**Supplementary Material**

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# **Section S1. Phases of the COVID-19 pandemic**

The coronavirus disease 2019 (COVID-19) pandemic in Qatar up to the end of the study duration was categorized into distinct phases based on the level of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) incidence and the predominant variant. These phases included the ancestral virus wave (February 28, 2020 - July 31, 2020),[1] a prolonged low incidence phase with the ancestral virus (August 1, 2020 - January 17, 2021),[2, 3] the Alpha wave (January 18, 2021 - March 7, 2021),[4] the Beta wave (March 8, 2021 - May 31, 2021),[5] and a prolonged low incidence Delta phase (June 1, 2021 - December 18, 2021).[6, 7] Of note that the latter part of the Alpha wave overlapped with the initial part of the Beta wave.

# **Section S2. Laboratory methods and variant ascertainment**

## **Real-time reverse-transcription polymerase chain reaction testing**

Nasopharyngeal and/or oropharyngeal swabs were collected for PCR testing and placed in Universal Transport Medium (UTM). Aliquots of UTM were: 1) extracted on KingFisher Flex (Thermo Fisher Scientific, USA), MGISP-960 (MGI, China), or ExiPrep 96 Lite (Bioneer, South Korea) followed by testing with real-time reverse-transcription PCR (RT-qPCR) using TaqPath COVID-19 Combo Kits (Thermo Fisher Scientific, USA) on an ABI 7500 FAST (Thermo Fisher Scientific, USA); 2) tested directly on the Cepheid GeneXpert system using the Xpert Xpress SARS-CoV-2 (Cepheid, USA); or 3) loaded directly into a Roche cobas 6800 system and assayed with the cobas SARS-CoV-2 Test (Roche, Switzerland). The first assay targets the viral S, N, and ORF1ab gene regions. The second targets the viral N and E-gene regions, and the third targets the ORF1ab and E-gene regions.

All PCR testing was conducted at the Hamad Medical Corporation Central Laboratory or Sidra Medicine Laboratory, following standardized protocols.

## **Classification of infections by variant type**

Surveillance for SARS-CoV-2 variants in Qatar is based on viral genome sequencing and multiplex RT-qPCR variant screening[8] of weekly-collected random positive clinical samples,[2, 9-13] complemented by deep sequencing of wastewater samples.[10, 13-15] Further details on the viral genome sequencing and multiplex RT-qPCR variant screening throughout the SARS-CoV-2 waves in Qatar can be found in previous publications.[2, 6, 9-12, 16-22]

# **Section S3. Study population and data sources**

Qatar's national and universal public healthcare system uses the Cerner-system advanced digital health platform to track all electronic health record encounters of each individual in the country, including all citizens and residents registered in the national and universal public healthcare system. Registration in the public healthcare system is mandatory for citizens and residents.

The databases analyzed in this study are data-extract downloads from the Cerner-system that have been implemented on a regular (twice weekly) schedule since onset of the pandemic by the Business Intelligence Unit at Hamad Medical Corporation (HMC). HMC is the national public healthcare provider in Qatar. At every download, all tests, COVID-19 vaccinations, hospitalizations related to COVID-19, and all death records regardless of cause are provided to the authors through .csv files. These databases have been analyzed throughout the pandemic not only for study-related purposes, but also to provide policymakers with summary data and analytics to inform the national response.

Every health encounter in the Cerner-system is linked to a unique individual through the HMC Number that links all records for this individual at the national level. Databases were merged and analyzed using the HMC Number to link all records whether for testing, vaccinations, hospitalizations, and deaths. All deaths in Qatar are tracked by the public healthcare system. All COVID-19-related healthcare was provided only in the public healthcare system. No private entity was permitted to provide COVID-19-related hospitalization. COVID-19 vaccination was also provided only through the public healthcare system. These health records were tracked throughout the COVID-19 pandemic using the Cerner system. This system has been implemented in 2013, before the onset of the pandemic. Therefore, we had all health records related to this study for all residents in Qatar throughout the pandemic.

