
		no event	3,027	16392	[9177, 25000]	9507	[5402, 15690]	-42%
	<40	infection	11	8082	[5546, 17416]	14287	[9736, 22825]	77%
		vaccination	30	13867	[10167, 20514]	25000	[15549, 25000]	80%
		infection & vaccination	-	-	-	-	-	reference
		no event	895	14961	[8695, 23892]	9253	[5403, 15506]	-38%
	>=40	infection	35	14466	[8632, 20363]	15194	[11372, 20467]	5%
		vaccination	604	18456	[10571, 25000]	24122	[14980, 25000]	31%
		infection & vaccination	2	12193	[6990, 17397]	25000	-	105%
		no event	2,132	16946	[9617, 25000]	9618	[5401, 15852]	-43%

- Regardless of immunity type, **younger individuals** showed a **greater increase** in S antibody levels after infection or vaccination, and a **faster decline** in the absence of these events, especially in the vaccine-induced group. The later pattern was not observed in the hybrid-induced group.

Summary table quantifying S antibody level changes between 1st and 2nd surveillance

Immunology	Age	Events	Population	1st Surveillance		2nd Surveillance		PER Comparison (/times)
					Median Range		Median Range	
TOTAL	-	-	6,728	8985 [2737, 10081]		10150 [3940, 21141]	13%	-
Vaccine induced population	All Age	infection	532	2069 [993, 4522]		25000 [16544, 25000]	1108%	61.6
		vaccination	697	3695 [1673, 8103]		17333 [8983, 25000]	369%	11.3
		infection & vaccination	53	3198 [1953, 5027]		25000 [24524, 25000]	682%	6.5
		no event	1,737	2352 [1073, 6284]		1923 [843, 6750]	-18%	0.4
	<40	infection	127	1932 [975, 3056]		21272 [14127, 25000]	1001%	13.0
		vaccination	24	1692 [919, 3297]		20670 [12212, 25000]	1122%	14.0
		infection & vaccination	4	1312 [1058, 1645]		25000 [24881, 25000]	1805%	-
		no event	372	1839 [875, 3928]		1421 [665, 3232]	-23%	0.6
	>=40	infection	405	2188 [997, 4774]		25000 [17503, 25000]	1043%	207.2
		vaccination	673	3847 [1773, 8222]		17261 [8920, 25000]	349%	11.4
		infection & vaccination	49	3610 [2290, 5713]		25000 [24397, 25000]	593%	5.6
		no event	1,365	2534 [1153, 7256]		2207 [899, 7736]	-13%	0.3
Hybrid induced population	All Age	infection	46	12827 [8039, 20485]		15133 [11249, 21662]	18%	reference
		vaccination	634	18231 [10465, 25000]		24179 [15048, 25000]	33%	reference
		infection & vaccination	2	12193 [6989, 17397]		25000 -	105%	reference
		no event	3,027	16392 [9177, 25000]		9507 [5402, 15690]	-42%	reference
	<40	infection	11	8082 [5546, 17416]		14287 [9736, 22825]	77%	reference
		vaccination	30	13867 [10167, 20514]		25000 [15549, 25000]	80%	reference
		infection & vaccination	-	- - -		- - -	-	reference
		no event	895	14961 [8695, 23892]		9253 [5403, 15506]	-38%	reference
	>=40	infection	35	14466 [8632, 20363]		15194 [11372, 20467]	5%	reference
		vaccination	604	18456 [10571, 25000]		24122 [14980, 25000]	31%	reference
		infection & vaccination	2	12193 [6990, 17397]		25000 -	105%	reference
		no event	2,132	16946 [9617, 25000]		9618 [5401, 15852]	-43%	reference

- Across various events, **infection** leads to a higher S antibody level increase in the vaccine-induced population, whereas **vaccination** prompts a greater rise in the hybrid-induced group.

Cohort Study Model Selection

Type III SS (Unadjusted Model)

Variables	Df	Sum Sq	Mean Sq	F value	Pr(>F)
sex	1	8.57E+07	8.57E+07	2.3	0.126436
age	1	1.20E+10	1.20E+10	327.0	< 2.2e-16 ***
edu	2	3.85E+08	1.92E+08	5.2	0.005281 **
otherdisease_S1	1	4.45E+07	4.45E+07	1.2	0.270448
S_num_S1	1	8.94E+10	8.94E+10	2438.8	< 2.2e-16 ***
event_after_S1	3	1.68E+11	5.61E+10	1531.2	< 2.2e-16 ***
immune_type	2	2.54E+09	1.27E+09	34.7	1.031e-15 ***
latest_immunology	1	2.27E+09	2.27E+09	62.0	4.051e-15 ***
Residuals	6565	2.41E+11	3.67E+07		

