Supplemental Online Content

Vo AD, La J, Wu JTY, et al. Factors associated with severe COVID-19 among vaccinated adults treated in US Veterans Affairs hospitals. *JAMA Netw Open*. 2022;5(10):e2240037. doi:10.1001/jamanetworkopen.2022.40037

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**eMethods.** Methods With Additional Details

**Cohort creation:**

The longitudinal cohort consisted of all patients who received an initial 2-dose series of mRNA COVID-19 vaccine (BNT162b2 or mRNA-1273) or a single dose of the Janssen adenovirus-based vaccine (Ad26.COV2.S) before 12/1/2021 and subsequently tested positive for SARS-CoV-2 infection (PCR or antigen) within the Veterans Affairs Healthcare System (VA) through 2/28/2022. The study period includes intervals during which the original strain, delta variant (7/1/2021-12/15/2021), and omicron variant 12/16/2021-2/28/2021) were predominant.

“Fully vaccinated” with the primary vaccination series was defined as 14 days after the second dose of an mRNA vaccine or 14 days after a single dose of the Janssen vaccine. “Boosted” was defined as 7 days after an additional vaccine dose of any type. SARS-CoV-2 infection was defined by a positive PCR or antigen test at a VA facility. Only the first breakthrough infection was included, and the first positive test after vaccination was used to define the start time of that breakthrough infection.

**Data sources and uses:**

Data were obtained from the VA COVID-19 shared data resource and the Corporate Data Warehouse (CDW) that encompasses the clinical electronic health records (EHR) of all VA patients and facilities. See eTable 1 for a complete listing of definitions and data sources.

The primary outcome was severe breakthrough infection, defined by either: death 2-28 days after a positive test; medical/surgical hospitalization within 14 days of the positive test and documented SpO2 < 94%, receipt of any supplemental oxygen, or receipt of dexamethasone; or mechanical ventilation. The comparator was non-severe breakthrough infection: no hospitalization, or hospitalization that did not meet criteria for severe disease.

For descriptive purposes, a total of 4 categories of severity were defined (non-severe disease and not hospitalized, non-severe but hospitalized, severe and survived, or died within 28 days of the first positive test), but these were not analyzed separately (see eTable 4). Admissions to psychiatric units, a VA community living center, or a VA domiciliary were not included in the hospitalization definition, nor were admissions to acute care facilities lasting less than 1 day; all such patients were classified as having not been hospitalized, i.e. as having non-severe breakthrough infection. A random sample of 25 patients who died underwent manual chart review to determine whether death was attributable to COVID-19 (see eResults).

Patients who were hospitalized and survived but for whom data about severity could not be determined were excluded.

Demographic data included age in years at the time of breakthrough infection, biologic sex, self-reported race and ethnicity, US region, and urban/rural residence as defined by US Census criteria. Age was classified as < 40, ≥40 - <45, ≥45 - <50 (referent group), ≥50 - < 55, ≥55 - <60, ≥60 - <65, ≥65 - <70, ≥70 - <75, ≥75 - <80, and ≥80. Vaccination data included dates of each vaccination dose and the vaccine manufacturer. Occurrence of a previous SARS-CoV-2 infection before vaccination was defined as a positive test any time before day 14 after completing the initial vaccination series. Time from receipt of vaccination was assessed as a categorical variable defined as months since vaccination or receipt of booster.
Occurrence of a previous SARS-CoV-2 infection before vaccination was defined as a positive test any time before day 14 after completing the initial vaccination series. Use of monoclonal antibody therapy to prevent severe Covid-19 after breakthrough infection was recorded as a dichotomous variable.

Comorbidities recorded in the patients’ records at the time of infection were assessed using the Chronic Conditions Warehouse (CCW) during the 3 years prior to vaccination. Some comorbidities in the CCW were excluded from the multivariable modeling on the basis of being deemed (by PM and WBE) as redundant, or very unlikely to be related to Covid-19 outcomes, or present at very low frequencies.

Body mass index (BMI) in kg/m$^2$ was calculated from weight and height and was classified into underweight (BMI < 18.5), normal weight (BMI ≥18 - < 25, referent group), overweight (≥25 - < 30), and obesity grade I (≥30 - < 35), II (≥35 - < 40), and severe (≥ 40); in the approximately 30% of patients for whom height was not available, the US averages for men (1.78 m) and women (1.63 m) were used to impute BMI.

Definitions of immunocompromised patients:

Medication administration data within the VA were reviewed, and medications known to increase risk of infectious diseases were classified into five categories: cytotoxic chemotherapy within 6 months, glucocorticoids (oral prednisone or oral or IV methylprednisolone) at any dose within 1 month, cytokine-blocking drugs (e.g., anti-TNF, -IL-6R, -IL-17), within 3 months, leukocyte-inhibiting drugs (e.g. methotrexate, azathioprine, JAK inhibitors, abatacept) within 3 months, and lymphocyte-depleting drugs (e.g. rituximab) within 18 months. Some potentially immunosuppressive medications were not included in the definition due to challenges distinguishing systemic from topical formulations (e.g., cyclosporine, tacrolimus, and multiple topical and inhaled glucocorticoids). Use of immunosuppressive drugs was assessed separately both shortly before vaccination and after vaccination but shortly before breakthrough infection. Different time intervals were used for different drug classes and based on their expected duration of impact and maximum length of a single prescription for outpatient drugs. A full list of drugs, their classifications, timing used to define recent use, and the numbers of patients receiving these drugs before vaccination and after vaccination (i.e., before breakthrough) are presented in eTable 2. The immunocompromised cohort also included patients with leukemia or lymphoma but not patients with HIV, based on the results of the analysis of the full cohort.

Time since Vaccination

Interpreting time-since-vaccination has risk for residual confounding, due to earlier availability to higher-risk patients, differential use and timing of boosting, and development of the delta and then the less-dangerous omicron variant. Thus, in addition to including time-since-initial-vaccination and time-since-boosting in the same multivariable models, we also analyzed non-immunocompromised patients who had not received boosters and stratified by age less than or greater than 65. The under-65 group was further limited to patients initially vaccinated after March 29, 2021, when vaccination was recommended for all US adults independent of health status.
Statistical Analysis:

The primary analysis evaluated exposures associated with development of severe compared to non-severe SARS-CoV-2 infection despite vaccination. Secondary analyses were conducted on subcohorts (Figure 1), to further explore the impacts of an immunocompromised state, age, and time since vaccination. Analyses stratified by sex, viral variant predominance, vaccine manufacturer, and urban or rural residence were also performed.

Multivariable logistic regression was used to assess the association of the binary outcome (severe vs non-severe breakthrough SARS-CoV-2 infection) with sets of independent variables, which were modeled either as binary or in categories (e.g. for geographic region) with one chosen as the referent. For some independent variables, missing data was treated by including an “unknown” category, so as to not need to exclude the patient from the analysis. For comorbidities, missing data was regarded as absence of the condition. Variables determined a priori to be of interest and those with adjusted odds ratios (aOR) ≥ 1.5 or ≤ 0.67 and statistical significance are presented in the main results. Results for all variables included in each multivariable are included in eTables, and it is apparent in those tables when a set of variables was excluded from an analysis. Findings were considered statistically significant at P<0.05 after adjustment for multiple comparisons using the Benjamini-Hochberg method, using the ranked P-values of that multivariable regression. The resulting cut-offs for actual P-values are reported below each of the eTables.

Ethical review of study

This study was approved by the VA Boston Research and Development committee as an exempt study prior to data collection and analysis with a waiver of informed consent.
**STROBE Statement**—Checklist of items that should be included in reports of cohort studies

| Item No | Item | Recommendation | Page No |
|---------|------|----------------|---------|
| **Title and abstract** | 1 | (a) Indicate the study’s design with a commonly used term in the title or the abstract  
(b) Provide in the abstract an informative and balanced summary of what was done and what was found | 3-4 |
| **Introduction** | 2 | Explain the scientific background and rationale for the investigation being reported | 5 |
| **Methods** | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| Study design | 4 | Present key elements of study design early in the paper | 5-8 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5-6 |
| | | (b) For matched studies, give matching criteria and number of exposed and unexposed (N/A) | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6-7 |
| 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 | 5-6, eMethods |
| Bias | 9 | Describe any efforts to address potential sources of bias (in Limitations) | 13-14 |
| Study size | 10 | Explain how the study size was arrived at (all available data were used) | 5-6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 5-6 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | 7-8 |
| | | (b) Describe any methods used to examine subgroups and interactions (same) | 7-8 |
| | | (c) Explain how missing data were addressed (only done for BMI) | 6 |
| | | (d) If applicable, explain how loss to follow-up was addressed | N/A |
### Results

| Category          | Item | Description                                                                                     | Reference |
|-------------------|------|-----------------------------------------------------------------------------------------------|-----------|
| Participants      | 13*  | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible,     | 8         |
|                   |      | examined for eligibility, confirmed eligible, included in the study, completing follow-up, and |           |
|                   |      | analysed (report number eligible = included)                                                   |           |
|                   |      | (b) Give reasons for non-participation at each stage (reasons for ineligibility are complex and | N/A       |
|                   |      | not of scientific interest)                                                                   |           |
|                   |      | (c) Consider use of a flow diagram (used to describe subsets)                                 | Fig1      |
| Descriptive data  | 14*  | (a) Give characteristics of study participants (eg demographic, clinical, social) and information | 8-9, eTable3 |
|                   |      | on exposures and potential confounders                                                        |           |
|                   |      | (b) Indicate number of participants with missing data for each variable of interest             | eTable4   |
|                   |      | (c) Summarise follow-up time (eg, average and total amount)                                   | 5-6       |
| Outcome data      | 15*  | Report numbers of outcome events or summary measures over time                                 | eTable3+4 |

### Main results

| Category          | Item | Description                                                                                     | Reference |
|-------------------|------|-----------------------------------------------------------------------------------------------|-----------|
|                   | 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 | Table1    |
|                   |      |                                                                                               | eTable3   |
|                   |      | (b) Report category boundaries when continuous variables were categorized                       | eTables   |
|                   |      | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 8-10      |
|                   |      |                                                                                               | eTables   |

### Other analyses

| Category          | Item | Description                                                                                     | Reference |
|-------------------|------|-----------------------------------------------------------------------------------------------|-----------|
|                   | 17   | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 9-10      |
|                   |      |                                                                                               | eTables   |

### Discussion

| Category          | Item | Description                                                                                     | Reference |
|-------------------|------|-----------------------------------------------------------------------------------------------|-----------|
| Key results       | 18   | Summarise key results with reference to study objectives                                         | 11-12     |
| 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 | 14-15     |
| Interpretation    | 20   | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 11-15     |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 13-15 |
|------------------|----|-------------------------------------------------|------|
| **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 | 16 |

*Give information separately for exposed and unexposed groups.*

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.
### eTable 1. Data Dictionary

| Variable           | Definition                                                                                                                                                                                                 |
|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Breakthrough infection | Positive SARS-CoV-2 test at least 14 days after the second dose of mRNA vaccine or first dose of adenoviral vaccine. Only the first breakthrough infection was analyzed |
| Non-severe         | Severity 1 or 2                                                                                                                                                                                             |
| Severe             | Severity 3, 4, or 5                                                                                                                                                                                          |
| Sex                | As recorded in structured data in the VA EHR                                                                                                                                                                |
| Race               | As recorded in structured data in the VA EHR                                                                                                                                                                |
| Ethnicity          | As recorded in structured data in the VA EHR                                                                                                                                                                |
| Age                | In years at time of breakthrough infection                                                                                                                                                                  |
| Age ranges         |                                                                                                                                                                                                            |
| Less than 40       | Age < 40                                                                                                                                                                                                   |
| 40-45              | Age ≥ 40 AND Age < 45                                                                                                                                                                                          |
| 45-50              | Age ≥ 45 AND Age < 50                                                                                                                                                                                          |
| 50-55              | Age ≥ 50 AND Age < 55                                                                                                                                                                                          |
| 55-60              | Age ≥ 55 AND Age < 60                                                                                                                                                                                          |
| 60-65              | Age ≥ 60 AND Age < 65                                                                                                                                                                                          |
| 65-70              | Age ≥ 65 AND Age < 70                                                                                                                                                                                          |
| 70-75              | Age ≥ 70 AND Age < 75                                                                                                                                                                                          |
| 75-80              | Age ≥ 75 AND Age < 80                                                                                                                                                                                          |
| 80 or greater      | Age ≥ 80                                                                                                                                                                                                   |
| BMI                | Calculated using most recent weight in kg within 5 years, and most recent height ever recorded. If height missing, then used US averages of 1.78m for males and 1.63m for females |
| BMI Class          |                                                                                                                                                                                                            |
| Underweight        | BMI < 18.5                                                                                                                                                                                                  |
| Normal             | BMI ≥ 18.5 AND BMI < 25                                                                                                                                                                                        |
| Overweight         | BMI ≥ 25 AND BMI < 30                                                                                                                                                                                         |
| Obesity I          | BMI ≥ 30 AND BMI < 35                                                                                                                                                                                         |
| Obesity II         | BMI ≥ 35 AND BMI < 40                                                                                                                                                                                         |
| Severe Obesity     | BMI ≥ 40                                                                                                                                                                                                   |
| Unknown            | Weight or height unavailable                                                                                                                                                                                   |
| Region             | Geographical region was defined based on the VA facility from which each patient received their full vaccination (second dose of mRNA vaccine or first dose of adenoviral vaccine) |
| Continental        | Arkansas, Colorado, Louisiana, Mississippi, Montana, Oklahoma, Texas, Utah, Wyoming                                                                                                                        |
| Region                | States                                                                 |
|-----------------------|-------------------------------------------------------------------------|
| Midwest               | Illinois, Indiana, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin |
| North Atlantic        | Connecticut, Delaware, District Of Columbia, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia |
| Pacific               | Alaska, Arizona, California, Hawaii, Idaho, Nevada, New Mexico, Oregon, Washington |
| Southeast             | Alabama, Florida, Georgia, Kentucky, Puerto Rico, South Carolina, Tennessee |
| Unknown               | Data on the VA facility not available                                    |