Demographic details for every HMC Number (individual) such as sex, age, and nationality are collected upon issuing of the universal health card, based on the Qatar Identity Card, which is a mandatory requirement by the Ministry of Interior to every citizen and resident in the country. Data extraction from the Qatar Identity Card to the digital health platform is performed electronically through scanning techniques.

All SARS-CoV-2 testing in any facility in Qatar is tracked nationally in one database, the national testing database. This database covers all testing in all locations and facilities throughout the country, whether public or private. Every polymerase chain reaction (PCR) test conducted in Qatar regardless of location or setting, are classified on the basis of symptoms and the reason for testing (clinical symptoms, contact tracing, surveys or random testing campaigns, individual requests, routine healthcare testing, pre-travel, at port of entry, post-antibody, or other).

Before November 1, 2022, SARS-CoV-2 testing in Qatar was done at a mass scale where about 5% of the population were tested every week.[2, 17] Based on the distribution of the reason for testing up to November 1, 2022, most of the tests in Qatar were conducted for routine reasons, such as being travel-related, and about 75% of cases were diagnosed not because of appearance of symptoms, but because of routine testing.[2, 17]

Further descriptions of the study population and the national databases were reported previously.[1, 2, 5, 16, 17, 23-25]

# **Section S4. Classification of coexisting conditions**

Coexisting conditions were ascertained and classified based on the ICD-10 codes for the conditions as recorded in the electronic health record encounters of each individual in the Cerner-system national database that includes all citizens and residents registered in the national and universal public healthcare system. The public healthcare system provides healthcare to the entire resident population of Qatar free of charge or at heavily subsidized costs, including prescription drugs. With the mass expansion of this sector in recent years, facilities have been built to cater to specific needs of subpopulations. For example, tens of facilities have been built, including clinics and hospitals, in localities with high density of craft and manual workers.[26]

All encounters for each individual were analyzed to determine the coexisting-condition classification for that individual, as part of a recent national analysis to assess healthcare needs and resource allocation. The Cerner-system national database includes encounters starting from 2013, after this system was launched in Qatar. As long as each individual had at least one encounter with a specific coexisting-condition diagnosis since 2013, this person was classified with this coexisting condition.

Individuals who have coexisting conditions but never sought care in the public healthcare system, or seek care exclusively in private healthcare facilities, were classified as individuals with no coexisting condition due to absence of recorded encounters for them.

# **Section S5. COVID-19 severity, criticality, and fatality classification**

Classification of COVID-19 case severity (acute-care hospitalizations),[27] criticality (intensive-care-unit hospitalizations),[27] and fatality[28] followed World Health Organization (WHO) guidelines. Assessments were made by trained medical personnel independent of study investigators and using individual chart reviews, as part of a national protocol applied to every hospitalized COVID-19 patient. Each hospitalized COVID-19 patient underwent an infection severity assessment every three days until discharge or death.

## **Severe COVID-19**

Severe COVID-19 disease was defined per WHO classification as a SARS-CoV-2 infected person with "oxygen saturation of <90% on room air, and/or respiratory rate of >30 breaths/minute in adults and children >5 years old (or ≥60 breaths/minute in children <2 months old or ≥50 breaths/minute in children 2-11 months old or ≥40 breaths/minute in children 1–5 years old), and/or signs of severe respiratory distress (accessory muscle use and inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs)".[27] Detailed WHO criteria for classifying SARS-CoV-2 infection severity can be found in the WHO technical report.[27]

## **Critical COVID-19**

Critical COVID-19 disease was defined per WHO classification as a SARS-CoV-2 infected person with "acute respiratory distress syndrome, sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy".[27] Detailed WHO criteria for classifying SARS-CoV-2 infection criticality can be found in the WHO technical report.[27]

