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Supplementary appendix

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Supplementary Appendix to:

Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden

Prof. Peter Nordström, PhD, Marcel Ballin, MSc, Anna Nordström, PhD

Affiliations

Department of Community Medicine and Rehabilitation, Unit of Geriatric Medicine, Umeå University, Umeå, Sweden (Peter Nordström, Marcel Ballin, Anna Nordström)

Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, Umeå, Sweden (Marcel Ballin, Anna Nordström)

School of Sport Sciences, UiT the Arctic University of Norway, Tromsø, Norway (Anna Nordström)

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Supplemental Table 1. Definitions of comorbidities.

Variable	Definition	Code Type	Codes
Comorbidities			
Myocardial infarction		ICD-10-SE	I21
Stroke		ICD-10-SE	I60-I64
Hypertension	Hypertension	ICD-10-SE	I10
	Angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker	ATC	C09
	Calcium-receptor blocker	ATC	C08
	Diuretic	ATC	C03
Diabetes	Diabetes	ICD-10-SE	E10, E11
	Antidiabetics	ATC	A10
Chronic obstructive pulmonary disease		ICD-10-SE	J40-J44
Asthma		ICD-10-SE	J45, J46
Cancer	Malignant neoplasm	ICD-10-SE	C
Renal failure/chronic kidney disease		ICD-10-SE	N17-N19
COVID-19		ICD-10-SE	U071

Definitions of comorbidities based on inpatient hospital data from 1998, data from outpatient specialist care since 2001, and data from the national prescription register since 2004. For the variables Hypertension and Diabetes was based on either ICD codes or ATC codes. The variables were defined based on both primary and secondary diagnoses.

ATC denotes Anatomical Therapeutic Chemical· ICD-10-SE denotes International Classification of Diseases, 10th Revision

Supplemental Table 2. Participant characteristics at different time intervals during follow-up in the natural immunity cohort. Each individual with a documented previous infection but not vaccinated (exposed) was matched to one individual with no documented previous infection or vaccination at baseline (unexposed).

