

Supplement

Supplement Table S1. Baseline characteristics of SARS-CoV-2 cases and test-negative controls included in at least one booster CVE analysis, VEBIS primary care study, Hungary, September 2022 -March 2023.

| Characteristics | 18+ included in at least first booster analyses (Full primary series + at least 1 booster VS. Unvaccinated) | | | | |
|---------------------------------------|--|------------|---------------------------------------|------------|---------|
| | SARS-CoV-2 cases (n = 247) | | Test-negative controls (n = 1,073) | | p-value |
| | n | % | n | % | |
| | Age (median [IQR]) | 53 [41–68] | | 51 [37–66] | |
| Missing | 0 | 0.00 | 0 | 0.00 | |
| Age group (years) | | | | | |
| 18-59 | 137 | 55.47 | 693 | 64.59 | |
| 60+ | 110 | 44.53 | 380 | 35.41 | 0.007 |
| Sex | | | | | |
| Female | 146 | 59.11 | 650 | 60.58 | |
| Male | 101 | 40.89 | 423 | 39.42 | 0.671 |
| Missing | 0 | 0.00 | 0 | 0.00 | |
| BMI^a | | | | | |
| max. 29 | 172 | 69.64 | 736 | 68.59 | |
| 30+ | 75 | 30.36 | 337 | 31.41 | 0.750 |
| Missing | 0 | 0.00 | 0 | 0.00 | |
| Symptoms | | | | | |
| Cough | 210 | 85.02 | 864 | 80.52 | 0.102 |
| Short breath | 31 | 12.55 | 148 | 13.81 | 0.604 |
| Sore throat | 212 | 85.83 | 845 | 78.75 | 0.012 |
| Coryza | 209 | 84.62 | 930 | 86.67 | 0.397 |
| Fever | 167 | 67.61 | 603 | 56.20 | 0.001 |
| Malaise | 222 | 89.88 | 860 | 80.15 | 0.000 |
| Myalgia | 166 | 67.21 | 534 | 49.77 | 0.000 |
| Headache | 171 | 69.23 | 600 | 55.97 | 0.000 |
| Anosmia | 17 | 6.88 | 28 | 2.61 | 0.001 |
| Ageusia | 14 | 5.67 | 24 | 2.24 | 0.004 |
| Chronic condition^{ba} | | | | | |
| Presence of chronic condition | 69 | 27.94 | 278 | 25.91 | 0.480 |
| No chronic condition | 174 | 70.45 | 784 | 73.07 | |
| Missing | 4 | 1.62 | 11 | 1.03 | |
| Chronic condition^{bb} | | | | | |
| Presence of chronic condition | 113 | 45.75 | 497 | 46.32 | 0.842 |