## **Fatal COVID-19**

COVID-19 death was defined per WHO classification as "a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19".[28] Detailed WHO criteria for classifying COVID-19 death can be found in the WHO technical report.[28]

# **Table S1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for case-control studies.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Item No | Recommendation | Main text page |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | Abstract |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Abstract |
| Introduction | | |  |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Introduction |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Introduction |
| Methods | | |  |
| Study design | 4 | Present key elements of study design | Methods (‘Study design’) |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Methods (‘Study population and data sources’ & ‘Study design’) & Sections S1-S3 in Supplementary Material |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls | Methods (‘Study design’) & Sections S3 & S5 in Supplementary Material |
| (*b*)For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Methods (‘Study design’) & Sections S2-S5 in Supplementary Material |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Methods (‘Study population and data sources’, ‘Study design’ & ‘Statistical analysis’, paragraph 1) & Sections S2-S5 in Supplementary Material |
| Bias | 9 | Describe any efforts to address potential sources of bias | Methods (‘Study design’ & ‘Statistical analysis’) |
| Study size | 10 | Explain how the study size was arrived at | Methods (‘Study population and data sources’ & ‘Study design’) |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Methods (‘Study design’ & ‘Statistical analysis’) |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Methods (‘Statistical analysis’) |
| (*b*) Describe any methods used to examine subgroups and interactions | Methods (‘Statistical analysis’) |
| (*c*) Explain how missing data were addressed | Not applicable, see Methods (‘Study population and data sources’) |
| (*d*) If applicable, explain how matching of cases and controls was addressed | Methods (‘Study design’& ‘Statistical analysis’) |
| (*e*) Describe any sensitivity analyses | Methods (‘Statistical analysis’, paragraph 5) |
| Results | | |  |
| Participants | 13 | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Results & Figures S1 & S2 in Supplementary Material |
| (b) Give reasons for non-participation at each stage |
| (c) Consider use of a flow diagram |
| Descriptive data | 14 | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Results, Tables 1 & 4 |
| (b) Indicate number of participants with missing data for each variable of interest | Not applicable, see Methods (‘Study population and data sources’) |
| Outcome data | 15 | Report numbers in each exposure category, or summary measures of exposure | Results, Tables 2 & 3, & Table S2 in Supplementary Material |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Results, Tables 2 & 3, Figure 2, & Table S2 in Supplementary Material |
| (*b*) Report category boundaries when continuous variables were categorized | Not applicable |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Not applicable |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Results (‘Sensitivity and supplementary analyses’) & Tables S3-S7 in Supplementary Material |
| Discussion | | |  |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion, paragraphs 1-2 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion, paragraphs 5-13 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Discussion, paragraph 9-13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Discussion, paragraph 10 |
| Other information | | |  |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Funding |

# **Figure S1*.* Flowchart describing the population selection process for investigating BNT162b2 vaccine effectiveness.**



PCR denotes polymerase chain reaction and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

\*PCR-positive SARS-CoV-2 tests were matched exactly one-to-one to PCR-negative SARS-CoV-2 tests according to sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing.

# **Table S2*.* Effectiveness of BNT162b2 and mRNA-1273 vaccines against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections at 7-90 days after the third vaccine dose.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Analyses | BNT162b2 vaccine effectiveness | | | | Effectiveness  % (95% CI)\* | mRNA-1273 vaccine effectiveness | | | | Effectiveness  % (95% CI)\* |
| **Cases**  **(PCR-positive tests)** | | **Controls**  **(PCR-negative tests)** | | **Cases**  **(PCR-positive tests)** | | **Controls**  **(PCR-negative tests)** | |
| **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| Asymptomatic infection†‡ | 20 | 31,818 | 56 | 31,782 | 73.5  (51.1 to 85.6) | 1 | 31,806 | 2 | 31,805 | 50.0  (-81.9 to 95.5) |
| Symptomatic infection†§ | 23 | 49,731 | 84 | 49,670 | 81.3  (67.0 to 89.5) | 0 | 49,693 | 6 | 49,687 | 100.0  (15.1 to 100.0)¶ |
| Severe COVID-19 infection‖ | 0 | 3,915 | 55 | 16,377 | 100.0  (93.1 to 100.0)¶ | 0 | 3,905 | 5 | 16,388 | 100.0  (-8.4 to 100.0)¶ |
| Critical COVID-19 infection‖ | 0 | 465 | 1 | 1,725 | 100.0  (-97.4 to 100.0)¶ | 0 | 465 | 0 | 1,724 | Omitted\*\* |
| Fatal COVID-19 infection‖ | 0 | 189 | 3 | 684 | 100.0  (-58.7 to 100.0)¶ | 0 | 188 | 0 | 684 | Omitted\*\* |