### Urban or rural residence
The most recent residence listed in VA records was used. For patients with multiple residences, the one closest to the vaccination site was used. Locations were defined as urban per US Census criteria, and all others were considered rural. VA also defines census regions as highly rural if they contain fewer than 7 residents per square mile. However, since only 0.4% of patients in this study resided in highly rural areas, they were combined with the rural group for analysis.

### Vaccine Type
Defined based on the type of the initial vaccination, as recorded in the VA COVID-19 Shared Data Resource. (Patients with first and second doses of different types were excluded.)

- **Janssen**: Patient considered vaccinated 14 days after 1<sup>st</sup> dose
- **Moderna**: Patient considered vaccinated 14 days after 2<sup>nd</sup> dose
- **Pfizer**: Patient considered vaccinated 14 days after 2<sup>nd</sup> dose

### Months since full vax at breakthrough
Days since full vax converted to months and discretized into multiple buckets of 1 month durations

- **4 or less**: Months ≤ 4
- **4-5**: 4 < Months AND Months ≤ 5
- **5-6**: 5 < Months AND Months ≤ 6
- **6-7**: 6 < Months AND Months ≤ 7
- **7-8**: 7 < Months AND Months ≤ 8
- **8-9**: 8 < Months AND Months ≤ 9
- **9-10**: 9 < Months AND Months ≤ 10
- **10-11**: 10 < Months AND Months ≤ 11
- **11-12**: 11 < Months AND Months ≤ 12
- **12 or more**: 12 < Months

### Boosted before breakthrough
Patients are considered fully boosted 7 days after receiving the booster shot. Thus, the patient was considered boosted before breakthrough if the breakthrough infection occurred at least 7 days after receiving the booster shot.

- **Not boosted**
- **1 or less**: Months ≤ 1

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| Months | Description |
|--------|-------------|
| 1-2    | 1 < Months AND Months ≤ 2 |
| 2-3    | 2 < Months AND Months ≤ 3 |
| 3-4    | 3 < Months AND Months ≤ 4 |
| 4-5    | 4 < Months AND Months ≤ 5 |
| 5-6    | 5 < Months AND Months ≤ 6 |
| 6 or more | 6 < Months |

**History of infection before vaccinated**
- Previous positive SARS-CoV-2 test (PCR or antigen) no later than 14 days after the second mRNA vaccine or first adenoviral vaccine. No time limit was applied, meaning any VA-diagnosed case from early 2020 should be captured.

**Delta Period**
- Between 7/1/2021 and 12/15/2021, inclusive

**Omicron Period**
- Between 12/16/2021 and 2/28/2022, inclusive

**Persistent positive test**
- Patients whose first breakthrough infection was persistent enough to last longer than the standard 6-week infection duration. Starting from the date of the first breakthrough infection, we required at least two additional positive tests in the subsequent 12 weeks, with at least one of them falling in the first 6 weeks and at least one falling in the second 6 weeks, and no negative tests in these 12 weeks

**Immune-suppressive medications before breakthrough**

| Medication | Description |
|------------|-------------|
| Chemotherapy | Order/dispensation of one of the drugs listed as chemotherapy in eTable 2 within 6 months before date of breakthrough infection |
| Cytokine-blocking | Order/dispensation of one of the drugs listed as cytokine-blocking in eTable 2 within 3 months before date of breakthrough infection |
| Glucocorticoids | Order/dispensation of one of the drugs listed as cytokine-blocking in eTable 2 within 1 month before date of breakthrough infection |
| Leukocyte-inhibitory | Order/dispensation of one of the drugs listed as cytokine-blocking in eTable 2 within 3 months before date of breakthrough infection |
| Lymphocyte-depleting | Order/dispensation of one of the drugs listed as cytokine-blocking in eTable 2 within 18 months before date of breakthrough infection |

**Immune-suppressive medications before initial vaccination**

| Medication | Description |
|------------|-------------|
| Chemotherapy | Order/dispensation of one of the drugs listed as chemotherapy in eTable 2 within 6 months before receipt of the first vaccine |
| Before vaccine Cytokine-blocking | Order/dispensation of one of the drugs listed as cytokine-blocking in eTable 2 within 3 months before receipt of the first vaccine |
|----------------------------------|--------------------------------------------------------------------------------------------------|
| Before vaccine Glucocorticoids   | Order/dispensation of one of the drugs listed as cytokine-blocking in eTable 2 within 1 month before receipt of the first vaccine |
| Before vaccine Leukocyte-inhibitory | Order/dispensation of one of the drugs listed as cytokine-blocking in eTable 2 within 3 months before receipt of the first vaccine |
| Before vaccine Lymphocyte-depleting | Order/dispensation of one of the drugs listed as cytokine-blocking in eTable 2 within 18 months before receipt of the first vaccine |
| Monoclonal Antibody              | Order/dispensation of one of the drugs listed as MAB in eTable 2 given at any time |

Comorbidities

- Acquired hypothyroidism
- Acute myocardial infarction
- Alzheimers disease and related disorders or senile dementia
- Anemia
- Anxiety disorders
- Asthma
- Atrial fibrillation
- Bipolar disorder
- Chronic kidney disease
- Chronic obstructive pulmonary disease and bronchiectasis
- Colorectal cancer
- Depression
- Diabetes
- Epilepsy
- Heart failure
- Human immunodeficiency virus and/or acquired immunodeficiency syndrome
- HIV/AIDS
- Hyperlipidemia
- Hypertension

These comorbidities were derived based on the diagnosis and procedure codes described in the CMS Chronic Conditions Warehouse algorithms (https://www2.ccwdata.org/web/guest/condition-categories) anytime in the 3 years prior to the date of full vaccination.
| Condition                                      | Description                                                                                           |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Ischemic heart disease                        |                                                                                                       |
| Leukemias and lymphomas                       |                                                                                                       |
| Liver disease cirrhosis and other liver conditions except viral hepatitis |                                                                                                       |
| Lung cancer                                   |                                                                                                       |
| Mobility impairments                          |                                                                                                       |
| Multiple sclerosis and transverse myelitis     |                                                                                                       |
| Peripheral vascular disease                   |                                                                                                       |
| Pressure and chronic ulcers                   |                                                                                                       |
| Prostate cancer                               |                                                                                                       |
| Schizophrenia and other psychotic disorders   |                                                                                                       |
| Tobacco use                                   |                                                                                                       |
| Viral hepatitis                               |                                                                                                       |
| COVID19 ICD used                               | Use of ICD-10 code U07.1 or J12.82 during an inpatient visit                                         |
| Inpatient Location                            | Location of inpatient visits derived from VistA's Patient Treatment File (PTF)                       |
| VA only                                       | VA acute care sites, excluding psychiatric, domiciliary, rehabilitation, or community living center (CLC) sites |
| VA and non-VA                                  | Inpatient visits to both VA and non-VA care sites                                                   |
| Non-VA only                                   | Patients receiving care from a non-VA hospital under VA auspices                                    |
| Unknown                                       | Data about location of care site was not found                                                         |
### eTable 2. List of Immunosuppressive Medications, With Classification

| Drug class       | Months<sup>a</sup> | Generic drug name                              | Patients receiving before vaccination | Patients receiving after vaccination and before breakthrough |
|------------------|---------------------|------------------------------------------------|---------------------------------------|----------------------------------------------------------|
| Chemotherapy     | 6                   | arsenic                                        | 6                                    | 12                                                       |
| Chemotherapy     | 6                   | asparaginase                                   | 0                                    | 0                                                        |
| Chemotherapy     | 6                   | asparaginase erwinia chrysanthemi              | 0                                    | 0                                                        |
| Chemotherapy     | 6                   | azacitidine                                    | 16                                   | 31                                                       |
| Chemotherapy     | 6                   | bendamustine                                   | 21                                   | 35                                                       |
| Chemotherapy     | 6                   | bleomycin                                      | 7                                    | 4                                                        |
| Chemotherapy     | 6                   | busulfan                                       | 0                                    | 0                                                        |
| Chemotherapy     | 6                   | cabazitaxel                                    | 2                                    | 10                                                       |
| Chemotherapy     | 6                   | calaspargase                                   | 0                                    | 0                                                        |
| Chemotherapy     | 6                   | capecitabine                                   | 31                                   | 69                                                       |
| Chemotherapy     | 6                   | carboplatin                                    | 49                                   | 171                                                      |
| Chemotherapy     | 6                   | carmustine                                     | 0                                    | 1                                                        |
| Chemotherapy     | 6                   | chlorambucil                                   | 3                                    | 3                                                        |
| Chemotherapy     | 6                   | cisplatin                                      | 14                                   | 69                                                       |
| Chemotherapy     | 6                   | cladribine                                     | 1                                    | 1                                                        |
| Chemotherapy     | 6                   | clofarabine                                    | 0                                    | 0                                                        |
| Chemotherapy     | 6                   | cyclophosphamide                               | 37                                   | 99                                                       |
| Chemotherapy     | 6                   | cytarabine                                     | 2                                    | 8                                                        |
| Chemotherapy     | 6                   | dacarbazine                                    | 8                                    | 7                                                        |
| Chemotherapy     | 6                   | dactinomycin                                   | 0                                    | 0                                                        |
| Chemotherapy     | 6                   | daunorubicin                                   | 0                                    | 1                                                        |
| Chemotherapy     | 6                   | decitabine                                     | 10                                   | 27                                                       |
| Chemotherapy     | 6                   | docetaxel                                      | 21                                   | 66                                                       |
| Chemotherapy     | 6                   | doxorubicin                                    | 35                                   | 105                                                      |
| Chemotherapy     | 6                   | epirubicin                                     | 2                                    | 8                                                        |
| Chemotherapy     | 6                   | eribulin                                       | 0                                    | 0                                                        |
| Chemotherapy     | 6                   | etoposide                                      | 10                                   | 60                                                       |
| Chemotherapy     | 6                   | fludarabine                                    | 2                                    | 1                                                        |
| Chemotherapy     | 6                   | gemcitabine                                    | 38                                   | 126                                                      |
| Chemotherapy     | 6                   | hydroxycamptothecin                            | 0                                    | 0                                                        |
| Chemotherapy     | 6                   | hydroxyurea                                    | 90                                   | 146                                                      |
| Chemotherapy     | 6                   | idarubicin                                     | 0                                    | 0                                                        |
| Chemotherapy     | 6                   | ifosfamide                                     | 0                                    | 2                                                        |
| Chemotherapy     | 6                   | irinotecan                                     | 19                                   | 47                                                       |