| | | | | | |
|--|-----|-------|-----|-------|-------|
| No chronic condition | 134 | 54.25 | 573 | 53.40 | |
| Missing | 0 | 0.00 | 3 | 0.28 | |
| Severity ^c | | | | | |
| 0 | 231 | 93.52 | 979 | 91.24 | |
| 1+ | 16 | 6.48 | 94 | 8.76 | 0.242 |
| Missing | 0 | 0.00 | 0 | 0.00 | |
| GP consultation ^d | | | | | |
| 0-1 | 27 | 10.93 | 145 | 13.51 | |
| 2+ | 220 | 89.07 | 928 | 86.49 | 0.277 |
| Missing | 0 | 0.00 | 0 | 0.00 | |
| 0-4 | 102 | 41.30 | 505 | 47.06 | |
| 5+ | 145 | 58.70 | 568 | 52.94 | 0.101 |
| Missing | 0 | 0.00 | 0 | 0.00 | |
| Smoking ^e | | | | | |
| Never or former | 191 | 77.33 | 798 | 74.37 | |
| Current | 32 | 12.96 | 225 | 20.97 | 0.011 |
| Missing | 24 | 9.72 | 50 | 4.66 | |
| Swab delay ^f | | | | | |
| max. 2 days | 119 | 48.18 | 630 | 58.71 | |
| 3+ days | 128 | 51.82 | 443 | 41.29 | 0.003 |
| Missing | 0 | 0.00 | 0 | 0.00 | |
| Previous SARS-CoV-2 test ^g | | | | | |
| Previous test | 98 | 39.68 | 215 | 20.04 | 0.000 |
| No previous test | 149 | 60.32 | 858 | 79.96 | |
| Missing | 0 | 0.00 | 0 | 0.00 | |
| Self-reported prior SARS-CoV-2 infection ^h | | | | | |
| Prior | 45 | 18.22 | 225 | 20.97 | 0.334 |
| No prior | 202 | 81.78 | 848 | 79.03 | |
| Missing | 0 | 0.00 | 0 | 0.00 | |
| Self-reported prior SARS-CoV-2 infection ^h | | | | | |
| Prior (60-365 days) | 13 | 6.05 | 109 | 11.39 | 0.020 |
| No prior | 202 | 93.95 | 848 | 88.61 | |
| Self-reported prior SARS-CoV-2 infection ^h | | | | | |
| Prior (366+ days) | 32 | 13.68 | 116 | 12.03 | 0.494 |
| No prior | 202 | 86.32 | 848 | 87.97 | |
| COVID-19 vaccination status | | | | | |
| Unvaccinated | | | | | |
| All | 57 | 23.08 | 234 | 21.81 | |
| 18-59 years (age) | 40 | 29.20 | 205 | 29.58 | |
| 60+ years (age) | 17 | 15.45 | 29 | 7.63 | |

Full primary series plus at least one booster dose

| | | | | | |
|---|-----|-------|-----|-------|-------|
| All | 190 | 76.92 | 839 | 78.19 | 0.664 |
| 18-59 years (age) | 97 | 70.80 | 488 | 70.42 | 0.928 |
| 60+ years (age) | 93 | 84.55 | 351 | 92.37 | 0.013 |
| 14-180 days (time since last vaccination) | 7 | 2.83 | 45 | 4.19 | 0.296 |
| 181-365 days (time since last vaccination) | 66 | 26.72 | 252 | 23.49 | 0.720 |
| 366+ days (time since last vaccination) | 117 | 47.37 | 542 | 50.51 | 0.501 |
| Homologous series ⁱ | 76 | 30.77 | 420 | 39.14 | 0.123 |
| Heterologous series ⁱ | 114 | 46.15 | 419 | 39.05 | 0.542 |

^a BMI calculated as weight/(height*height).

^{ba} The presence of chronic condition is defined as reporting at least one of the following conditions: diabetes, heart disease, lung disease, immunodeficiency.

^{bb} The presence of chronic condition is defined as reporting at least one of the following conditions: diabetes, heart disease, hypertension, lung disease, immunodeficiency, cancer, renal disease.

^c Severity: number of hospitalizations in the previous 12 months for chronic disease.

^d Number of GP consultations in the previous 12 months.

^e Former: stopped smoking at least 1 year before inclusion in the study. Current smoker: any smoking can be included: cigarettes, cigars, vaping, etc.

^f Swab delay: number of days between date of swab and date of onset.

^g Previous SARS-CoV-2 test: Has the patient had a previous SARS-CoV-2 test (e.g. PCR, antigen, both, unknown) related to his/her current symptoms?

^h Previous SARS-CoV-2 infection: Has the patient had a positive SARS-CoV-2 test prior to this illness episode? (At all, 60-365, 366+ days before current onset)

ⁱ Homologous series: primary series and at least one dose booster dose are all mRNA vaccines. Heterologous series: primary series and at least one dose booster are not all mRNA vaccines.