CI denotes confidence interval, COVID-19 coronavirus disease 2019, and PCR polymerase chain reaction.

\*Effectiveness was estimated with the use of a test-negative, case-control study design.

†Cases and controls were matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing.

‡An asymptomatic infection was defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection. That is, PCR testing done as part of a survey.

§A symptomatic infection was defined as a PCR-positive test that was done because of the presence of symptoms consistent with a respiratory tract infection.

‖Cases and controls were matched exactly one-to-five by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing. Severity, criticality,and fatality were defined according to the World Health Organization guidelines.

¶The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases. When 1:n matching was employed, the number of pairs was considered as 'n'. This approach provided only an approximate estimate for the 95% CI in these specific situations.

\*\*Effectiveness could not be estimated as there were no vaccinated persons among both cases and controls.

# **Figure S2. Flowchart describing the population selection process for investigating mRNA-1273 vaccine effectiveness.**



PCR denotes polymerase chain reaction and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

\*PCR-positive SARS-CoV-2 tests were matched exactly one-to-one to PCR-negative SARS-CoV-2 tests according to sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing.

# **Table S3*.* Sensitivity analysis assessing the impact of including tests for individuals with prior infections on the estimated effectiveness of the BNT162b2 vaccine against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections. The analysis involves modifying inclusion and exclusion criteria to include cases and controls with a prior SARS-CoV-2 infection 90 days or more before the study**'**s PCR-test.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Analyses | Cases  (PCR-positive tests) | | Controls  (PCR-negative tests) | | Effectiveness  % (95% CI)\* |
| **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| Two-dose analysis | | | | | |
| Asymptomatic infection†‡ | 2,521 | 32,683 | 5,147 | 30,057 | 76.8  (74.9 to 78.5) |
| Symptomatic infection†§ | 4,094 | 53,180 | 8,953 | 48,321 | 77.4  (76.1 to 78.7) |
| Severe COVID-19 infection‖ | 100 | 4,221 | 3,345 | 15,477 | 97.5  (96.5 to 98.2) |
| Critical COVID-19 infection‖ | 10 | 514 | 432 | 1,650 | 97.6  (94.0 to 99.0) |
| Fatal COVID-19 infection‖ | 13 | 215 | 270 | 648 | 91.1  (83.0 to 95.3) |
| Three-dose analysis | | | | | |
| Asymptomatic infection†‡ | 21 | 32,335 | 64 | 32,292 | 78.2  (59.3 to 88.3) |
| Symptomatic infection†§ | 25 | 51,559 | 101 | 51,483 | 84.4  (72.7 to 91.1) |
| Severe COVID-19 infection‖ | 0 | 3,993 | 62 | 17,091 | 100.0  (93.9 to 100.0)¶ |
| Critical COVID-19 infection‖ | 0 | 476 | 2 | 1,833 | 100.0  (-81.2 to 100.0)¶ |
| Fatal COVID-19 infection‖ | 0 | 194 | 3 | 737 | 100.0  (-58.7 to 100.0)¶ |

CI denotes confidence interval, COVID-19 coronavirus disease 2019, PCR polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

\*Effectiveness was estimated with the use of a test-negative, case-control study design.