	At least 3 months follow-up		At least 6 months follow-up		At least 9 months follow-up	
	Exposed N=774,313	Unexposed N=703,574	Exposed N=431,509	Unexposed N=352,258	Exposed N=156,022	Unexposed N=147,212
Baseline date, mean	26 December 2020	18 December 2020	16 November 2020	7 November 2020	16 September 2020	6 September 2020
Age, mean ± SD	37·0±17·7	37·7±18·9	34·5±17·0	35·2±19·0	35·0±18·0	38·0±20·8
Female sex, N (%)	390,519 (50·4)	364,711 (51·8)	219,982 (51·0)	182,524 (51·8)	81,292 (52·1)	75,632 (51·4)
Homemaker service, N (%)	10,366 (1·3)	8,958 (1·3)	7,312 (1·7)	5,606 (1·6)	3,112 (2·0)	2,837 (1·9)
Born in Sweden, N (%)	586,222 (75·7)	529,089 (75·2)	317,195 (73·5)	253,834 (72·1)	107,569 (68·9)	102,881 (69·9)
Marital status, N (%)						
Married	258,391 (33·4)	215,815 (30·7)	128,224 (29·7)	95,386 (27·1)	45,793 (29·4)	42,574 (28·9)
Not married	437,248 (56·5)	407,801 (58·0)	262,051 (60·7)	217,971 (61·9)	92,895 (59·5)	84,985 (57·7)
Divorced	64,633 (8·3)	62,279 (8·9)	33,380 (7·7)	29,201 (8·3)	13,931 (8·9)	14,085 (9·6)
Widow/widower	11,447 (1·5)	14,340 (2·0)	6,440 (1·5)	7,760 (2·2)	2,830 (1·8)	4,773 (3·2)
Other	2,594 (0·3)	3,339 (0·5)	1,414 (0·3)	1,940 (0·6)	573 (0·4)	795 (0·5)
Education, N (%)						
Elementary school for < 9 years	24,711 (3·2)	28,842 (4·1)	14,204 (3·3)	16,329 (4·6)	6,338 (4·1)	8,632 (5·9)
Elementary school for 9 years	88,764 (11·5)	87,849 (12·5)	49,345 (11·4)	43,495 (12·3)	18,209 (11·7)	18,601 (12·6)
Secondary school for 2 years	103,227 (13·3)	98,306 (14·0)	50,840 (11·8)	45,036 (12·8)	20,325 (13·0)	21,887 (14·9)
Secondary school for >2 years	186,706 (24·1)	151,851 (21·6)	107,090 (24·8)	75,781 (21·5)	37,316 (23·9)	30,470 (20·7)
University	259,968 (33·6)	220,027 (31·3)	138,908 (32·2)	98,520 (28·0)	46,483 (29·8)	38,462 (21·1)
Unknown	110,937 (14·3)	116,699 (16·6)	71,122 (16·5)	73,097 (20·8)	27,351 (17·5)	29,160 (19·8)
Comorbidities, N (%)						
Myocardial infarction	5,585 (0·7)	5,961 (0·8)	2,445 (0·6)	2,579 (0·7)	1,273 (0·8)	1,544 (1·0)
Stroke	5,261 (0·7)	5,239 (0·7)	2,869 (0·7)	2,500 (0·7)	1,244 (0·8)	1,404 (1·0)
Diabetes	28,047 (3·6)	30,443 (4·3)	13,142 (3·0)	11,806 (3·4)	6,462 (4·1)	6,139 (4·2)
Hypertension	81,452 (10·5)	84,803 (12·1)	34,392 (8·0)	33,244 (9·4)	15,393 (9·9)	18,763 (12·7)
Kidney failure	4,678 (0·6)	4,475 (0·6)	2,496 (0·6)	1,905 (0·5)	1,251 (0·8)	1,013 (0·7)
COPD	3,929 (0·5)	3,851 (0·5)	1,995 (0·5)	1,675 (0·5)	1,061 (0·7)	1,002 (0·7)
Asthma	53,911 (7·0)	46,107 (6·6)	31,202 (7·2)	23,383 (6·6)	11,537 (7·4)	9,379 (6·4)
Depression	103,649 (13·4)	99,835 (14·2)	55,185 (12·8)	46,210 (13·1)	19,705 (12·6)	19,078 (13·0)
Cancer	13,807 (1·8)	14,340 (2·0)	6,299 (1·5)	6,137 (1·7)	2,836 (1·8)	3,526 (2·4)

COPD denotes chronic obstructive pulmonary disease. SD denotes standard deviation.

Supplemental Table 3. Participant characteristics for individuals remaining after more than 2 months of follow-up in the one-dose and two-dose hybrid immunity cohorts, respectively. In these cohorts, each individual with a documented previous infection but not vaccinated (unexposed), was matched to one individual that had received one (one-dose hybrid immunity) respectively two doses (two-dose hybrid immunity) of vaccine (exposed).

