

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Contents

Supplementary Table 1 – demographic, epidemiological and clinical characteristics of HCW breakthrough cases..... 2

Supplementary table 2 – prevalence of symptoms and clinical outcomes within a cohort of vaccinated HCWs with a breakthrough infection 4

Supplementary table 3 - Comparison of cases with peri-infection Nab..... 6
(included in the case-control study) and those without, who were not included 6

Supplementary table 4 – Sensitivity analysis of the matching algorithm 8

Legends to Supplementary Figures 11

Supplementary Table 1 – demographic, epidemiological and clinical characteristics of HCW breakthrough cases (n=39)

| SARS-CoV-2 Breakthrough infections | | |
|---|---------------|-------------------|
| | Number | % of total |
| Sex (Female) | 25 | 64.1% |
| Median age (years) | 42.1 | Range 24-66 |
| Average age (years) | 42.05 | |
| HCW profession | | |
| Nursing | 18 | 46.2% |
| Administration & maintenance | 10 | 25.6% |
| Allied professions | 6 | 15.4% |
| Physicians | 5 | 12.8% |
| Comorbidities: Any comorbidity | | |
| CLL | 1 | 2.6% |
| ITP | 1 | 2.6% |
| Metabolic syndrome (Obesity, DM, dyslipidemia, HTN) | 6 | 15.4% |
| Thyroid disorder | 3 | 7.7% |
| Other (migraines, fibromyalgia, osteoporosis, PCOS) | 4 | 10.3% |
| Indication for SARS-CoV-2 testing | | |
| Exposure | 27 | 69.2% |
| Symptoms | 11 | 28.2% |
| Screening | 1 | 2.6% |

| Presumed source of exposure | | |
|--|-------------|------------------------|
| Unvaccinated household member | 21 | 53.8% |
| Unvaccinated patient | 7 | 17.9% |
| Unvaccinated contact in the community | 5 | 12.8% |
| Unvaccinated HCW | 4 | 10.3% |
| Unknown | 2 | 5.1% |
| PCR results | | |
| Infectious (at least one test with N-gene Ct<30) | 29 | 74.3% |
| Presumably non-infectious (N-gene Ct value >30 on all tests) | 10 | 25.6% |
| Borderline result (repeated N-gene Ct>35 and asymptomatic) | 6 | 15.4% |
| SARS-CoV-2 variant | | |
| | n=33 | |
| B.1.1.7 | 28 | 84.8% |
| Wild type | 1 | 3.0% |
| Rapid antigen test | | |
| | n=36 | |
| Positive | 17 | 47.2% |
| Post-infection Anti-N IgG (Days 8-72) | | |
| | n=22 | Range 0.1- 38.6 |
| Positive | 16 | 72.7% |

Supplementary table 2 – prevalence of symptoms and clinical outcomes within a cohort of vaccinated HCWs with a breakthrough infection

| Symptom prevalence | Number of cases | % of total |
|------------------------------------|-----------------|------------|
| Asymptomatic | 13 | 33.3% |
| Congestion | 14 | 35.9% |
| Myalgia (including backache) | 11 | 28.2% |
| Anosmia and/or ageusia | 11 | 28.2% |
| Cough | 10 | 25.6% |
| Weakness | 9 | 23.1% |
| Headache | 9 | 23.1% |
| Fever and/or rigors | 8 | 21% |
| Sore throat | 6 | 15.4% |
| Fatigue | 5 | 12.8% |
| Nausea and/or vomiting | 4 | 10.3% |
| Dyspnea | 3 | 7.7% |
| Diarrhea | 3 | 7.7% |
| Clinical course and outcome | | |
| 1 negligible symptom | 4 | 10.3% |

| | | |
|--|-------|-------|
| 2 or more symptoms | 22 | 56.4% |
| Hospital admission or workup due to COVID-19 | 0 | 0.0% |
| Long-COVID-19 symptoms | | |
| Long-COVID-19 symptoms (at >14 days) | 11/39 | 28.2% |
| Long-COVID-19 symptoms (at 6 weeks) | 7/36 | 19.4% |

Supplementary table 3 - Comparison of cases with peri-infection Nab

(included in the case-control study) and those without, who were not included

| | n = 17 | n = 22 | P value |
|--|----------------------|---------------------|----------------|
| Age | 40.59 | 43.09 | |
| Mean, (standard deviation, range) | (11.25,24.00-66.00) | (8.47, 27.00-59.00) | |
| Lowest Ct | 24.65 | 26.12 | |
| Mean, (standard deviation, range) | (7.16, 16.99 -36.97) | (6.45, 18.18-39.07) | |
| Sex (female), n (%) | 11 (64.71%) | 14 (63.64%) | 0.999 |
| HCW profession | | | 0.23 |
| Physician | 1 (5.88%) | 4 (18.18%) | |
| Nursing | 6 (35.29%) | 12 (54.55%) | |
| Logistics and maintenance | 6 (35.29%) | 4 (18.18%) | |
| Allied health professionals | 4 (23.53%) | 2 (9.09%) | |
| Indication for SARS-CoV-2 testing | | | 0.17 |
| Exposure | 14 (82.35%) | 13 (59.09%) | |
| Symptoms | 2 (11.76%) | 9 (40.90%) | |
| Screening | 1 (5.88%) | 0 (0.00%) | |
| Symptoms during full infection course | | | 0.54 |
| Asymptomatic | 7 (41.18%) | 6 (27.27%) | |