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| Therapy Type        | Count | Drug Name     | Total 1 | Total 2 |
|--------------------|-------|---------------|---------|---------|
| Chemotherapy       | 6     | ixabepilone   | 0       | 0       |
| Chemotherapy       | 6     | lomustine     | 0       | 1       |
| Chemotherapy       | 6     | mechlorethamine | 0     | 1       |
| Chemotherapy       | 6     | melphalan     | 0       | 2       |
| Chemotherapy       | 6     | mercaptopurine | 28     | 41      |
| Chemotherapy       | 6     | mitomycin c   | 0       | 0       |
| Chemotherapy       | 6     | mitoxantrone  | 0       | 1       |
| Chemotherapy       | 6     | nelarabine    | 0       | 0       |
| Chemotherapy       | 6     | oxaliplatin   | 33      | 91      |
| Chemotherapy       | 6     | paclitaxel    | 46      | 141     |
| Chemotherapy       | 6     | pegasparagase | 0       | 1       |
| Chemotherapy       | 6     | pemetrexed    | 18      | 50      |
| Chemotherapy       | 6     | pralatrexate  | 0       | 0       |
| Chemotherapy       | 6     | procarbazine  | 0       | 1       |
| Chemotherapy       | 6     | temozolomide  | 7       | 7       |
| Chemotherapy       | 6     | thioquanine   | 0       | 1       |
| Chemotherapy       | 6     | thiotepe      | 0       | 1       |
| Chemotherapy       | 6     | topotecan     | 0       | 1       |
| Chemotherapy       | 6     | trabectedin   | 0       | 1       |
| Chemotherapy       | 6     | trifluridine  | 4       | 16      |
| Chemotherapy       | 6     | valrubicin    | 0       | 1       |
| Chemotherapy       | 6     | vinblastine   | 8       | 7       |
| Chemotherapy       | 6     | vincristine   | 13      | 52      |
| Chemotherapy       | 6     | vindesine     | 0       | 0       |
| Chemotherapy       | 6     | vinorelbine   | 0       | 2       |
| Cytokine-blocking  | 3     | adalimumab    | 532     | 630     |
| Cytokine-blocking  | 3     | anakinra      | 6       | 7       |
| Cytokine-blocking  | 3     | benralizumab  | 32      | 59      |
| Cytokine-blocking  | 3     | brodalumab    | 0       | 0       |
| Cytokine-blocking  | 3     | canakinumab   | 0       | 0       |
| Cytokine-blocking  | 3     | certolizumab  | 36      | 46      |
| Cytokine-blocking  | 3     | dupilumab     | 95      | 148     |
| Cytokine-blocking  | 3     | etanercept    | 188     | 203     |
| Cytokine-blocking  | 3     | golimumab     | 11      | 13      |
| Cytokine-blocking  | 3     | infliximab    | 102     | 151     |
| Cytokine-blocking  | 3     | ixekizumab    | 46      | 88      |
| Cytokine-blocking  | 3     | mepolizumab   | 56      | 64      |
| Cytokine-blocking  | 3     | rilonacept    | 0       | 0       |
| Category                     | Drug名称 | Count | Count |
|------------------------------|-----------|-------|-------|
| Cytokine-blocking            | sarilumab | 0     | 1     |
| Cytokine-blocking            | secukinumab | 59    | 60    |
| Cytokine-blocking            | tocilizumab | 21    | 88    |
| Cytokine-blocking            | ustekinumab | 60    | 80    |
| Glucocorticoids              | methylprednisolone | 1026 | 3760 |
| Glucocorticoids              | prednisone | 2009 | 4675 |
| Leukocyte-inhibitory         | abatacept | 41    | 57    |
| Leukocyte-inhibitory         | azathioprine | 177   | 210   |
| Leukocyte-inhibitory         | baricitinib | 1    | 73    |
| Leukocyte-inhibitory         | belimumab | 5     | 5     |
| Leukocyte-inhibitory         | dimethyl fumarate | 0    | 0     |
| Leukocyte-inhibitory         | fingolimod | 19   | 20    |
| Leukocyte-inhibitory         | leflunomide | 129  | 168   |
| Leukocyte-inhibitory         | methotrexate | 629  | 789   |
| Leukocyte-inhibitory         | mycophenolate | 229  | 389   |
| Leukocyte-inhibitory         | mycophenolic | 54   | 119   |
| Leukocyte-inhibitory         | natalizumab | 3    | 7     |
| Leukocyte-inhibitory         | rapamycin | 4     | 9     |
| Leukocyte-inhibitory         | sirolimus | 42    | 67    |
| Leukocyte-inhibitory         | teriflunomide | 14  | 12    |
| Leukocyte-inhibitory         | tofacitinib | 71   | 84    |
| Leukocyte-inhibitory         | upadacitinib | 1   | 5     |
| Leukocyte-inhibitory         | vedolizumab | 41   | 54    |
| Lymphocyte-depleting         | alemtuzumab | 1    | 6     |
| Lymphocyte-depleting         | obinutuzumab | 13  | 27    |
| Lymphocyte-depleting         | ocrelizumab | 48   | 111   |
| Lymphocyte-depleting         | rituximab | 164   | 452   |

*Prescription within this number of months before vaccination or before breakthrough infection was used to define use.*
### eTable 3. Full Cohort, Data and Analysis, Univariable and Multivariable

|                        | Overall | Non-severe | Severe | Univariable OR (CI) | Multivariable OR (CI) | P (multi) |
|------------------------|---------|------------|--------|---------------------|-----------------------|-----------|
| **N**                  | 110760  | 100148     | 10612  |                     |                       |           |
| **Sex (%)**            |         |            |        |                     |                       |           |
| Male                   | 97614 (88.1) | 87389 (87.3) | 10225 (96.4) | 1.0 (referent) | 1.0 (referent) |           |
| Female                 | 13146 (11.9) | 22759 (22.7) | 387 (3.6) | 0.26 (0.23 - 0.29) | 0.67 (0.60 - 0.75) | <1.0E-08 |
| **Age ranges (%)**     |         |            |        |                     |                       |           |
| Less than 40           | 13114 (11.8) | 13004 (13.0) | 110 (1.0) | 0.49 (0.37 - 0.64) | 0.57 (0.44 - 0.75) | 6.0E-05  |
| 40-45                  | 6241 (5.6) | 6153 (6.1) | 88 (0.8) | 0.83 (0.62 - 1.10) | 0.88 (0.66 - 1.18) | 0.40      |
| 45-50                  | 6307 (5.7) | 6200 (6.2) | 107 (1.0) | 1.0 (referent)      | 1.0 (referent)       |           |
| 50-55                  | 9721 (8.8) | 9444 (9.4) | 277 (2.6) | 1.70 (1.36 - 2.13) | 1.60 (1.27 - 2.01) | 5.0E-05  |
| 55-60                  | 10934 (9.9) | 10458 (10.4) | 476 (4.5) | 2.64 (2.13 - 3.26) | 2.24 (1.80 - 2.78) | <1.0E-08 |
| 60-65                  | 12971 (11.7) | 12082 (12.1) | 889 (8.4) | 4.26 (3.48 - 5.22) | 3.24 (2.64 - 3.99) | <1.0E-08 |
| 65-70                  | 12353 (11.2) | 11013 (11.0) | 1340 (12.6) | 7.05 (5.78 - 8.61) | 4.82 (3.93 - 5.92) | <1.0E-08 |
| 70-75                  | 18327 (16.5) | 15703 (15.7) | 2624 (24.7) | 9.68 (7.96 - 11.8) | 6.63 (5.42 - 8.11) | <1.0E-08 |
| 75-80                  | 11562 (10.4) | 9546 (9.5) | 2016 (19.0) | 12.2 (10.1 - 14.9) | 8.72 (7.10 - 10.7) | <1.0E-08 |
| 80 or greater          | 9230 (8.3) | 6545 (6.5) | 2685 (25.3) | 23.8 (19.5 - 28.9) | 16.6 (13.5 - 20.4) | <1.0E-08 |
| **Race (%)**           |         |            |        |                     |                       |           |
| American Indian or Alaska Native | 890 (0.8) | 802 (0.8) | 88 (0.8) | 0.92 (0.74 - 1.15) | 1.33 (1.04 - 1.71) | 0.02      |
| Asian                  | 1581 (1.4) | 1525 (1.5) | 56 (0.5) | 0.31 (0.24 - 0.40) | 0.82 (0.61 - 1.09) | 0.17      |
| Black or African American | 26953 (24.3) | 24790 (24.8) | 2163 (20.4) | 0.73 (0.69 - 0.77) | 0.97 (0.91 - 1.03) | 0.28      |
| Native Hawaiian or other Pacific Islander | 1142 (1.0) | 1066 (1.1) | 76 (0.7) | 0.60 (0.47 - 0.75) | 0.88 (0.68 - 1.13) | 0.31      |
| White                  | 71665 (64.7) | 64018 (63.9) | 7647 (72.1) | 1.0 (referent)      | 1.0 (referent)       |           |
| Unknown                | 8529 (7.7) | 7947 (7.9) | 582 (5.5) | 0.61 (0.56 - 0.67) | 0.91 (0.81 - 1.01) | 0.06      |
| **Ethnicity Hispanic/Latino (%)** | 11259 (10.2) | 10505 (10.5) | 754 (7.1) | 0.64 (0.59 - 0.69) | 1.01 (0.93 - 1.11) | 0.77      |
| Hispanic or Latino     | 93400 (84.3) | 83941 (83.8) | 9459 (89.1) | 1.0 (referent)      | 1.0 (referent)       |           |
| Not Hispanic or Latino | 6101 (5.5) | 5702 (5.7) | 399 (3.8) | 0.62 (0.56 - 0.69) | 1.03 (0.90 - 1.17) | 0.70      |
| **US Region (%)**      |         |            |        |                     |                       |           |
| Continental            | 18140 (16.4) | 16243 (16.2) | 1897 (17.9) | 1.05 (0.98 - 1.11) | 1.16 (1.08 - 1.24) | 4.0E-05   |
| Midwest                | 21889 (19.8) | 19561 (19.5) | 2328 (21.9) | 1.07 (1.00 - 1.13) | 0.99 (0.92 - 1.06) | 0.69      |
| North Atlantic         | 23790 (21.5) | 21584 (21.6) | 2206 (20.8) | 0.92 (0.86 - 0.97) | 0.93 (0.87 - 1.00) | 0.05      |
| Pacific                | 20232 (18.3) | 18523 (18.5) | 1709 (16.1) | 0.83 (0.77 - 0.88) | 0.96 (0.89 - 1.03) | 0.27      |
| Southeast              | 24404 (22.0) | 21954 (21.9) | 2450 (23.1) | 1.0 (referent)      | 1.0 (referent)       |           |
| Unknown                | 2305 (2.1) | 2283 (2.3) | 22 (0.2) | 0.09 (0.06 - 0.13) | 0.33 (0.21 - 0.50) | 3.2E-07   |
| **Period of dominant variant (%)** |         |            |        |                     |                       |           |
| Period                  | (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | p-value |
|------------------------|---------|---------|---------|---------|---------|---------|
| **Pre-delta period**   | 2888 (2.6) | 2251 (2.2) | 637 (6.0) | 1.0 (referent) | 1.0 (referent) | 0.42 |
| **Delta period**       | 29493 (26.6) | 24762 (24.7) | 4731 (44.6) | 2.45 (2.35 - 2.55) | 0.95 (0.83 - 1.08) | 0.42 |
| **Omicron period**     | 78379 (70.8) | 73135 (73.0) | 5244 (49.4) | 0.36 (0.35 - 0.38) | 0.49 (0.42 - 0.56) | <1.0E-08^a |

**Vaccine type (%)**

| Vaccine Type | (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | p-value |
|--------------|---------|---------|---------|---------|---------|---------|
| Janssen      | 11066 (10.0) | 10028 (10.0) | 1038 (9.8) | 0.95 (0.88 - 1.02) | 1.30 (1.20 - 1.41) | <1.0E-08^a |
| Moderna      | 45530 (41.1) | 41289 (41.2) | 4241 (40.0) | 0.94 (0.90 - 0.98) | 0.79 (0.75 - 0.83) | <1.0E-08^a |
| Pfizer       | 54164 (48.9) | 48831 (48.8) | 5333 (50.3) | 1.0 (referent) | 1.0 (referent) | 0.03 |

**History of infection before vaccinated (%)**

| (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | p-value |
|---------|---------|---------|---------|---------|---------|---------|
| 4373 (3.9) | 3959 (4.0) | 414 (3.9) | 0.99 (0.89 - 1.09) | 0.69 (0.61 - 0.78) | <1.0E-08^a |