	One-dose hybrid immunity		Two-dose hybrid immunity	
	Exposed N=53,646	Unexposed N=187,469	Exposed N=147,930	Unexposed N=78,720
Baseline date, mean	28 April 2021	23 May 2021	30 May 2021	27 May 2021
Age, mean ± SD	45·4±16·4	40·9±14·8	47·8±16·1	47·2±15·4
Female sex, N (%)	31,886 (59·4)	94,857 (50·6)	88,332 (59·7)	40,188 (51·1)
Homemaker service, N (%)	864 (1·6)	2,455 (1·3)	7,503 (5·1)	2,041 (2·6)
Born in Sweden, N (%)	41,018 (76·5)	117,024 (62·4)	114,830 (77·6)	48,240 (61·3)
Marital status, N (%)				
Married	23,262 (43·4)	70,031 (37·4)	67,975 (46·0)	33,431 (42·5)
Not married	23,318 (43·5)	92,698 (49·4)	57,430 (38·8)	31,011 (39·4)
Divorced	5,790 (10·8)	19,900 (10·6)	17,277 (11·7)	11,489 (14·6)
Widow/widower	1,027 (1·9)	2,634 (1·4)	4,666 (3·2)	1,978 (2·5)
Other	249 (0·5)	2,206 (1·2)	582 (0·4)	811 (1·0)
Education, N (%)				
Elementary school for < 9 years	1,913 (3·6)	9,374 (5·0)	6,340 (4·3)	5,043 (6·4)
Elementary school for 9 years	5,105 (9·5)	25,908 (13·8)	12,598 (8·5)	8,728 (11·1)
Secondary school for 2 years	9,174 (17·1)	31,910 (17·0)	28,950 (19·6)	17,043 (21·7)
Secondary school for > 2 years	13,148 (24·5)	53,614 (28·6)	33,884 (22·9)	19,482 (24·7)
University	23,200 (43·2)	59,728 (31·9)	62,939 (42·5)	26,005 (33·0)
Unknown	1,106 (2·1)	6,935 (3·7)	3,219 (2·2)	2,419 (3·1)
Comorbidities, N (%)				
Myocardial infarction	659 (1·2)	1,552 (0·8)	2,208 (1·5)	1,137 (1·4)
Stroke	609 (1·1)	1,311 (0·7)	2,743 (1·9)	968 (1·2)
Diabetes	3,511 (6·5)	8,442 (4·5)	13,205 (8·9)	5,232 (6·6)
Hypertension	9,873 (18·4)	21,4 (11·4)	33,800 (22·8)	13,993 (17·8)
Kidney failure	902 (1·7)	1,352 (0·7)	2,113 (1·4)	868 (1·1)
COPD	528 (1·0)	1,122 (0·6)	1,621 (1·1)	817 (1·0)
Asthma	3,245 (6·0)	9,941 (5·3)	9,317 (6·3)	3,962 (5·0)
Depression	10,466 (19·5)	30,870 (16·5)	31,678 (21·4)	14,039 (17·8)
Cancer	1,769 (3·3)	3,412 (1·8)	5,190 (3·5)	2,135 (2·7)

COPD denotes chronic obstructive pulmonary disease. SD denotes standard deviation.

Supplemental Table 4. Type of SARS-CoV-2 genotypes based on whole genome sequencing week 5-40, 2021 in Sweden. Data was derived from the Public Health Agency of Sweden (<https://www.folkhalsomyndigheten.se/smittskydd-beredskap/utbrott/aktuella-utbrott/covid-19/statistik-och-analyser/sars-cov-2-virusvarianter-av-sarskild-betydelse/>)