Supplement Table S2. COVID-19 vaccine effectiveness estimates for at least first booster vaccination among 18+ adults, VEBIS primary care study, Hungary, September 2022 -March 2023.

| Population | Time since last booster vaccination (days) | Adjusted CVE (95% CI)* | N | Vaccinated cases | Unvaccinated cases | Vaccinated controls | Unvaccinated controls |
|--|--|------------------------|-------|------------------|--------------------|---------------------|-----------------------|
| Adults aged 18 years and above | 14+ | 20.4 (-13.9; 44.4) | 1,320 | 190 | 57 | 839 | 234 |
| Adults aged 18 years and above (plus adjustment for previous SARS-CoV-2 infection) | 14+ | 20.4 (-14.0; 44.4) | 1,320 | 190 | 57 | 839 | 234 |
| Adults aged 18 years and above (plus adjustment for previous SARS-CoV-2 test) | 14+ | 20.3 (-14.9; 44.7) | 1,320 | 190 | 57 | 839 | 234 |
| Adults aged 18 years and above reporting no previous SARS-CoV-2 test | 14+ | 29.5 (-9.4; 54.6) | 1,007 | 112 | 37 | 671 | 187 |
| Adults aged 18 years and above reporting previous SARS-CoV-2 test | 14+ | 10.5 (-114.6; 43.1) | 313 | 78 | 20 | 168 | 47 |
| Adults aged 18-59 years | 14+ | 2.3 (-50.0; 36.3) | 830 | 97 | 40 | 488 | 205 |
| Adults aged 18-59 years (plus adjustment for previous SARS-CoV-2 infection) | 14+ | 1.4 (-51.5; 35.8) | 830 | 97 | 40 | 488 | 205 |
| Adults aged 18-59 years and above (plus adjustment for previous SARS-CoV-2 test) | 14+ | 0.7 (-53.8; 35.9) | 830 | 97 | 40 | 488 | 205 |
| Adults aged 60 years and above | 14+ | 56.8 (11.9; 78.8) | 490 | 93 | 17 | 351 | 29 |
| Adults aged 60 years and above (plus adjustment for previous SARS-CoV-2 infection) | 14+ | 57.7 (13.3; 79.4) | 490 | 93 | 17 | 351 | 29 |
| Adults aged 60 years and above (plus adjustment for previous SARS-CoV-2 test) | 14+ | 58.3 (14.2; 79.7) | 490 | 93 | 17 | 351 | 29 |

| | | | | | | | |
|--|---------|----------------------------|-----|-----|----|-----|-----|
| Adults aged 18 years and above | 14-180 | 63.8 (-14.0; 88.5) | 343 | 7 | 57 | 45 | 234 |
| Adults aged 18 years and above | 181-365 | 57.4 (30.5; 73.9) | 609 | 66 | 57 | 252 | 234 |
| Adults aged 18 years and above | 14-365 | 55.4 (28.9; 72.1) | 661 | 73 | 57 | 297 | 234 |
| Adults aged 18 years and above (plus adjustment for previous SARS-CoV-2 infection) | 14-365 | 54.6 (27.4; 71.6) | 661 | 73 | 57 | 297 | 234 |
| Adults aged 18 years and above (plus adjustment for previous SARS-CoV-2 test) | 14-365 | 55.9 (29.0; 72.6) | 661 | 73 | 57 | 297 | 234 |
| Adults aged 18 years and above reporting no previous SARS-CoV-2 test | 14-365 | 57.6 (24.2; 76.3) | 488 | 38 | 37 | 226 | 187 |
| Adults aged 18 years and above reporting previous SARS-CoV-2 test | 14-365 | 51.5 (-16.5; 79.8) | 173 | 35 | 20 | 71 | 47 |
| Adults aged 18 years and above | 366+ | -18.9 (-83.2; 22.8) | 950 | 117 | 57 | 542 | 234 |
| Adults aged 18 years and above (plus adjustment for previous SARS-CoV-2 infection) | 366+ | -19.1 (-83.5; 22.7) | 950 | 117 | 57 | 542 | 234 |
| Adults aged 18 years and above (plus adjustment for previous SARS-CoV-2 test) | 366+ | -20.0 (-86.0; 22.5) | 950 | 117 | 57 | 542 | 234 |
| Adults aged 18-59 years | 14-365 | 52.9 (15.2; 73.9) | 461 | 38 | 40 | 178 | 205 |
| Adults aged 60 years and above | 14-365 | 72.3 (32.0; 88.7) | 200 | 35 | 17 | 119 | 29 |
| Adults aged 18-59 years | 366+ | -85.7 (-225.5; -5.9) | 614 | 59 | 40 | 310 | 205 |
| Adults aged 60 years and above | 366+ | 39.8 (-31.0; 72.3) | 336 | 58 | 17 | 232 | 29 |