**Months since full vax at breakthrough (%)**

| (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | p-value |
|---------|---------|---------|---------|---------|---------|---------|
| 4 or less | 12497 (11.3) | 10983 (11.0) | 1514 (14.3) | 1.0 (referent) | 1.0 (referent) | 0.33 |
| 4-5      | 7216 (6.5) | 6355 (6.3) | 861 (8.1) | 0.98 (0.90 - 1.07) | 1.06 (0.95 - 1.18) | 0.01 |
| 5-6      | 8148 (7.4) | 7039 (7.0) | 1109 (10.5) | 1.14 (1.05 - 1.24) | 1.01 (0.91 - 1.12) | 0.87 |
| 6-7      | 8902 (8.0) | 7763 (7.8) | 1139 (10.7) | 1.06 (0.98 - 1.16) | 1.08 (0.97 - 1.20) | 0.15 |
| 7-8      | 11739 (10.6) | 10665 (10.6) | 1074 (10.1) | 0.73 (0.67 - 0.79) | 1.13 (1.02 - 1.26) | 0.02^a |
| 8-9      | 19118 (17.3) | 17873 (17.8) | 1245 (11.7) | 0.51 (0.47 - 0.55) | 1.15 (1.03 - 1.28) | 0.01^a |
| 9-10     | 19997 (18.1) | 18570 (18.5) | 1427 (13.4) | 0.56 (0.52 - 0.60) | 1.16 (1.03 - 1.30) | 0.01^a |
| 10-11    | 15731 (14.2) | 14252 (14.2) | 1479 (13.9) | 0.75 (0.70 - 0.81) | 1.34 (1.19 - 1.51) | 1.4E-06^a |
| 11-12    | 6519 (5.9) | 5853 (5.8) | 666 (6.3) | 0.83 (0.75 - 0.91) | 1.47 (1.28 - 1.69) | 7.1E-08^a |
| 12 or more | 893 (0.8) | 795 (0.8) | 98 (0.9) | 0.89 (0.72 - 1.11) | 1.57 (1.22 - 2.04) | 5.7E-04^a |

**Months since boosted at breakthrough (%)**

| (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | p-value |
|---------|---------|---------|---------|---------|---------|---------|
| Not boosted | 81039 (73.2) | 72483 (72.4) | 8556 (80.6) | 1.0 (referent) | 1.0 (referent) | 0.03 |
| 1 or less | 5755 (5.2) | 5401 (5.4) | 354 (3.3) | 0.56 (0.50 - 0.62) | 0.56 (0.49 - 0.63) | <1.0E-08^a |
| 1-2      | 7732 (7.0) | 7341 (7.3) | 391 (3.7) | 0.45 (0.41 - 0.50) | 0.43 (0.38 - 0.48) | <1.0E-08^a |
| 2-3      | 8550 (7.7) | 7996 (8.0) | 554 (5.2) | 0.59 (0.54 - 0.64) | 0.46 (0.41 - 0.51) | <1.0E-08^a |
| 3-4      | 4633 (4.2) | 4197 (4.2) | 436 (4.1) | 0.88 (0.80 - 0.97) | 0.54 (0.48 - 0.61) | <1.0E-08^a |
| 4-5      | 1749 (1.6) | 1543 (1.5) | 206 (1.9) | 1.13 (0.98 - 1.31) | 0.59 (0.50 - 0.70) | <1.0E-08^a |
| 5-6      | 370 (0.3) | 320 (0.3) | 50 (0.5) | 1.32 (0.98 - 1.78) | 0.68 (0.48 - 0.95) | 0.02^a |
| 6 or more | 932 (0.8) | 867 (0.9) | 65 (0.6) | 0.64 (0.49 - 0.82) | 0.78 (0.59 - 1.03) | 0.08 |

**Immune-suppressive medications before breakthrough (%)**

| (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | p-value |
|---------|---------|---------|---------|---------|---------|---------|
| Before breakthrough | 1006 (0.9) | 696 (0.7) | 310 (2.9) | 4.30 (3.76 - 4.92) | 2.71 (2.27 - 3.24) | <1.0E-08^a |
| Before breakthrough Cytokine-blocking | 1601 (1.4) | 1401 (1.4) | 200 (1.9) | 1.35 (1.17 - 1.57) | 1.66 (1.32 - 2.09) | 1.6E-05^a |
| Before breakthrough Glucocorticoids | 7544 (6.8) | 5723 (5.7) | 1821 (17.2) | 3.42 (3.23 - 3.62) | 2.34 (2.18 - 2.50) | <1.0E-08^a |

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| Category                              | Before breakthrough Leukocyte-inhibitory | Before breakthrough Lymphocyte-depleting | Immune-suppressive medications before initial vaccination (%) | Before vaccine Chemotherapy | Before vaccine Cytokine-blocking | Before vaccine Glucocorticoids | Before vaccine Leukocyte-inhibitory | Before vaccine Lymphocyte-depleting | Persistent positive test (%) | BMI Class (%) |
|---------------------------------------|-----------------------------------------|----------------------------------------|---------------------------------------------------------------|-----------------------------|---------------------------------|---------------------------------|----------------------------------|----------------------------------|-----------------------------|------------------|
| before initial vaccination (%)        | 1924 (1.7)                              | 1438 (1.4)                             | 486 (4.6)                                                    | 3.29 (2.97 - 3.66)          | 2.80 (2.39 - 3.28)              | <1.0E-08                         | 585 (0.5)                      | 406 (0.4)                        | 179 (1.7)                          | 4.21 (3.53 - 5.03) | 2.07 (1.57 - 2.72) | 2.1E-07<sup>a</sup> |
| before initial vaccination (%)        | 1368 (1.2)                              | 1099 (1.1)                             | 269 (2.5)                                                    | 2.34 (2.05 - 2.68)          | 0.80 (0.65 - 0.98)              | 0.03<sup>a</sup>                 | 1211 (1.1)                     | 1096 (1.1)                      | 115 (1.1)                          | 4.34 (3.27 - 5.76) | 1.07 (0.69 - 1.65) | 0.77<sup>a</sup>         |
| persistent positive test (%)         | 462 (0.4)                               | 359 (0.4)                              | 103 (1.0)                                                    | 2.72 (2.19 - 3.39)          | 1.26 (0.98 - 1.62)              | 0.07<sup>a</sup>                | 1368 (1.2)                     | 1099 (1.1)                      | 269 (2.5)                          | 2.34 (2.05 - 2.68) | 0.80 (0.65 - 0.98) | 0.03<sup>a</sup>         |
| before initial vaccination (%)        | 1368 (1.2)                              | 1099 (1.1)                             | 269 (2.5)                                                    | 2.34 (2.05 - 2.68)          | 0.80 (0.65 - 0.98)              | 0.03<sup>a</sup>                | 1368 (1.2)                     | 1099 (1.1)                      | 269 (2.5)                          | 2.34 (2.05 - 2.68) | 0.80 (0.65 - 0.98) | 0.03<sup>a</sup>         |
| persistent positive test (%)         | 462 (0.4)                               | 359 (0.4)                              | 103 (1.0)                                                    | 2.72 (2.19 - 3.39)          | 1.26 (0.98 - 1.62)              | 0.07<sup>a</sup>                | 1368 (1.2)                     | 1099 (1.1)                      | 269 (2.5)                          | 2.34 (2.05 - 2.68) | 0.80 (0.65 - 0.98) | 0.03<sup>a</sup>         |
| BMI Class (%)                         | Underweight                             | Normal                                 | Overweight                                                  | <1.0E-08                     | <1.0E-08<sup>a</sup>             | <1.0E-08<sup>a</sup>            | <1.0E-08<sup>a</sup>            | 1.0 (referent)                  | Normal                                 | <1.0E-08<sup>a</sup>             | <1.0E-08<sup>a</sup>            |
| comorbidities (%)                    | Acquired hypothyroid                     | Acute myocardial infarction            | Alzheimer's disease and related disorders or senile dementia | 3050 (2.8)                  | 1915 (1.9)                      | 1135 (10.7)                     | 6.14 (5.69 - 6.63)             | 2.01 (1.83 - 2.20)              | Acquired hypothyroid                     | 3050 (2.8)                  | 1915 (1.9)                      | 1135 (10.7)                     |
| comorbidities (%)                    | Depression                              | Epilepsy                               | Chronic obstructive pulmonary disease and bronchiectasis     | 83377 (7.5)                 | 6103 (6.1)                      | 2234 (21.1)                     | 4.11 (3.90 - 4.33)             | 1.65 (1.54 - 1.76)              | Depression                              | 83377 (7.5)                 | 6103 (6.1)                      | 2234 (21.1)                     |
| comorbidities (%)                    | Diabetic                                | Obstructive pulmonary disease and bronchiectasis | 83377 (7.5)                 | 6103 (6.1)                      | 2234 (21.1)                     | 4.11 (3.90 - 4.33)             | 1.65 (1.54 - 1.76)              | Domestic violence                     | 83377 (7.5)                 | 6103 (6.1)                      | 2234 (21.1)                     |
| comorbidities (%)                    | Epilepsy                                | Domestic violence                      | Domestic violence                                           | 83377 (7.5)                 | 6103 (6.1)                      | 2234 (21.1)                     | 4.11 (3.90 - 4.33)             | 1.65 (1.54 - 1.76)              | Domestic violence                      | 83377 (7.5)                 | 6103 (6.1)                      | 2234 (21.1)                     |
| comorbidities (%)                    | Epilepsy                                | Domestic violence                      | Domestic violence                                           | 83377 (7.5)                 | 6103 (6.1)                      | 2234 (21.1)                     | 4.11 (3.90 - 4.33)             | 1.65 (1.54 - 1.76)              | Domestic violence                      | 83377 (7.5)                 | 6103 (6.1)                      | 2234 (21.1)                     |
| comorbidities (%)                    | Epilepsy                                | Domestic violence                      | Domestic violence                                           | 83377 (7.5)                 | 6103 (6.1)                      | 2234 (21.1)                     | 4.11 (3.90 - 4.33)             | 1.65 (1.54 - 1.76)              | Domestic violence                      | 83377 (7.5)                 | 6103 (6.1)                      | 2234 (21.1)                     |
| Condition                                      | Cases   | Controls | OR (95% CI) | p-value | Adjusted p-value |
|-----------------------------------------------|---------|----------|-------------|---------|------------------|
| Heart failure                                 | 5444 (4.9) | 3681 (3.7) | 1763 (16.6) | 5.22 (4.91 - 5.55) | 1.74 (1.61 - 1.88) | <1.0E-08^a |
| HIV/AIDS                                      | 874 (0.8)  | 791 (0.8)  | 83 (0.8)    | 0.99 (0.79 - 1.24) | 1.30 (1.01 - 1.68) | 0.04   |
| Hyperlipidemia                                | 31511 (28.4) | 27624 (27.6) | 3887 (36.6) | 1.52 (1.46 - 1.58) | 0.79 (0.75 - 0.84) | <1.0E-08^a |
| Hypertension                                  | 38909 (35.1) | 33190 (33.1) | 5719 (53.9) | 2.36 (2.26 - 2.46) | 1.09 (1.03 - 1.15) | 0.004^a |
| Ischemic heart disease                        | 11007 (9.9)  | 8720 (8.7)  | 2287 (21.6) | 2.88 (2.74 - 3.03) | 0.98 (0.92 - 1.05) | 0.56   |
| Leukemias and lymphomas                       | 1336 (1.2)  | 993 (1.0)   | 343 (3.2)   | 3.34 (2.95 - 3.78) | 1.87 (1.61 - 2.17) | <1.0E-08^a |
| Liver disease: cirrhosis and other liver conditions except viral hepatitis | 4193 (3.8)  | 3568 (3.6)  | 625 (5.9)   | 1.69 (1.55 - 1.85) | 1.36 (1.23 - 1.51) | <1.0E-08^a |
| Lung cancer                                   | 824 (0.7)   | 573 (0.6)   | 251 (2.4)   | 4.21 (3.62 - 4.89) | 1.61 (1.36 - 1.92) | 5.0E-08^a |
| Mobility impairments                          | 1030 (0.9)  | 728 (0.7)   | 302 (2.8)   | 4.00 (3.49 - 4.58) | 1.92 (1.63 - 2.26) | <1.0E-08^a |
| Multiple sclerosis and transverse myelitis     | 454 (0.4)   | 362 (0.4)   | 92 (0.9)    | 2.41 (1.92 - 3.03) | 2.86 (2.17 - 3.78) | <1.0E-08^a |
| Peripheral vascular disease                   | 3097 (2.8)  | 2241 (2.2)  | 856 (8.1)   | 3.83 (3.53 - 4.16) | 1.26 (1.14 - 1.39) | 5.4E-06^a |
| Pressure and chronic ulcers                   | 1347 (1.2)  | 872 (0.9)   | 475 (4.5)   | 5.33 (4.76 - 5.98) | 1.58 (1.37 - 1.81) | <1.0E-08^a |
| Prostate cancer                               | 3815 (3.4)  | 3182 (3.2)  | 633 (6.0)   | 1.93 (1.77 - 2.11) | 0.90 (0.81 - 0.99) | 0.03^a  |
| Schizophrenia and other psychotic disorders    | 2755 (2.5)  | 2320 (2.3)  | 435 (4.1)   | 1.80 (1.62 - 2.00) | 1.71 (1.51 - 1.93) | <1.0E-08^a |
| Tobacco use                                   | 9322 (8.4)  | 8114 (8.1)  | 1208 (11.4) | 1.46 (1.37 - 1.55) | 1.31 (1.21 - 1.42) | <1.0E-08^a |
| Viral hepatitis                               | 1416 (1.3)  | 1180 (1.2)  | 236 (2.2)   | 1.91 (1.66 - 2.20) | 0.98 (0.83 - 1.16) | 0.82    |