Week number, 2021	Type of SARS-CoV-2 variant				Total number of genomes sequenced ‡	Genomes sequenced of total number of cases (%)
	Alfa (B.1.1.7) Number of cases (% of total)*	Beta (B.1.351) Number of cases (% of total)	Gamma (P.1) Number of cases (% of total)	Delta (B.1.617.2) Number of cases (% of total) †		
5	1121 (31.0)	90 (2.5)	6 (0.2)		3620	18
6	2338 (45.2)	175 (3.5)	5 (0.1)		4956	23
7	3319 (56.1)	223 (3.8)	10 (0.2)		5921	25
8	4458 (63.5)	216 (3.1)	10 (0.1)		7023	26
9	4716 (70.2)	157 (2.3)	6 (<0.1)		6718	24
10	6161 (76.4)	248 (3.1)	6 (<0.1)		8061	28
11	5631 (73.0)	287 (3.7)	9 (0.1)		7713	23
12	6723 (78.9)	333 (3.9)	15 (0.2)		8522	22
13	3693 (69.6)	270 (5.1)	6 (0.1)	18 (0.3)	5309	14
14	3999 (76.5)	140 (2.7)	3 (<0.1)	19 (0.4)	5229	13
15	3734 (76.6)	92 (1.9)	7 (0.1)	26 (0.5)	4874	12
16	3509 (79.7)	115 (2.6)	4 (<0.1)	27 (0.6)	4404	12
17	3516 (77.5)	68 (1.5)	0	20 (0.4)	4537	13
18	4059 (89.5)	78 (1.7)	5 (0.1)	21 (0.5)	4533	13
19	3276 (90.8)	64 (1.8)	13 (0.4)	29 (0.8)	3607	14
20	3383 (90.1)	71 (1.9)	9 (0.2)	40 (1.1)	3753	21
21	1943 (87.6)	39 (1.8)	13 (0.6)	60 (2.7)	2219	28
22	1746 (76.1)	15 (0.7)	31 (1.4)	248 (10.8)	2293	25
23	1509 (64.1)	8 (0.3)	14 (0.6)	576 (24.4)	2356	54
24	1232 (64.2)	8 (0.4)	10 (0.5)	560 (29.1)	1919	67
25	828 (57.2)	7 (0.5)	10 (0.7)	483 (33.4)	1447	73
26	522 (38.1)	2 (0.2)	5 (0.4)	757 (55.3)	1370	73
27	263 (22.7)	1 (<0.1)	3 (0.2)	841 (72.7)	1157	76
28	102 (7.6)	0	3 (0.2)	1213 (90.1)	1341	71
29	57 (3.2)	1 (<0.1)	1 (<0.1)	1692 (96.2)	1758	66
30	36 (1.8)	0	0	2005 (97.4)	2058	59
31	20 (0.8)	1 (<0.1)	0	2601 (98.7)	2636	57
32	9 (0.3)	0	0	3372 (97.9)	3444	59
33	5 (0.2)	0	1 (<0.1)	3324 (96.3)	3452	53
34	4 (0.1)	0	0	3210 (97.7)	3286	49
35	1 (<0.1)	0	1 (<0.1)	3089 (97.7)	3162	44
36	0	0	0	2925 (87.0)	3016	38
37	0	0	0	2528 (97.9)	2579	41
38	0	0	0	1865 (97.4)	1915	44
39	1 (<0.1)	0	0	2033 (97.5)	2085	49
40	0	0	0	2112 (97.6)	2165	52

* Also includes B.1.1.7 with the mutation E484K.

† Also includes subgroups to B.1.617.2 with designations beginning with AY

‡ The total number of fully sequenced cases also includes those where sequencing has been performed but where genetic group could not be determined

Supplemental Table 5. Risk of SARS-CoV-2 reinfection for individuals with one-dose hybrid immunity (exposed) compared to individuals with natural immunity (unexposed). Exposed individuals had a documented previous infection followed by one dose of vaccine. Unexposed individuals were unvaccinated and had a documented previous infection at baseline. In each matched pair, baseline date for both the exposed and unexposed individual was set as the first dose of vaccine in the exposed individual. Outcome events were traced from 14 days after baseline until a maximum follow-up of 281 (mean 52) days.

	One-dose hybrid immunity (N=481,159)		Natural immunity (N=481,159)		Hazard ratio (95% CI)	
	No. of events	IR/100,000 person-days	No. of events	IR/100,000 person-days	Adjusted for age and baseline date	Fully adjusted*
Total cohort (N=962,318)	639	2.8	1,662	6.2	0.42 (0.38-0.46)	0.42 (0.38-0.46)
Subgroups						
Follow up 14-days-2 months (N=962,318)	599	2.8	1,313	7.1	0.42 (0.38-0.47)	0.42 (0.38-0.47)
Follow up \geq 2 months (N=241,115)	40	0.85	349	1.7	0.56 (0.41-0.78)	0.55 (0.39-0.76)
Men (N=476,140)	253	2.3	797	5.9	0.39 (0.34-0.46)	0.38 (0.33-0.45)
Women (N=486,178)	386	3.2	865	6.4	0.45 (0.39-0.50)	0.45 (0.39-0.50)
<50 years (N=677,125)	288	1.8	1,062	5.6	0.33 (0.29-0.38)	0.32 (0.28-0.37)
50-64 years (N=212,600)	164	3.2	343	5.8	0.48 (0.40-0.59)	0.46 (0.38-0.56)
65-79 years (N=55,452)	148	10.5	171	11.4	0.60 (0.48-0.74)	0.57 (0.45-0.72)
\geq 80 years (N=17,141)	47	4.7	63	15.1	0.63 (0.41-0.97)	0.58 (0.38-0.89)
Homemaker service (N=17,078)	42	11.2	66	13.9	0.66 (0.41-1.03)	0.65 (0.41-1.02)
Any comorbidity (N=314,492)	334	4.3	650	7.6	0.47 (0.41-0.54)	0.47 (0.41-0.54)