| | | | |
|--|-------------|-------------|------|
| Symptomatic | 10 (58.82%) | 16 (72.72%) | |
| Rapid antigen test performed (n=36) | n = 15 | n = 21 | 0.70 |
| Positive | 7 (46.66%) | 10 (47.62%) | |
| Variant of concern (number tested = 33) | n = 14 | n = 19 | 0.67 |
| B.1.1.7. U.K. | 13 (92.86%) | 15 (78.95%) | |

Supplementary table 4 – Sensitivity analysis of the matching algorithm

To confirm the robustness of the matching criteria, we also selected other controls from the cohort, after changing the matching criteria, allowing a +/- 5 years difference in age and without matching for gender. The results are presented in Supplementary Table 4:

Supplementary table 4 - a. population characteristics and b. outcomes of the sensitivity analysis

| | Cases (n=22) | Controls (n=108) | |
|---|---------------------|-------------------------|--------------|
| a. Population characteristics | | | |
| Female | 14 (64%) | 90 (83.3%) | |
| Median age (years) | 44 | 43 | |
| Average age (years) | 43 | 42.72 | |
| Comorbidities | | | |
| Immunosuppression | 1 (4.5%) | 3 (2.77%) | |
| Autoimmune disease | 0 (0%) | 5 (4.63%) | |
| BMI>30 | 0 (0%) | 0 (0%) | |
| 2 nd vaccine dose to ab test interval (D) (average/median) | 36.2 / 36 | 36.5 / 28.5 | |
| b. Outcomes | | | |
| | Cases (n=22) | Controls (n=108) | Ratio |

| Peri-infection Nab titers | n = 22 | n = 108 | |
|--|------------------------------------|-------------------------------------|------------------------------|
| Observed Geometric Mean Nab titer (95%CI) | 192.80 (95% CI: 81.82 – 454.30) | 560.10 (95% CI: 442.80 – 708.60) | |
| Geometric mean Nab titer predicted by GEE model | 192.79 (95%CI: 65.33 – 568.95) | 556.13 (95%CI: 413.93 – 747.18) | 0.347 95%CI 0.158-0.761 |
| Peri-infection anti-S IgG titers | n=22 | n=106 | |
| Observed Geometric mean | 11.22 (95% CI: 5.71 – 22.04) | 21.99 (95% CI: 18.86 – 26.65) | |
| Predicted IgG titer by GEE model | 11.21 (95%CI: 5.25- 23.96) | 21.70 (95% CI: 17.45-26.99) | 0.517 95% CI: 0.301-0.888 |
| Peak Nab titer | n=12 | n=57 | |
| Observed Geometric mean | 152.20 (95% CI: 29.89 – 775.10) | 975.40 (95% CI: 710.80- 1338.00) | |
| Predicted Geometric mean by GEE model | 152.22 (95% CI: 30.68-755.21) | 864.54 (95% CI: 638.04 -1171.45) | 0.176 95%CI: 0.048 -0.645 |
| Peak anti-S IgG | n=20 | n=98 | |
| Observed geometric mean | 16.27 (95% CI: 7.46 – 35.51) | 31.60 (95% CI: 27.80 – 35.93) | |

| | | | |
|--|-------------------------------|--------------------------------|------------------------------|
| Predicted geometric mean by GEE model | 16.27 (95% CI: 7.44-35.59) | 31.17 (95% CI: 28.68-36.43) | 0.522 95% CI: 0.279-0.977 |
|--|-------------------------------|--------------------------------|------------------------------|

Legends to Supplementary Figures

Figure S1: Matching Algorithm – Control source cohort – all fully vaccinated HCW participating in the Sheba serology study, who have Nab results recorded. 2nd dose to Nab test time interval = interval (in days) since 2nd vaccine dose and Nab test. A larger difference between the case and control was allowed, depending on the time interval. As the interval of the cases increase, greater differences among their controls are allowed with the following matching caliper: For cases with a time interval of up to 10 day, +/- 1 day difference is allowed for matched controls, for 11-20 days, +/- 3 days is allowed, for 21-40 days, +/- 5 days is allowed and for longer intervals (>40 days), up to +/- 10 days is allowed. Immunosuppression status included: organ transplantation, hematologic malignancy, chemotherapy and biologic therapy, steroid use, and post-splenectomy. Matching by age aimed to be stringent, but was allowed to gradually relax to yield at least four controls, following the rules where, initially only matched cases with difference of up to +/-1 year are included, if this yields less than 4 controls, difference of +/-5 years is allowed and then +/-10 years, if this fails to yield a cluster of 4 matched controls, this criterion was further extended to include all in the age category of <65 (eventually in 2 cases).

Figure S2: Peak IgG plotted against Peri-infection IgG, where two separate measurements were available.