^a Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.035 for this analysis. OR = odds ratio. CI = 95% confidence interval.
eTable 4. Full Cohort Data, 4 Levels of Severity

| Demographic information | Overall | Non-severe | Non-severe | Severe, Survived | Severe, Died\(^a\) |
|-------------------------|---------|------------|------------|------------------|-------------------|
| N                       | 110760  | 96070      | 4078       | 9057             | 1555              |
| Sex = male (%)          | 97614 (88.1) | 83524 (86.9) | 3865 (94.8) | 8691 (96.0)      | 1534 (98.6)       |
| Age ranges (%)          |         |            |            |                  |                   |
| Less than 40            | 13114 (11.8) | 12831 (13.4) | 173 (4.2)  | 106 (1.2)        | 4 (0.3)           |
| 40-45                   | 6241 (5.6)   | 6061 (6.3)   | 92 (2.3)   | 85 (0.9)         | 3 (0.2)           |
| 45-50                   | 6307 (5.7)   | 6103 (6.4)   | 97 (2.4)   | 105 (1.2)        | 2 (0.1)           |
| 50-55                   | 9721 (8.8)   | 9243 (9.6)   | 201 (4.9)  | 263 (2.9)        | 14 (0.9)          |
| 55-60                   | 10934 (9.9)  | 10149 (10.6) | 309 (7.6)  | 444 (4.9)        | 32 (2.1)          |
| 60-65                   | 12971 (11.7)| 11579 (12.1)| 503 (12.3) | 812 (9.0)        | 77 (5.0)          |
| 65-70                   | 12353 (11.2)| 10437 (10.9)| 576 (14.1)| 1190 (13.1)      | 150 (9.6)         |
| 70-75                   | 18327 (16.5)| 14901 (15.5)| 802 (19.7)| 2268 (25.0)      | 356 (22.9)        |
| 75-80                   | 11562 (10.4)| 8966 (9.3)   | 580 (14.2)| 1687 (18.6)      | 329 (21.2)        |
| 80 or greater           | 9230 (8.3)  | 5800 (6.0)  | 745 (18.3)| 2097 (23.2)      | 588 (37.8)        |
| Race (%)                |         |            |            |                  |                   |
| American Indian or Alaska Native | 890 (0.8) | 771 (0.8)  | 31 (0.8)  | 74 (0.8)         | 14 (0.9)          |
| Asian                   | 1581 (1.4)  | 1494 (1.6)  | 31 (0.8)  | 49 (0.5)         | 7 (0.5)           |
| Black or African American | 26953 (24.3) | 23458 (24.4)| 1332 (32.7)| 1881 (20.8)     | 282 (18.1)        |
| Native Hawaiian or other Pacific Islander | 1142 (1.0) | 1029 (1.1) | 37 (0.9)  | 60 (0.7)         | 16 (1.0)          |
| White                   | 71665 (64.7)| 61626 (64.1)| 2392 (58.7)| 6485 (71.6)     | 1162 (74.7)       |
| Unknown                 | 8529 (7.7)  | 7692 (8.0)  | 255 (6.3) | 508 (5.6)        | 74 (4.8)          |
| Ethnicity Hispanic/Latino (%) |         |            |            |                  |                   |
| Hispanic or Latino      | 11259 (10.2)| 10154 (10.6)| 351 (8.6) | 659 (7.3)        | 95 (6.1)          |
| Not Hispanic or Latino  | 93400 (84.3)| 80382 (83.7)| 3559 (87.3)| 8040 (88.8)     | 1419 (91.3)       |
| Unknown                 | 6101 (5.5)  | 5534 (5.8)  | 168 (4.1) | 358 (4.0)        | 41 (2.6)          |
| US Region (%)           |         |            |            |                  |                   |
| Continental             | 18140 (16.4)| 15626 (16.3)| 617 (15.1)| 1633 (18.0)      | 264 (17.0)        |
| Midwest                 | 21889 (19.8)| 18789 (19.6)| 772 (18.9)| 1971 (21.8)      | 357 (23.0)        |
| North Atlantic          | 23790 (21.5)| 20663 (21.5)| 921 (22.6)| 1879 (20.7)      | 327 (21.0)        |
| Pacific                 | 20232 (18.3)| 17853 (18.6)| 670 (16.4)| 1459 (16.1)      | 250 (16.1)        |
| Southeast               | 24404 (22.0)| 20881 (21.7)| 1073 (26.3)| 2097 (23.2)     | 353 (22.7)        |
| Unknown                 | 2305 (2.1)  | 2258 (2.4)  | 25 (0.6)  | 18 (0.2)         | 4 (0.3)           |
| Period of dominant variant |        |            |            |                  |                   |
| Pre-delta period (%)    | 1774 (1.6)  | 1858 (1.9)  | 393 (9.6) | 546 (6.0)        | 91 (5.9)          |
| Period       | 2021 Delta (%) | 2022 Delta (%) | 2022 Omicron (%) | 2023 Delta (%) | 2023 Omicron (%) |
|-------------|----------------|----------------|------------------|----------------|-----------------|
|             | 29493 (26.6)   | 23517 (24.5)   | 1245 (30.5)      | 3995 (44.1)    | 736 (47.3)      |
|             | 78379 (70.8)   | 70695 (73.6)   | 2440 (59.8)      | 4516 (49.9)    | 728 (46.8)      |

**Vaccination-related**

**Vaccine type (%)**

| Vaccine | 2021 (%) | 2022 (%) | 2023 (%) |
|---------|----------|----------|----------|
| Janssen | 11066 (10.0) | 9652 (10.0) | 376 (9.2) |
| Moderna | 45530 (41.1) | 39831 (41.5) | 1458 (35.8) |
| Pfizer  | 54164 (48.9) | 46587 (48.5) | 2244 (55.0) |

**Months since full vax at breakthrough (%)**

| Months       | 2021 (%) | 2022 (%) | 2023 (%) |
|--------------|----------|----------|----------|
| 4 or less    | 12497 (11.3) | 10216 (10.6) | 767 (18.8) |
| 4-5          | 7216 (6.5) | 6078 (6.3) | 277 (6.8) |
| 5-6          | 8148 (7.4) | 6721 (7.0) | 318 (7.8) |
| 6-7          | 8902 (8.0) | 7434 (7.7) | 329 (8.1) |
| 7-8          | 11739 (10.6) | 10301 (10.7) | 364 (8.9) |
| 8-9          | 19118 (17.3) | 17411 (18.1) | 462 (11.3) |
| 9-10         | 19997 (18.1) | 17948 (18.7) | 622 (15.3) |
| 10-11        | 15731 (14.2) | 13677 (14.2) | 575 (14.1) |
| 11-12        | 6519 (5.9) | 5548 (5.8) | 305 (7.5) |
| 12 or more   | 893 (0.8) | 736 (0.8) | 59 (1.4) |

**Months since boosted at breakthrough (%)**

| Months       | 2021 (%) | 2022 (%) | 2023 (%) |
|--------------|----------|----------|----------|
| Not boosted  | 81039 (73.2) | 69486 (72.3) | 2997 (73.5) |
| 1 or less    | 5755 (5.2) | 5186 (5.4) | 215 (5.3) |
| 1-2          | 7732 (7.0) | 7098 (7.4) | 243 (6.0) |
| 2-3          | 8550 (7.7) | 7706 (8.0) | 290 (7.1) |
| 3-4          | 4633 (4.2) | 4007 (4.2) | 190 (4.7) |
| 4-5          | 1749 (1.6) | 1454 (1.5) | 89 (2.2) |
| 5-6          | 370 (0.3) | 299 (0.3) | 21 (0.5) |
| 6 or more    | 932 (0.8) | 834 (0.9) | 33 (0.8) |

**History of infection before vaccination (%)**

| Infection before vaccination | 2021 (%) | 2022 (%) |
|-----------------------------|----------|----------|
| Persistent positive test    | 462 (0.4) | 331 (0.3) |

**Immune-suppressive medications after vaccination (i.e. before breakthrough) (%)**

| Medication Type          | 2021 (%) | 2022 (%) |
|--------------------------|----------|----------|
| Chemotherapy             | 1006 (0.9) | 607 (0.6) |
| Cytokine-blocking        | 1601 (1.4) | 1334 (1.4) |
| Glucocorticoids          | 7544 (6.8) | 5375 (5.6) |
| Leukocyte-inhibitory     | 1924 (1.7) | 1334 (1.4) |
| Lymphocyte-depleting     | 585 (0.5) | 374 (0.4) |
| Immune-suppressive medications before initial vaccination (%) |        |        |        |        |        |
|-------------------------------------------------------------|--------|--------|--------|--------|--------|
| Chemotherapy                                                | 430 (0.4) | 291 (0.3) | 25 (0.6) | 79 (0.9) | 35 (2.3) |
| Cytokine-blocking                                            | 1211 (1.1) | 1047 (1.1) | 49 (1.2) | 97 (1.1) | 18 (1.2) |
| Glucocorticoids                                              | 2754 (2.5) | 1981 (2.1) | 143 (3.5) | 515 (5.7) | 115 (7.4) |
| Leukocyte-inhibitory                                        | 1368 (1.2) | 1042 (1.1) | 57 (1.4) | 206 (2.3) | 63 (4.1) |
| Lymphocyte-depleting                                        | 223 (0.2) | 141 (0.1) | 12 (0.3) | 51 (0.6) | 19 (1.2) |

| BMI Class (%)                                                |        |        |        |        |        |
|-------------------------------------------------------------|--------|--------|--------|--------|--------|
| Underweight                                                 | 677 (0.6) | 435 (0.5) | 61 (1.5) | 142 (1.6) | 39 (2.5) |
| Normal                                                      | 14394 (13.0) | 11420 (11.9) | 879 (21.6) | 1699 (18.8) | 396 (25.5) |
| Overweight                                                  | 32707 (29.5) | 28448 (29.6) | 1344 (33.0) | 2477 (27.3) | 438 (28.2) |
| Obesity I                                                   | 31156 (28.1) | 27612 (28.7) | 945 (23.2) | 2237 (24.7) | 362 (23.3) |
| Obesity II                                                  | 16862 (15.2) | 14864 (15.5) | 471 (11.5) | 1351 (14.9) | 176 (11.3) |
| Severe Obesity                                              | 10641 (9.6) | 9221 (9.6) | 289 (7.1) | 1008 (11.1) | 123 (7.9) |
| Unknown                                                     | 4323 (3.9) | 4070 (4.2) | 89 (2.2) | 143 (1.6) | 21 (1.4) |