*Adjusted for age, baseline date, sex, marital status, homemaker service, place of birth, education, and comorbidities according to Table 1. CI denotes confidence interval. IR denotes incidence rate.

Supplemental Table 6. Risk of SARS-CoV-2 reinfection for individuals with two-dose hybrid immunity (exposed) compared to individuals with natural immunity (unexposed). Exposed individuals had a documented previous infection followed by vaccination with two doses. Unexposed individuals were unvaccinated and had a documented previous infection at baseline. In each matched pair, baseline date for both the exposed and unexposed individual was set as the date of second dose of vaccine in the exposed individual. Outcome events were traced from 14 days after baseline until a maximum follow-up of 278 (mean 66) days.

	Two-dose hybrid immunity (N=283,905)		Natural immunity (N=283,905)		Hazard ratio (95% CI)	
	No. of events	IR/100,000 person-days	No. of events	IR/100,000 person-days	Adjusted for age and baseline date	Fully adjusted*
Total cohort (N=567,810)	438	1.9	808	5.7	0.35 (0.32-0.40)	0.34 (0.31-0.39)
Subgroups						
Follow up 14-days-2 months (N=567,810)	260	1.9	656	6.1	0.31 (0.27-0.36)	0.31 (0.26-0.36)
Follow up ≥2 months (N=226,650)	178	1.0	152	1.9	0.47 (0.37-0.59)	0.44 (0.35-0.56)
Men (N=269,891)	149	1.6	395	5.7	0.37 (0.31-0.45)	0.36 (0.30-0.44)
Women (N=297,919)	289	2.0	413	5.7	0.35 (0.30-0.41)	0.34 (0.29-0.40)
<50 years (N=422,920)	229	1.6	489	5.1	0.34 (0.29-0.39)	0.33 (0.28-0.39)
50-64 years (N=104,914)	89	1.5	189	5.8	0.33 (0.26-0.42)	0.31 (0.24-0.41)
65-79 years (N=27,400)	55	2.8	69	7.5	0.45 (0.31-0.64)	0.39 (0.26-0.58)
≥80 years (N=12,576)	65	5.1	61	14.6	0.46 (0.32-0.65)	0.46 (0.31-0.67)
Homemaker service (N=12,907)	79	4.9	49	13.3	0.39 (0.27-0.57)	0.40 (0.27-0.59)
Any comorbidity (N=184,548)	237	2.4	320	6.8	0.38 (0.32-0.45)	0.37 (0.31-0.45)
Vaccine schedule						
Two doses of BNT162b2 or mRNA-1273 (N=511,644)	379	1.9	765	6.2	0.33 (0.30-0.38)	0.32 (0.28-0.37)
Two doses of ChAdOx1 nCoV-19 (N=24,356)	33	2.1	19	2.3	0.75 (0.41-1.38)	0.75 (0.41-1.37)

*Adjusted for age, baseline date, sex, marital status, homemaker service, place of birth, education, and comorbidities according to Table 1. CI denotes confidence interval. IR denotes incidence rate.

Supplemental Figure 1. Infection pressure during follow-up.