* adjusted for symptom onset week, age, sex, and presence of at least one chronic condition including diabetes, immunodeficiency, lung disease, and heart disease
CVE: COVID-19 vaccine effectiveness
CI: confidence interval

Supplement Table S3. Protection conferred by prior infection and/or vaccine effectiveness COVID-19 vaccine effectiveness for at least first booster vaccination among 18+ adults (reference group: no prior infection and no vaccination), VEBIS primary care study, Hungary, September 2022 -March 2023.

| Population | Time since last booster vaccination (days) | Adjusted CVE (95% CI)* | N | Vaccinated cases | Unvaccinated cases | Vaccinated controls | Unvaccinated controls |
|---|--|---------------------------|-------|------------------|--------------------|---------------------|-----------------------|
| Adults aged 18 years and above unvaccinated, previously infected (60-365 days) VS. unvaccinated, never infected | 14+ | -246.1 (-929.3; -16.4) | 244 | 8 | 40 | 20 | 176 |
| Adults aged 18 years and above unvaccinated, previously infected (366+ days) VS. unvaccinated, never infected | 14+ | -210.8 (-787; -8.9) | 263 | 9 | 40 | 38 | 176 |
| Adults aged 18 years and above vaccinated, never infected VS. unvaccinated, never infected | 14+ | 12.0 (-34.4; 42.4) | 1,050 | 162 | 40 | 672 | 176 |
| Adults aged 18 years and above vaccinated, previously infected (60-365 days) VS. unvaccinated, never infected | 14+ | 84.8 (50.1; 95.4) | 310 | 5 | 40 | 89 | 176 |
| Adults aged 18 years and above vaccinated, previously infected (366+ days) VS. unvaccinated, never infected | 14+ | -45.3 (-191.6; 27.6) | 317 | 23 | 40 | 78 | 176 |
| Adults aged 18-59 years unvaccinated, previously infected (60-365 days) VS. unvaccinated, never infected | 14+ | -367 (-1395.1; -45.9) | 203 | 8 | 25 | 17 | 153 |
| Adults aged 18-59 years unvaccinated, previously infected (366+ days) VS. unvaccinated, never infected | 14+ | -212.4 (-882.2; 0.6) | 220 | 7 | 25 | 35 | 153 |
| Adults aged 18-59 years vaccinated, never infected VS. unvaccinated, never infected | 14+ | -18.6 (-99.0; 29.3) | 620 | 75 | 25 | 367 | 153 |