| Comorbidities (%)                                           |        |        |        |        |        |
|-------------------------------------------------------------|--------|--------|--------|--------|--------|
| Acquired hypothyroid                                         | 4965 (4.5) | 3945 (4.1) | 228 (5.6) | 655 (7.2) | 137 (8.8) |
| Acute myocardial infarction                                  | 787 (0.7) | 493 (0.5) | 80 (2.0) | 191 (2.1) | 23 (1.5) |
| Alzheimers disease and related disorders or senile dementia  | 3050 (2.8) | 1526 (1.6) | 389 (9.5) | 915 (10.1) | 220 (14.1) |
| Anemia                                                      | 8134 (7.3) | 5507 (5.7) | 761 (18.7) | 1546 (17.1) | 320 (20.6) |
| Anxiety disorders                                           | 26281 (23.7) | 23412 (24.4) | 931 (22.8) | 1717 (19.0) | 221 (14.2) |
| Asthma                                                      | 3518 (3.2) | 3083 (3.2) | 123 (3.0) | 284 (3.1) | 28 (1.8) |
| Atrial fibrillation                                         | 5799 (5.2) | 3843 (4.0) | 456 (11.2) | 1258 (13.9) | 242 (15.6) |
| Bipolar disorder                                            | 6297 (5.7) | 5271 (5.5) | 383 (9.4) | 577 (6.4) | 66 (4.2) |
| Chronic kidney disease                                      | 11832 (10.7) | 8060 (8.4) | 1011 (24.8) | 2293 (25.3) | 468 (30.1) |
| Chronic obstructive pulmonary disease and bronchiectasis     | 8337 (7.5) | 5669 (5.9) | 434 (10.6) | 1947 (21.5) | 287 (18.5) |
| Colorectal cancer                                           | 608 (0.5) | 442 (0.5) | 45 (1.1) | 96 (1.1) | 25 (1.6) |
| Depression                                                  | 22542 (20.4) | 19538 (20.3) | 979 (24.0) | 1786 (19.7) | 239 (15.4) |
| Diabetes                                                    | 26083 (23.5) | 20471 (21.3) | 1448 (35.5) | 3534 (39.0) | 630 (40.5) |
| Epilepsy                                                    | 1081 (1.0) | 768 (0.8) | 102 (2.5) | 184 (2.0) | 27 (1.7) |
| Heart failure                                               | 5444 (4.9) | 3156 (3.3) | 525 (12.9) | 1470 (16.2) | 293 (18.8) |
| Human immunodeficiency virus and/or acquired immunodeficiency syndrome HIV/AIDS | 874 (0.8) | 752 (0.8) | 39 (1.0) | 72 (0.8) | 11 (0.7) |
| Hyperlipidemia                                              | 31511 (28.4) | 26140 (27.2) | 1484 (36.4) | 3360 (37.1) | 527 (33.9) |
| Hypertension                                                | 38909 (35.1) | 31113 (32.4) | 2077 (50.9) | 4860 (53.7) | 859 (55.2) |
| Ischemic heart disease                                      | 11007 (9.9) | 7949 (8.3) | 771 (18.9) | 1921 (21.2) | 366 (23.5) |
| Condition                                      | Case A | Case B | Case C | Case D | Case E |
|------------------------------------------------|--------|--------|--------|--------|--------|
| Leukemias and lymphomas                       | 1336 (1.2) | 922 (1.0) | 71 (1.7) | 247 (2.7) | 96 (6.2) |
| Liver disease cirrhosis and other liver conditions except viral hepatitis | 4193 (3.8) | 3267 (3.4) | 301 (7.4) | 521 (5.8) | 104 (6.7) |
| Lung cancer                                    | 824 (0.7) | 525 (0.5) | 48 (1.2) | 200 (2.2) | 51 (3.3) |
| Mobility impairments                           | 1030 (0.9) | 580 (0.6) | 148 (3.6) | 271 (3.0) | 31 (2.0) |
| Multiple sclerosis and transverse myelitis      | 454 (0.4) | 332 (0.3) | 30 (0.7) | 85 (0.9) | 7 (0.5) |
| Peripheral vascular disease                    | 3097 (2.8) | 1946 (2.0) | 295 (7.2) | 699 (7.7) | 157 (10.1) |
| Pressure and chronic ulcers                    | 1347 (1.2) | 656 (0.7) | 216 (5.3) | 390 (4.3) | 85 (5.5) |
| Prostate cancer                                | 3815 (3.4) | 2943 (3.1) | 239 (5.9) | 529 (5.8) | 104 (6.7) |
| Schizophrenia and other psychotic disorders     | 2755 (2.5) | 2095 (2.2) | 225 (5.5) | 382 (4.2) | 53 (3.4) |
| Tobacco use                                    | 9322 (8.4) | 7560 (7.9) | 554 (13.6) | 1092 (12.1) | 116 (7.5) |
| Viral hepatitis                                 | 1416 (1.3) | 1052 (1.1) | 128 (3.1) | 206 (2.3) | 30 (1.9) |

*a We explored whether use of ICD-10 codes could be used to improve specificity among hospitalized patients, particularly since use was lower among patients who died or required mechanical ventilation. However, review of 25 cases of patients who died indicated that COVID-19 was the cause of death in the great majority even if the ICD-10 codes were not used: 11/13 with use of the code vs. 10/12 without, and with SARS-CoV-2 likely contributing to complex illnesses in several of the other cases. Therefore, ICD-10 codes for COVID-19 were not used in case definitions.*
### eTable 5. Subcohorts, Data for Patients Younger and Older Than 50 Years, Analysis for Patients Younger Than 50 Years

|                  | Greater than age 50 | Less than age 50 | Non-severe, less than 50 | Severe, less than 50 | Multivariable OR (CI) | P      |
|------------------|---------------------|------------------|--------------------------|----------------------|-----------------------|--------|
| N                | 85098               | 25662            | 25357                    | 305                  |                       |        |
| Sex (%)          |                     |                  |                          |                      |                       |        |
| Male             | 78268 (92.0)        | 19346 (75.4)     | 19082 (75.3)             | 264 (86.6)           | 0.47 (0.33 - 0.67)    | 3.1E-05 |
| Female           | 6316 (8.0)          | 6275 (24.7)      | 41 (13.4)                | 41 (13.4)            | 0.47 (0.33 - 0.67)    | 3.1E-05 |
| Age ranges (%)   |                     |                  |                          |                      |                       |        |
| Less than 40     | 13114 (51.1)        | 13004 (51.3)     | 110 (36.1)               | 110 (36.1)           | 1.22 (1.10 - 1.36)    | 1.2E-04 |
| 40-45            | 6241 (24.3)         | 6153 (24.3)      | 88 (28.9)                | 88 (28.9)            | 1.22 (1.10 - 1.36)    | 1.2E-04 |
| 45-50            | 6307 (24.6)         | 6200 (24.5)      | 107 (35.1)               | 107 (35.1)           | 1.22 (1.10 - 1.36)    | 1.2E-04 |
| 50-55            | 9721 (11.4)         |                  |                          |                      |                       |        |
| 55-60            | 10934 (12.8)        |                  |                          |                      |                       |        |
| 60-65            | 12971 (15.2)        |                  |                          |                      |                       |        |
| 65-70            | 12353 (14.5)        |                  |                          |                      |                       |        |
| 70-75            | 18327 (21.5)        |                  |                          |                      |                       |        |
| 75-80            | 11562 (13.6)        |                  |                          |                      |                       |        |
| 80 or greater    | 9230 (10.8)         |                  |                          |                      |                       |        |
| Age per 5-year increase | 1.22 (1.10 - 1.36) | 1.2E-04 | 1.22 (1.10 - 1.36) | 1.2E-04 | 1.22 (1.10 - 1.36) | 1.2E-04 |
| Race (%)         |                     |                  |                          |                      |                       |        |
| American Indian or Alaska Native | 626 (0.7) | 264 (1.0) | 256 (1.0) | 8 (2.6) | 2.96 (1.39 - 6.28) | 0.005 |
| Asian            | 759 (0.9)           | 822 (3.2)        | 816 (3.2)                | 6 (2.0)              | 0.85 (0.37 - 1.97)    | 0.70   |
| Black or African American | 21252 (25.0) | 5701 (22.2) | 5638 (22.2) | 63 (20.7) | 0.84 (0.61 - 1.15) | 0.27   |
| Native Hawaiian or other Pacific Islander | 798 (0.9) | 344 (1.3) | 342 (1.3) | 2 (0.7) | 0.57 (0.14 - 2.34) | 0.44   |
| White            | 5625 (6.6)          | 2904 (11.3)      | 2874 (11.3)              | 30 (9.8)             | 1.0 (referent)        |        |
| Unknown          | 56038 (65.9)        | 15627 (60.9)     | 15431 (60.9)             | 196 (64.3)           | 1.00 (0.64 - 1.55)    | 0.99   |
| Ethnicity Hispanic/Latino (%) |     |                  |                          |                      |                       |        |
| Hispanic or Latino | 6850 (8.0) | 4409 (17.2) | 4365 (17.2) | 44 (14.4) | 0.87 (0.61 - 1.24) | 0.45   |
| Not Hispanic or Latino | 74494 (87.5) | 18906 (73.7) | 18669 (73.6) | 237 (77.7) | 1.0 (referent) |        |
| Unknown          | 3754 (4.4)          | 2347 (9.1)       | 2323 (9.2)               | 24 (7.9)             | 1.36 (0.82 - 2.25)    | 0.23   |
| US Region (%)    |                     |                  |                          |                      |                       |        |
| Continental      | 13575 (16.0)        | 4565 (17.8)      | 4492 (17.7)              | 73 (23.9)            | 1.10 (0.78 - 1.55)    | 0.59   |
| Midwest          | 17725 (20.8)        | 4164 (16.2)      | 4113 (16.2)              | 51 (16.7)            | 0.83 (0.56 - 1.22)    | 0.34   |
| North Atlantic   | 18426 (21.7)        | 5364 (20.9)      | 5309 (20.9)              | 55 (18.0)            | 0.75 (0.52 - 1.09)    | 0.13   |
| Pacific          | 14739 (17.3)        | 5493 (21.4)      | 5441 (21.5)              | 52 (17.0)            | 0.79 (0.53 - 1.15)    | 0.22   |
| Period of dominant variant (%) | Pre-delta period | Delta period | Omicron period |
|-------------------------------|-----------------|-------------|---------------|
| Southeast                     | 19480 (22.9)    | 4924 (19.2) | 4855 (19.1)   |
| Unknown                       | 1153 (1.4)      | 1152 (4.5)  | 1147 (4.5)    |
| Period of dominant variant (%)|                 |             |               |
| Pre-delta period              | 1.0 (referent)  |             |               |
| Delta period                  | 24712 (29.0)    | 4781 (18.6) | 4666 (18.4)   |
| Omicron period                | 57746 (67.9)    | 20633 (80.4)| 20449 (80.6)  |
| Vaccine type (%)              |                 |             |               |
| Janssen                       | 7503 (8.8)      | 3563 (13.9) | 3496 (13.8)   |
| Moderna                       | 36379 (42.7)    | 9151 (35.7) | 9059 (35.7)   |
| Pfizer                        | 41216 (48.4)    | 12948 (50.5)| 12802 (50.5)  |
| History of infection before vaccinated (%) |                 |             |               |
| 4 or less                     | 8486 (10.0)     | 4011 (15.6) | 3943 (15.5)   |
| 4-5                           | 5379 (6.3)      | 1837 (7.2)  | 1804 (7.1)    |
| 5-6                           | 6521 (7.7)      | 1627 (6.3)  | 1601 (6.3)    |
| 6-7                           | 6700 (7.9)      | 2202 (8.6)  | 2170 (8.6)    |
| 7-8                           | 7930 (9.3)      | 3809 (14.8)| 3770 (14.9)   |
| 8-9                           | 13320 (15.7)    | 5798 (22.6)| 5757 (22.7)   |
| 9-10                          | 16676 (19.6)    | 3321 (12.9)| 3289 (13.0)   |
| 10-11                         | 13907 (16.3)    | 1824 (7.1)  | 1806 (7.1)    |
| 11-12                         | 5455 (6.4)      | 1064 (4.1)  | 1048 (4.1)    |
| 12 or more                    | 724 (0.9)       | 169 (0.7)   | 169 (0.7)     |
| Months since full vax at breakthrough (%) |                 |             |               |
| Not boosted                   | 59003 (69.3)    | 22036 (85.9)| 21758 (85.8)  |
| 1 or less                     | 4655 (5.5)      | 1100 (4.3)  | 1093 (4.3)    |
| 1-2                           | 6656 (7.8)      | 1076 (4.2)  | 1071 (4.2)    |
| 2-3                           | 7825 (9.2)      | 725 (2.8)   | 719 (2.8)     |
| 3-4                           | 4343 (5.1)      | 290 (1.1)   | 287 (1.1)     |
| 4-5                           | 1624 (1.9)      | 125 (0.5)   | 123 (0.5)     |
| 5-6                           | 330 (0.4)       | 40 (0.2)    | 39 (0.2)      |
| 6 or more                     | 662 (0.8)       | 270 (1.1)   | 267 (1.1)     |
| Months since boosted at breakthrough (%) |                 |             |               |
| Not boosted                   | 59003 (69.3)    | 22036 (85.9)| 21758 (85.8)  |
| 1 or less                     | 4655 (5.5)      | 1100 (4.3)  | 1093 (4.3)    |
| 1-2                           | 6656 (7.8)      | 1076 (4.2)  | 1071 (4.2)    |
| 2-3                           | 7825 (9.2)      | 725 (2.8)   | 719 (2.8)     |
| 3-4                           | 4343 (5.1)      | 290 (1.1)   | 287 (1.1)     |
| Immune-suppressive medications before breakthrough (%) |                 |             |               |
| Chemotherapy (%)              | 942 (1.1)       | 64 (0.2)    | 62 (0.2)      |
| Cytokine-blocking (%)         | 1251 (1.5)      | 350 (1.4)   | 346 (1.4)     |
| Glucocorticoids (%)           | 6467 (7.6)      | 1077 (4.2)  | 1039 (4.1)    |
| Leukocyte-inhibitory (%)      | 1702 (2.0)      | 222 (0.9)   | 215 (0.8)     |
| Lymphocyte-depleting (%)      | 497 (0.6)       | 88 (0.3)    | 80 (0.3)      |