Adjusted Model

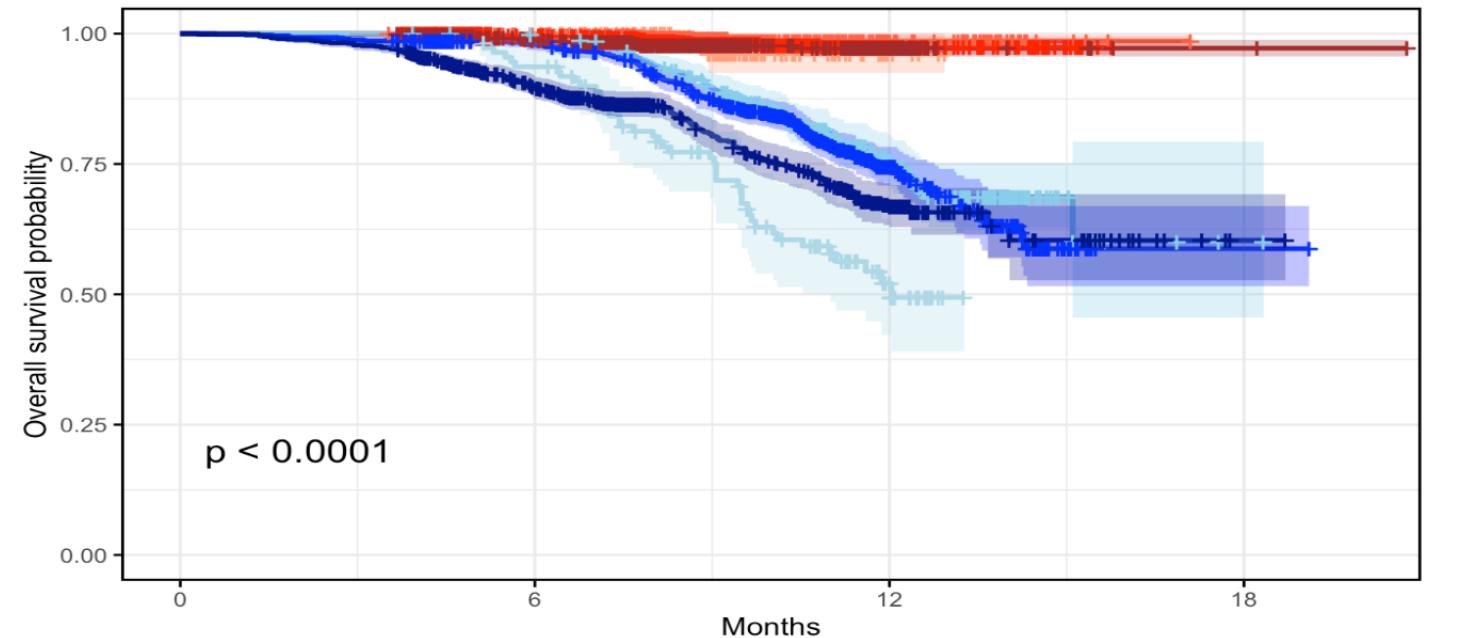
Variables	Df	Sum Sq	Mean Sq	F value	Pr(>F)
immune_type	2	5.04E+09	2.52E+09	68.8	<2e-16 ***
event_after_S1	3	1.56E+11	5.20E+10	1417.0	<2e-16 ***
latest_immunology	1	1.04E+10	1.04E+10	283.1	<2e-16 ***
S_num_S1	1	1.04E+11	1.04E+11	2827.0	<2e-16 ***
age	1	1.96E+07	1.96E+07	0.5	<2e-16 ***
Residuals	6569	2.41E+11	3.67E+07		

Analysis of Variance Table

Model 1: S_num_S2 ~ immune_type + event_after_S1 + latest_immunology + S_num_S1 + age

Model 2: S_num_S2 ~ sex + age + edu + otherdisease_S1 + S_num_S1 + event_after_S1 + immune_type + latest_immunology

Res.Df	RSS	Df	Sum of Sq	F	Pr(>F)
1	6569	2.4089e+11			
2	6565	2.4071e+11	4	177914962	1.2131 0.3029



Number at risk

Strata	0	6	12	18
hybrid-induced, <20	201	182	5	0
hybrid-induced, 20-40	753	651	48	0
hybrid-induced, 40-60	1194	992	86	0
hybrid-induced, >60	810	621	79	2
vac-induced, <20	111	103	20	0
vac-induced, 20-40	408	404	120	1
vac-induced, 40-60	783	691	150	1
vac-induced, >60	862	657	179	1