†Cases and controls were matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing.

‡An asymptomatic infection was defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection. That is, PCR testing done as part of a survey.

§A symptomatic infection was defined as a PCR-positive test that was done because of the presence of symptoms consistent with a respiratory tract infection.

‖Cases and controls were matched exactly one-to-five by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing. Severity, criticality, and fatality were defined according to the World Health Organization guidelines.

¶The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases. When 1:n matching was employed, the number of pairs was considered as 'n'. This approach provided only an approximate estimate for the 95% CI in these specific situations.

# **Table S4*.* Sensitivity analysis assessing the impact of including tests for individuals with prior infections and matching by prior infection status on the estimated effectiveness of the BNT162b2 vaccine against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections. The analysis involves modifying inclusion and exclusion criteria to include cases and controls with a prior SARS-CoV-2 infection 90 days or more before the study's PCR-test and matching cases and controls based on prior infection status.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Analyses | Cases  (PCR-positive tests) | | Controls  (PCR-negative tests) | | Effectiveness  % (95% CI)\* |
| **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| Two-dose analysis | | | | | |
| Asymptomatic infection†‡ | 2,497 | 32,580 | 5,042 | 30,035 | 75.5  (73.6 to 77.3) |
| Symptomatic infection†§ | 4,021 | 52,236 | 8,599 | 47,658 | 76.2  (74.7 to 77.5) |
| Severe COVID-19 infection‖ | 93 | 4,167 | 3,143 | 15,211 | 97.0  (96.0 to 97.8) |
| Critical COVID-19 infection‖ | 10 | 505 | 433 | 1,580 | 96.9  (93.0 to 98.7) |
| Fatal COVID-19 infection‖ | 13 | 210 | 267 | 622 | 90.2  (81.5 to 94.8) |
| Three-dose analysis | | | | | |
| Asymptomatic infection†‡ | 20 | 32,205 | 54 | 32,171 | 72.3  (48.9 to 85.0) |
| Symptomatic infection†§ | 24 | 50,618 | 86 | 50,556 | 77.5  (62.5 to 86.5) |
| Severe COVID-19 infection‖ | 0 | 3,935 | 60 | 16,701 | 100.0  (93.7 to 100.0)¶ |
| Critical COVID-19 infection‖ | 0 | 466 | 1 | 1,769 | 100.0  (-97.4 to 100.0)¶ |
| Fatal COVID-19 infection‖ | 0 | 189 | 3 | 703 | 100.0  (-58.7 to 100.0)¶ |

CI denotes confidence interval, COVID-19 coronavirus disease 2019, PCR polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

\*Effectiveness was estimated with the use of a test-negative, case-control study design.

†Cases and controls were matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, reason for PCR testing, and prior SARS-CoV-2 infection status.

‡An asymptomatic infection was defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection. That is, PCR testing done as part of a survey.

§A symptomatic infection was defined as a PCR-positive test that was done because of the presence of symptoms consistent with a respiratory tract infection.

‖Cases and controls were matched exactly one-to-five by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, reason for PCR testing, and prior SARS-CoV-2 infection status. Severity, criticality, and fatality were defined according to the World Health Organization guidelines.

¶The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases. When 1:n matching was employed, the number of pairs was considered as 'n'. This approach provided only an approximate estimate for the 95% CI in these specific situations.