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| Therapy (%)                  | 391 (0.5) | 39 (0.2) | 38 (0.1) | 1 (0.3) | 0.71 (0.05 - 9.34) | 0.79 |
|-----------------------------|-----------|----------|----------|---------|-------------------|------|
| Cytokine-blocking (%)       | 922 (1.1) | 289 (1.1) | 288 (1.1) | 1 (0.3) | 0.13 (0.01 - 1.30) | 0.08 |
| Glucocorticoids (%)         | 2377 (2.8) | 377 (1.5) | 360 (1.4) | 17 (5.6) | 1.84 (1.01 - 3.33) | 0.05 |
| Leukocyte-inhibitory (%)    | 1209 (1.4) | 159 (0.6) | 154 (0.6) | 5 (1.6) | 1.48 (0.45 - 4.93) | 0.52 |
| Lymphocyte-depleting (%)    | 193 (0.2) | 30 (0.1) | 28 (0.1) | 2 (0.7) | 0.59 (0.09 - 3.80) | 0.58 |
| Persistent positive test (%)| 404 (0.5) | 58 (0.2) | 56 (0.2) | 2 (0.7) | 1.09 (0.25 - 4.88) | 0.91 |
| BMI Class (%)               |           |          |          |         |                   |      |
| Underweight                 | 591 (0.7) | 86 (0.3) | 83 (0.3) | 3 (1.0) | 2.83 (0.70 - 11.4) | 0.14 |
| Normal                      | 11472 (13.5) | 2922 (11.4) | 2890 (11.4) | 32 (10.5) | 1.0 (referent) |      |
| Overweight                  | 25795 (30.3) | 6912 (26.9) | 6851 (27.0) | 61 (20.0) | 0.76 (0.49 - 1.19) | 0.23 |
| Obesity I                   | 24261 (28.5) | 6895 (26.9) | 6798 (26.8) | 97 (31.8) | 1.16 (0.76 - 1.77) | 0.50 |
| Obesity II                  | 12843 (15.1) | 4019 (15.7) | 3978 (15.7) | 41 (13.4) | 0.73 (0.44 - 1.19) | 0.20 |
| Severe Obesity              | 7870 (9.2) | 2771 (10.8) | 2715 (10.7) | 56 (18.4) | 1.24 (0.77 - 2.00) | 0.37 |
| Unknown                     | 2266 (2.7) | 2057 (8.0) | 2042 (8.1) | 15 (4.9) | 0.89 (0.45 - 1.74) | 0.73 |
| Comorbidities (%)           |           |          |          |         |                   |      |
| Acquired hypothyroidism     | 4393 (5.2) | 572 (2.2) | 561 (2.2) | 11 (3.6) | 1.03 (0.51 - 2.05) | 0.94 |
| Acute myocardial infarction | 749 (0.9) | 38 (0.1) | 31 (0.1) | 7 (2.3) | 2.08 (0.54 - 8.00) | 0.29 |
| Alzheimers disease and related disorders or senile dementia | 3005 (3.5) | 45 (0.2) | 39 (0.2) | 6 (2.0) | 5.33 (1.83 - 15.6) | 0.002a |
| Anemia                      | 7295 (8.6) | 839 (3.3) | 810 (3.2) | 29 (9.5) | 1.64 (1.02 - 2.63) | 0.04 |
| Anxiety disorders           | 16675 (19.6) | 9606 (37.4) | 9475 (37.4) | 131 (43.0) | 1.06 (0.81 - 1.40) | 0.66 |
| Asthma                      | 2524 (3.0) | 994 (3.9) | 973 (3.8) | 21 (6.9) | 1.48 (0.92 - 2.39) | 0.10 |
| Atrial fibrillation         | 5701 (6.7) | 98 (0.4) | 96 (0.4) | 2 (0.7) | 0.58 (0.13 - 2.66) | 0.49 |
| Bipolar disorder            | 4288 (5.0) | 2009 (7.8) | 1969 (7.8) | 40 (13.1) | 1.34 (0.92 - 1.96) | 0.13 |
| Chronic kidney disease      | 11069 (13.0) | 763 (3.0) | 715 (2.8) | 48 (15.7) | 2.38 (1.55 - 3.66) | 7.8E-05a |
| Chronic obstructive pulmonary disease and bronchiectasis | 8150 (9.6) | 187 (0.7) | 177 (0.7) | 10 (3.3) | 1.81 (0.88 - 3.74) | 0.11 |
| Colorectal cancer           | 589 (0.7) | 19 (0.1) | 19 (0.1) | 0 (0.0) | ND                |      |
| Depression                  | 15229 (17.9) | 7313 (28.5) | 7206 (28.4) | 107 (35.1) | 1.05 (0.78 - 1.40) | 0.76 |
| Diabetes                    | 24430 (28.7) | 1653 (6.4) | 1595 (6.3) | 58 (19.0) | 1.57 (1.07 - 2.29) | 0.02 |
| Epilepsy                    | 891 (1.0) | 190 (0.7) | 183 (0.7) | 7 (2.3) | 1.29 (0.53 - 3.12) | 0.57 |
| Heart failure               | 5322 (6.3) | 122 (0.5) | 110 (0.4) | 12 (3.9) | 2.02 (0.92 - 4.47) | 0.08 |
| Human immunodeficiency virus and/or acquired immunodeficiency syndrome HIV/AIDS | 688 (0.8) | 186 (0.7) | 184 (0.7) | 2 (0.7) | 0.64 (0.15 - 2.67) | 0.54 |
| Hyperlipidemia              | 27594 (32.4) | 3917 (15.3) | 3852 (15.2) | 65 (21.3) | 0.66 (0.48 - 0.92) | 0.01 |
| Hypertension                | 35573 (41.8) | 3336 (13.0) | 3251 (12.8) | 85 (27.9) | 1.23 (0.89 - 1.69) | 0.20 |
| Ischemic heart disease      | 10764 (12.6) | 243 (0.9) | 228 (0.9) | 15 (4.9) | 1.13 (0.51 - 2.53) | 0.76 |
| Leukemias and lymphomas     | 1268 (1.5) | 68 (0.3) | 61 (0.2) | 7 (2.3) | 6.34 (2.38 - 16.9) | 2.2E-04a |
| Condition                                                                 | Cases   | Controls | Adjusted OR (95% CI) | P-value |
|---------------------------------------------------------------------------|---------|----------|----------------------|---------|
| Liver disease cirrhosis and other liver conditions except viral hepatitis| 3386 (4.0) | 807 (3.1) | 1.85 (1.21 - 2.85)  | 0.005a  |
| Lung cancer                                                               | 820 (1.0) | 4 (0.0)  | ND                   | 0.005a  |
| Mobility impairments                                                      | 939 (1.1) | 91 (0.4)  | 3.98 (1.83 - 8.65)  | 5.0E-04a |
| Multiple sclerosis and transverse myelitis                                 | 326 (0.4) | 128 (0.5) | 4.71 (1.82 - 12.2)  | 0.001a  |
| Peripheral vascular disease                                               | 3050 (3.6) | 47 (0.2)  | 2.26 (0.62 - 8.24)  | 0.22    |
| Pressure and chronic ulcers                                               | 1306 (1.5) | 41 (0.2)  | 1.05 (0.30 - 3.69)  | 0.94    |
| Prostate cancer                                                           | 3803 (4.5) | 12 (0.0)  | ND                   | 0.005a  |
| Schizophrenia and other psychotic disorders                               | 2148 (2.5) | 607 (2.4) | 1.61 (0.92 - 2.81)  | 0.09    |
| Tobacco use                                                               | 7134 (8.4) | 2188 (8.5) | 1.21 (0.84 - 1.73)  | 0.30    |
| Viral hepatitis                                                            | 1310 (1.5) | 106 (0.4) | 1.98 (0.70 - 5.60)  | 0.20    |
| Death from breakthrough infection                                          | 1546 (1.8) | 9 (0.0)   | ND                   | 0.005a  |

*a Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.006 for this analysis. OR = odds ratio. CI = 95% confidence interval.
eAppendix. Additional Results

Use of ICD-10 codes in the definition of hospitalization for Covid-19?
We explored whether use of ICD-10 codes (U07.1 or J12.82 during hospitalization) could be used to improve specificity among hospitalized patients, particularly since use was lower in the group of patients who died or required mechanical ventilation (79.3% versus 91.4% in other hospitalized patients). However, review of 25 randomly selected cases of patients who died indicated that Covid-19 was the cause of death in the great majority who died within 28 days even if the ICD-10 codes were not used: 11/13 with use of the code vs. 10/12 without, and with SARS-CoV-2 likely contributing to complex illnesses in several of the other cases. Therefore, ICD-10 codes for COVID-19 were not used to refine case definitions.

Body Mass Index (BMI)
After adjustment for comorbidities, the only BMI classes strongly associated with risk were underweight (BMI < 18, OR 1.53, CI 1.24 - 1.87) and severe obesity (BMI > 40, OR 1.23, CI 1.12 - 1.35) relative to normal weight. In addition to low BMI, two other surrogate markers of poor health were significantly associated with risk: mobility impairments (OR 1.92, CI 1.63 – 2.26) and pressure ulcers (OR 1.58, CI 1.37 – 1.81).

Monoclonal Antibody Therapy:
At least 8,522 patients received monoclonal antibody (MAB) therapy prior to hospitalization to prevent disease progression (list of drug names is in eTable 2). Among 14,021 immunocompromised patients, 2,073 (14.8%) received MAB therapy, compared to 6,467 (6.7%) of non-immunocompromised patients. Immunocompromised patients treated with MAB had a 12.3% rate of severe disease, compared with 21.1% among all immunocompromised patients. Among non-immunocompromised patients not adjusted for potential confounding factors that may impact probability of progression to severe disease, patients treated with MAB had an 8.5% rate of severe disease, compared to 7.9% among all non-IC patients. Use of MAB was not included in statistical modeling, for two reasons. First, it is given only to outpatients after a positive test, and only to those considered to be at high risk of severe disease. Therefore, outside of a prospective trial, there are reasons to expect it to be associated with both non-severe and severe disease. Second, it is anticipated that data on use of MAB are likely to be missing, due to receipt outside the VA.

Patients <50 Years of Age:
The characteristics of patients < 50 and > 50 are shown in eTable 5, as are the results of multivariable logistic regression for the group < 50. Overall risk of severe disease in patients < 50 was low (305 / 25,662 = 1.2%), and death was rare (9 / 25,662 = 0.04%). The low number of severe cases in this group limits interpretability; however, a small set of risk factors indicating severe chronic health problems met criteria for statistical significance after correction for multiple comparisons: CKD, hematologic malignancy, multiple sclerosis, chronic liver disease, Alzheimer’s/dementia, mobility impairments, and receipt of glucocorticoids shortly before breakthrough infection. The self-reported racial category of American Indian or Alaska Native also met criteria for statistical significance. Although this finding cannot be ignored, the fact that
it is based on results for only 264 patients is reason to anticipate that it may not be valid. Examination of results for other subgroups in the eTables makes it clear that excess risk in this racial/ethnic group was driven by a small (but higher than other ethnicities) number of severe cases in non-immune-suppressed, relatively young patients.