| | | | | | | | |
|---|-----|-----------------------|-----|----|----|-----|-----|
| Adults aged 18-59 years vaccinated, previously infected (60-365 days) VS. unvaccinated, never infected | 14+ | 63.0 (-28.0; 89.3) | 244 | 4 | 25 | 62 | 153 |
| Adults aged 18-59 years vaccinated, previously infected (366+ days) VS. unvaccinated, never infected | 14+ | -108.1 (-382.9; 10.3) | 255 | 18 | 25 | 59 | 153 |
| Adults aged 60 years and above unvaccinated, previously infected (60-365 days) VS. unvaccinated, never infected | 14+ | 49.5 (-1307.0; 98.2) | 41 | 0 | 15 | 3 | 23 |
| Adults aged 60 years and above unvaccinated, previously infected (366+ days) VS. unvaccinated, never infected | 14+ | -54.8 (-2388.4; 90.4) | 43 | 2 | 15 | 3 | 23 |
| Adults aged 60 years and above vaccinated, never infected VS. unvaccinated, never infected | 14+ | 55.1 (1.2; 79.6) | 430 | 87 | 15 | 305 | 23 |
| Adults aged 60 years and above vaccinated, previously infected (60-365 days) VS. unvaccinated, never infected | 14+ | 87.6 (26.4; 97.9) | 66 | 1 | 15 | 27 | 23 |
| Adults aged 60 years and above vaccinated, previously infected (366+ days) VS. unvaccinated, never infected | 14+ | 39.0 (-138.4; 84.4) | 62 | 5 | 15 | 19 | 23 |

* adjusted for symptom onset week, age, sex, and presence of at least one chronic condition including diabetes, immunodeficiency, lung disease, and heart disease

CVE: COVID-19 vaccine effectiveness (When comparing unvaccinated patients, the measure of effect is the protection conferred by infection rather than vaccine effectiveness.)

CI: confidence interval

Supplement Table S4. Baseline characteristics of those had previous SARS-CoV-2 test and those without previous SARS-CoV-2 test, VEBIS primary care study, Hungary, September 2022 -March 2023.

| Characteristics | Previous SARS-CoV-2 test VS. No previous SARS-CoV-2 test | | | | | p-value |
|--|--|-------|--|-------|-------|---------|
| | Previous SARS-CoV-2 test (n = 432) | | No previous SARS-CoV-2 test (n = 1,531) | | | |
| | n | % | n | % | | |
| Age (median [IQR]) | 49 [35–64.5] | | 48 [34–63] | | 0.155 | |
| Missing | 0 | 0.00 | 0 | 0.00 | | |
| Age group (years) | | | | | | |
| 18-59 | 288 | 66.67 | 1064 | 69.50 | | |
| 60+ | 144 | 33.33 | 467 | 30.50 | 0.262 | |
| Sex | | | | | | |
| Female | 268 | 62.04 | 904 | 59.05 | | |
| Male | 164 | 37.96 | 627 | 40.95 | 0.263 | |
| Missing | 0 | 0.00 | 0 | 0.00 | | |
| BMI ^a | | | | | | |
| max. 29 | 300 | 69.44 | 1,060 | 69.24 | | |
| 30+ | 132 | 30.56 | 471 | 30.76 | 0.934 | |
| Missing | 0 | 0.00 | 0 | 0.00 | | |
| Chronic condition ^{ba} | | | | | | |
| Presence of chronic condition | 128 | 29.63 | 328 | 21.42 | 0.000 | |
| No chronic condition | 301 | 69.68 | 1,185 | 77.40 | | |
| Missing | 3 | 0.69 | 18 | 1.18 | | |
| Chronic condition ^{bb} | | | | | | |
| Presence of chronic condition | 201 | 46.53 | 591 | 38.60 | 0.003 | |
| No chronic condition | 231 | 53.47 | 936 | 61.14 | | |
| Missing | 0 | 0.00 | 4 | 0.26 | | |
| Severity ^c | | | | | | |
| 0 | 399 | 92.36 | 1,419 | 92.68 | | |
| 1+ | 33 | 7.64 | 112 | 7.32 | 0.820 | |
| GP consultation ^d | | | | | | |
| 0-1 | 48 | 11.11 | 235 | 15.35 | 0.027 | |
| 2+ | 384 | 88.89 | 1,296 | 84.65 | | |
| Missing | 0 | 0.00 | 0 | 0.00 | | |
| 0-4 | 178 | 41.20 | 759 | 49.58 | 0.002 | |
| 5+ | 254 | 58.80 | 772 | 50.42 | | |
| Missing | 0 | 0.00 | 0 | 0.00 | | |