# **Table S5*.* Sensitivity analysis assessing the impact of matching by exact age, instead of matching by 10-year age group, on the estimated effectiveness of the BNT162b2 vaccine against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Analyses | Cases  (PCR-positive tests) | | Controls  (PCR-negative tests) | | Effectiveness  % (95% CI)\* |
| **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| Two-dose analysis | | | | | |
| Asymptomatic infection†‡ | 1,792 | 27,347 | 3,595 | 25,544 | 77.7  (75.5 to 79.7) |
| Symptomatic infection†§ | 2,597 | 38,847 | 5,499 | 35,945 | 76.3  (74.5 to 78.0) |
| Severe COVID-19 infection‖ | 29 | 2,946 | 1,234 | 8,999 | 98.6  (97.3 to 99.3) |
| Critical COVID-19 infection‖ | 3 | 297 | 144 | 768 | 98.7  (90.9 to 99.8) |
| Fatal COVID-19 infection‖ | 3 | 110 | 51 | 301 | 100.0  (92.0 to 100.0)¶ |
| Three-dose analysis | | | | | |
| Asymptomatic infection†‡ | 9 | 26,764 | 18 | 26,755 | 60.0  (-3.0 to 84.5) |
| Symptomatic infection†§ | 9 | 37,049 | 31 | 37,027 | 78.6  (48.2 to 91.1) |
| Severe COVID-19 infection‖ | 0 | 2,736 | 20 | 9,378 | 100.0  (79.7 to 100.0)\*\* |
| Critical COVID-19 infection‖ | 0 | 260 | 0 | 808 | Omitted†† |
| Fatal COVID-19 infection‖ | 0 | 95 | 0 | 314 | Omitted†† |

CI denotes confidence interval, COVID-19 coronavirus disease 2019, and PCR polymerase chain reaction.

\*Effectiveness was estimated with the use of a test-negative, case-control study design.

†Cases and controls were matched exactly one-to-one by sex, age, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing.

‡An asymptomatic infection was defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection. That is, PCR testing done as part of a survey.

§A symptomatic infection was defined as a PCR-positive test that was done because of the presence of symptoms consistent with a respiratory tract infection.

‖Cases and controls were matched exactly one-to-five by sex, age, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing. Severity, criticality, and fatality were defined according to the World Health Organization guidelines.

¶Effectiveness and 95% CI were estimated with the use of McNemar's test because conditional logistic regression failed to converge, as all vaccinated cases were matched to vaccinated controls. As 1:n matching was employed, the number of pairs was considered as 'n'. This approach provided only an approximate estimate for the 95% CI in this specific situation.

\*\*The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases. As 1:n matching was employed, the number of pairs was considered as 'n'. This approach provided only an approximate estimate for the 95% CI in these specific situations.

††Effectiveness could not be estimated as there were no vaccinated persons among both cases and controls.

# **Table S6*.* Sensitivity analysis assessing the impact of matching by exact coexisting-condition status, instead of matching by the number of coexisting conditions, on the estimated effectiveness of the BNT162b2 vaccine against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Analyses | Cases  (PCR-positive tests) | | Controls  (PCR-negative tests) | | Effectiveness  % (95% CI)\* |
| **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| Two-dose analysis | | | | | |
| Asymptomatic infection†‡ | 1,948 | 30,214 | 4,021 | 28,141 | 75.9  (73.8 to 77.9) |
| Symptomatic infection†§ | 2,881 | 45,931 | 6,373 | 42,439 | 76.4  (74.7 to 77.9) |
| Severe COVID-19 infection‖ | 16 | 769 | 426 | 1,539 | 97.2  (94.0 to 98.7) |
| Critical COVID-19 infection‖ | 1 | 130 | 72 | 250 | 97.4  (80.9 to 99.6) |
| Fatal COVID-19 infection‖ | 2 | 36 | 21 | 54 | 92.8  (44.6 to 99.1) |
| Three-dose analysis | | | | | |
| Asymptomatic infection†‡ | 15 | 29,899 | 44 | 29,870 | 76.3  (51.0 to 88.5) |
| Symptomatic infection†§ | 16 | 44,503 | 53 | 44,466 | 78.7  (57.9 to 89.2) |
| Severe COVID-19 infection‖ | 0 | 663 | 7 | 1,594 | 100.0  (30.6 to 100.0)¶ |
| Critical COVID-19 infection‖ | 0 | 116 | 0 | 258 | Omitted\*\* |
| Fatal COVID-19 infection‖ | 0 | 28 | 0 | 54 | Omitted\*\* |

CI denotes confidence interval, COVID-19 coronavirus disease 2019, and PCR polymerase chain reaction.

\*Effectiveness was estimated with the use of a test-negative, case-control study design.

†Cases and controls were matched exactly one-to-one by sex, 10-year age group, nationality, type of coexisting condition, calendar week of PCR test, and reason for PCR testing.

‡An asymptomatic infection was defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection. That is, PCR testing done as part of a survey.

§A symptomatic infection was defined as a PCR-positive test that was done because of the presence of symptoms consistent with a respiratory tract infection.

‖Cases and controls were matched exactly one-to-five by sex, 10-year age group, nationality, type of coexisting condition, calendar week of PCR test, and reason for PCR testing. Severity, criticality, and fatality were defined according to the World Health Organization guidelines.

¶The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases. When 1:n matching was employed, the number of pairs was considered as 'n'. This approach provided only an approximate estimate for the 95% CI in these specific situations.

\*\*Effectiveness could not be estimated as there were no vaccinated persons among both cases and controls.

# **Table S7*.* Additional analysis assessing the effectiveness of mRNA vaccination, with either the BNT162b2 or mRNA-1273 vaccine, against asymptomatic, symptomatic, severe COVID-19, critical COVID-19, and fatal COVID-19 infections.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Analyses | Cases  (PCR-positive tests) | | Controls  (PCR-negative tests) | | Effectiveness  % (95% CI)\* |
| **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| Two-dose analysis | | | | | |
| Asymptomatic infection†‡ | 2,957 | 32,205 | 5,468 | 29,694 | 75.1  (73.1 to 76.9) |
| Symptomatic infection†§ | 4,538 | 51,389 | 9,024 | 46,903 | 76.6  (75.2 to 77.9) |
| Severe COVID-19 infection‖ | 103 | 4,149 | 3,125 | 14,952 | 96.6  (95.4 to 97.5) |
| Critical COVID-19 infection‖ | 11 | 506 | 431 | 1,534 | 97.0  (93.1 to 98.7) |
| Fatal COVID-19 infection‖ | 13 | 211 | 235 | 631 | 90.0  (80.5 to 94.9) |
| Three-dose analysis | | | | | |
| Asymptomatic infection†‡ | 23 | 31,813 | 62 | 31,774 | 75.0  (54.1 to 86.4) |
| Symptomatic infection†§ | 24 | 49,709 | 96 | 49,637 | 82.8  (70.2 to 90.0) |
| Severe COVID-19 infection‖ | 0 | 3,915 | 59 | 16,367 | 100.0  (93.5 to 100.0)¶ |
| Critical COVID-19 infection‖ | 0 | 465 | 1 | 1,723 | 100.0  (-97.4 to 100.0)¶ |
| Fatal COVID-19 infection‖ | 0 | 189 | 3 | 683 | 100.0  (-58.7 to 100.0)¶ |

CI denotes confidence interval, COVID-19 coronavirus disease 2019, and PCR polymerase chain reaction.

\*Effectiveness was estimated with the use of a test-negative, case-control study design.

†Cases and controls were matched exactly one-to-one by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing.

‡An asymptomatic infection was defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection. That is, PCR testing done as part of a survey.

§A symptomatic infection was defined as a PCR-positive test that was done because of the presence of symptoms consistent with a respiratory tract infection.

‖Cases and controls were matched exactly one-to-five by sex, 10-year age group, nationality, number of coexisting conditions, calendar week of PCR test, and reason for PCR testing. Severity, criticality, and fatality were defined according to the World Health Organization guidelines.

¶The 95% CI was estimated with the use of McNemar's test because of zero events among exposed cases. When 1:n matching was employed, the number of pairs was considered as 'n'. This approach provided only an approximate estimate for the 95% CI in these specific situations.

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