| | | | | | | |
|--|---|-----|-------|-------|-------|-------|
| Smoking ^e | | | | | | |
| | Never or former | 313 | 72.45 | 1,126 | 73.55 | |
| | Current | 82 | 18.98 | 340 | 22.21 | 0.305 |
| | Missing | 37 | 8.56 | 65 | 4.25 | |
| Swab delay ^f | | | | | | |
| | max. 2 days | 243 | 56.25 | 873 | 57.02 | 0.775 |
| | 3+ days | 189 | 43.75 | 658 | 42.98 | |
| | Missing | 0 | 0.00 | 0 | 0.00 | |
| Case status | | | | | | |
| | SARS-CoV-2 case | 132 | 30.56 | 223 | 14.57 | 0.000 |
| | Test-negative control | 300 | 69.44 | 1,308 | 85.43 | |
| | Missing | 0 | 0.00 | 0 | 0.00 | |
| Self-reported prior SARS-CoV-2 infection ^g | | | | | | |
| | Prior | 134 | 31.02 | 296 | 19.33 | 0.000 |
| | No prior | 298 | 68.98 | 1,235 | 80.67 | |
| | Missing | 0 | 0.00 | 0 | 0.00 | |
| Self-reported prior SARS-CoV-2 infection ^g | | | | | | |
| | Prior (60-365 days) | 70 | 19.02 | 126 | 9.26 | 0.000 |
| | No prior | 298 | 80.98 | 1,235 | 90.74 | |
| Self-reported prior SARS-CoV-2 infection ^g | | | | | | |
| | Prior (366+ days) | 64 | 17.68 | 170 | 12.10 | 0.005 |
| | No prior | 298 | 82.32 | 1,235 | 87.90 | |
| COVID-19 vaccination status | | | | | | |
| Unvaccinated | | | | | | |
| | All | 67 | 15.51 | 224 | 14.63 | |
| | 18-59 years (age) | 56 | 19.44 | 189 | 17.76 | |
| | 60+ years (age) | 11 | 7.64 | 35 | 7.49 | |
| Full primary series plus at least one booster dose | | | | | | |
| | All | 246 | 56.94 | 783 | 51.14 | 0.755 |
| | 18-59 years (age) | 137 | 47.57 | 448 | 42.11 | 0.861 |
| | 60+ years (age) | 109 | 75.69 | 335 | 71.73 | 0.924 |
| | 14-180 days (time since last vaccination) | 18 | 4.17 | 34 | 2.22 | 0.075 |
| | 181-365 days (time since last vaccination) | 88 | 20.37 | 230 | 15.02 | 0.188 |
| | 366+ days (time since last vaccination) | 140 | 32.41 | 519 | 33.90 | 0.540 |
| | Homologous series ^h | 130 | 30.09 | 366 | 23.91 | 0.319 |
| | Heterologous series ^h | 116 | 26.85 | 417 | 27.24 | 0.677 |

^a BMI calculated as weight/(height*height).

^{ba} The presence of chronic condition is defined as reporting at least one of the following conditions: diabetes, heart disease, lung disease, immunodeficiency.

^{bb} The presence of chronic condition is defined as reporting at least one of the following conditions: diabetes, heart disease, hypertension, lung disease, immunodeficiency, cancer, renal disease.

^c Severity: number of hospitalizations in the previous 12 months for chronic disease.

^d Number of GP consultations in the previous 12 months.

^e Former: stopped smoking at least 1 year before inclusion in the study. Current smoker: any smoking can be included: cigarettes, cigars, vaping, etc.

^f Swab delay: number of days between date of swab and date of onset.

^g Previous SARS-CoV-2 infection: Has the patient had a positive SARS-CoV-2 test prior to this illness episode? (At all, 60-365, 366+ days before current onset)

^h Homologous series: primary series and at least one dose booster dose are all mRNA vaccines. Heterologous series: primary series and at least one dose booster are not all mRNA vaccines.