**Urban and rural location**

The most recent residence listed in VA records was used. For patients with multiple residences, the one closest to the vaccination site was used. Locations were defined as urban per US Census criteria, and all others were considered rural. VA also defines census regions as highly rural if they contain fewer than 7 residents per square mile. However, since only 0.4% (425 / 110,760) of patients in this study resided in highly rural areas, they were combined with the rural group for analysis. 3.8% of patients had unknown classification of residence and were excluded from this subset analysis. Severity data were missing for 110 / 21,007 (0.52%) of rural and 267 / 71,432 (0.37%) of urban patients, indicating that there was not skewed usage of non-VA hospitals, at least not those contracted with the VA for reimbursement. Among all patients with a hospitalization documented, 1.3% of the 12,856 patients for whom severity could be determined were hospitalized only at a non-VA hospital, compared to 21.5% of the 391 patients for whom severity could not be determined and who were therefore excluded from the study.
## eTable 6. Subcohort Immunocompromised, Data and Analysis

|                                      | Overall | Non-severe | Severe | Multivariable OR (CI) | P       |
|--------------------------------------|---------|------------|--------|----------------------|---------|
| N                                    | 14021   | 11062      | 2959   |                      |         |
| **Sex (%)**                          |         |            |        |                      |         |
| Male                                 | 12505   | 9653       | 2852   | 1.0 (referent)       |         |
| Female                               | 1516    | 1409       | 107    | 0.59 (0.47 - 0.74)   | 4.0E-06 |
| **Age ranges (%)**                   |         |            |        |                      |         |
| Less than 40                         | 848     | 829        | 19     | 0.69 (0.37 - 1.29)   | 0.25    |
| 40-45                                | 524     | 506        | 18     | 0.98 (0.52 - 1.86)   | 0.95    |
| 45-50                                | 636     | 613        | 23     | 1.0 (referent)       |         |
| 50-55                                | 1004    | 925        | 79     | 2.06 (1.27 - 3.36)   | 0.004   |
| 55-60                                | 1228    | 1093       | 135    | 2.52 (1.58 - 4.02)   | 9.9E-05 |
| 60-65                                | 1733    | 1467       | 266    | 3.51 (2.24 - 5.51)   | 4.3E-08 |
| 65-70                                | 1874    | 1452       | 422    | 5.01 (3.21 - 7.83)   | <1.0E-08|
| 70-75                                | 2955    | 2122       | 833    | 6.79 (4.37 - 10.6)   | <1.0E-08|
| 75-80                                | 1841    | 1274       | 422    | 7.71 (4.93 - 12.1)   | <1.0E-08|
| 80 or greater                       | 1378    | 781        | 597    | 12.7 (8.04 - 19.9)   | <1.0E-08|
| **Race (%)**                         |         |            |        |                      |         |
| American Indian or Alaska Native     | 95      | 81         | 14     | 0.98 (0.52 - 1.82)   | 0.94    |
| Asian                                | 117     | 102        | 15     | 1.08 (0.59 - 1.99)   | 0.80    |
| Black or African American            | 3339    | 2691       | 648    | 1.07 (0.95 - 1.21)   | 0.25    |
| Native Hawaiian or other Pacific Islander | 130    | 110        | 20     | 0.89 (0.53 - 1.50)   | 0.66    |
| White                                | 9554    | 7438       | 2116   | 1.0 (referent)       |         |
| Unknown                              | 786     | 640        | 146    | 0.99 (0.79 - 1.24)   | 0.93    |
| **Ethnicity Hispanic/Latino (%)**    |         |            |        |                      |         |
| Hispanic or Latino                   | 1094    | 912        | 182    | 1.06 (0.87 - 1.29)   | 0.55    |
| Not Hispanic or Latino               | 12426   | 9731       | 2695   | 1.0 (referent)       |         |
| Unknown                              | 501     | 419        | 82     | 0.94 (0.70 - 1.25)   | 0.66    |
| **US Region (%)**                    |         |            |        |                      |         |
| Continental                          | 2314    | 1835       | 479    | 1.03 (0.89 - 1.19)   | 0.68    |
| Midwest                              | 2973    | 2297       | 676    | 0.95 (0.83 - 1.09)   | 0.45    |
| North Atlantic                       | 3047    | 2419       | 628    | 0.88 (0.76 - 1.00)   | 0.06    |
| Pacific                              | 2096    | 1665       | 431    | 0.95 (0.82 - 1.11)   | 0.55    |
| Southeast                            | 3449    | 2708       | 741    | 1.0 (referent)       |         |
| Unknown                              | 142     | 138        | 4      | 0.30 (0.10 - 0.84)   | 0.02    |
| **Period of dominant variant (%)**   |         |            |        |                      |         |
| Pre-delta period                     | 501     | 299        | 202    | 1.0 (referent)       |         |
|                          | Delta period       | Omicron period      | Vaccine type (%) | History of infection before vaccinated (%) | Months since full vax at breakthrough (%) | Months since boosted at breakthrough (%) | Immune-suppressive medications before breakthrough (%) | Immune-suppressive medications before initial vaccination (%) |
|--------------------------|--------------------|---------------------|------------------|--------------------------------------------|-------------------------------------------|------------------------------------------|-------------------------------------------------------|----------------------------------------------------------|
|                          | 4422 (31.5)        | 3146 (28.4)         | 1276 (43.1)      | 0.74 (0.57 - 0.96)                         | 0.02 a                                    |                                          |                                                      |                                                          |
|                          | 9098 (64.9)        | 7617 (68.9)         | 1481 (50.1)      | 0.44 (0.33 - 0.58)                         | 1.2E-08 a                                 |                                          |                                                      |                                                          |
| Vaccine type (%)         |                    |                     |                  |                                            |                                           |                                          |                                                      |                                                          |
| Janssen                  | 1172 (8.4)         | 940 (8.5)           | 232 (7.8)        | 1.01 (0.93 - 1.33)                         | 0.24                                      |                                          |                                                      |                                                          |
| Moderna                  | 6098 (43.5)        | 4860 (43.9)         | 1238 (41.8)      | 0.78 (0.71 - 0.86)                         | 5.7E-07 a                                 |                                          |                                                      |                                                          |
| Pfizer                   | 6751 (48.1)        | 5262 (47.6)         | 1489 (50.3)      | 1.0 (referent)                             |                                          |                                          |                                                      |                                                          |
| History of infection     |                    |                     |                  |                                            |                                           |                                          |                                                      |                                                          |
| before vaccinated (%)    | 636 (4.5)          | 515 (4.7)           | 121 (4.1)        | 0.61 (0.48 - 0.78)                         | 8.6E-05 a                                 |                                          |                                                      |                                                          |
| Months since            |                    |                     |                  |                                            |                                           |                                          |                                                      |                                                          |
| full vax at breakthrough | 4 or less          | 1672 (11.9)         | 1225 (11.1)      | 1.0 (referent)                             |                                          |                                          |                                                      |                                                          |
|                          | 4-5                | 975 (7.0)           | 743 (6.7)        | 1.09 (0.86 - 1.37)                         | 0.49                                      |                                          |                                                      |                                                          |
|                          | 5-6                | 1159 (8.3)          | 831 (7.5)        | 1.14 (0.91 - 1.41)                         | 0.25                                      |                                          |                                                      |                                                          |
|                          | 6-7                | 1140 (8.1)          | 845 (7.6)        | 1.04 (0.83 - 1.30)                         | 0.74                                      |                                          |                                                      |                                                          |
|                          | 7-8                | 1336 (9.5)          | 1083 (9.8)       | 0.93 (0.74 - 1.17)                         | 0.52                                      |                                          |                                                      |                                                          |
|                          | 8-9                | 2069 (14.8)         | 1759 (15.9)      | 0.99 (0.79 - 1.24)                         | 0.90                                      |                                          |                                                      |                                                          |
|                          | 9-10               | 2488 (17.7)         | 2070 (18.7)      | 1.13 (0.90 - 1.42)                         | 0.30                                      |                                          |                                                      |                                                          |
|                          | 10-11              | 2160 (15.4)         | 1709 (15.9)      | 1.33 (1.04 - 1.70)                         | 0.02 a                                    |                                          |                                                      |                                                          |
|                          | 11-12              | 915 (6.5)           | 710 (6.4)        | 1.39 (1.05 - 1.85)                         | 0.02 a                                    |                                          |                                                      |                                                          |
|                          | 12 or more         | 107 (0.8)           | 87 (0.8)         | 0.94 (0.53 - 1.68)                         | 0.84                                      |                                          |                                                      |                                                          |
| Immune-suppressive       |                    |                     |                  |                                            |                                           |                                          |                                                      |                                                          |
| medications behind      |                    |                     |                  |                                            |                                           |                                          |                                                      |                                                          |
| breakthrough (%)         | Not boosted        | 9408 (67.1)         | 7234 (65.4)      | 2174 (73.5)                                | 1.0 (referent)                            |                                          |                                                      |                                                          |
|                          | 1 or less          | 663 (4.7)           | 541 (4.9)        | 122 (4.1)                                  | 0.78 (0.62 - 0.99)                        | 0.04                                      |                                          |                                                          |
|                          | 1-2                | 878 (6.3)           | 734 (6.6)        | 144 (4.9)                                  | 0.63 (0.51 - 0.78)                        | 1.8E-05 a                                 |                                          |                                                          |
|                          | 2-3                | 1107 (7.9)          | 903 (8.2)        | 204 (6.9)                                  | 0.69 (0.57 - 0.83)                        | 1.0E-04 a                                 |                                          |                                                          |
|                          | 3-4                | 1040 (7.4)          | 883 (8.0)        | 157 (5.3)                                  | 0.51 (0.41 - 0.63)                        | <1.0E-08 a                                |                                          |                                                          |
|                          | 4-5                | 670 (4.8)           | 563 (5.1)        | 107 (3.6)                                  | 0.54 (0.42 - 0.70)                        | 2.1E-06 a                                 |                                          |                                                          |
|                          | 5-6                | 141 (1.0)           | 109 (1.0)        | 32 (1.1)                                   | 0.78 (0.49 - 1.23)                        | 0.29                                      |                                          |                                                          |
|                          | 6 or more          | 114 (0.8)           | 95 (0.9)         | 19 (0.6)                                   | 0.81 (0.47 - 1.41)                        | 0.46                                      |                                          |                                                          |
| Immune-suppressive       |                    |                     |                  |                                            |                                           |                                          |                                                      |                                                          |
| medications before       |                    |                     |                  |                                            |                                           |                                          |                                                      |                                                          |
| breakthrough (%)         | Before breakthrough| 1006 (7.2)          | 696 (6.3)        | 310 (10.5)                                 | 2.21 (1.83 - 2.67)                        | <1.0E-08 a                                |                                          |                                                          |
|                          | Chemotherapy       | 1601 (11.4)         | 1401 (12.7)      | 200 (6.8)                                  | 1.41 (1.12 - 1.78)                        | 0.004 a                                   |                                          |                                                          |
|                          | Cytokine-blocking  | 7544 (53.8)         | 5723 (51.7)      | 1821 (61.5)                                | 1.91 (1.70 - 2.14)                        | <1.0E-08 a                                |                                          |                                                          |
|                          | Glucocorticoids    | 1924 (13.7)         | 1438 (13.0)      | 486 (16.4)                                 | 2.42 (2.05 - 2.85)                        | <1.0E-08 a                                |                                          |                                                          |
|                          | Lymphocyte-depleting| 585 (4.2)           | 406 (3.7)        | 179 (6.0)                                  | 1.94 (1.47 - 2.54)                        | <1.0E-08 a                                |                                          |                                                          |
| Immune-suppressive       |                    |                     |                  |                                            |                                           |                                          |                                                      |                                                          |
| medications before       |                    |                     |                  |                                            |                                           |                                          |                                                      |                                                          |
| initial vaccination (%)  | Before vaccine      | 430 (3.1)           | 316 (2.9)        | 114 (3.9)                                  | 0.87 (0.66 - 1.15)                        | 0.32                                      |                                          |                                                          |
|                          | Chemotherapy       | 1211 (8.6)          | 1096 (9.9)       | 115 (3.9)                                  | 0.59 (0.45 - 0.79)                        | 2.9E-04 a                                 |                                          |                                                          |
|                          | Cytokine-blocking  | 2754 (19.6)         | 2124 (19.2)      | 630 (21.3)                                 | 1.22 (1.08 - 1.38)                        | 0.002 a                                   |                                          |                                                          |
|                          | Glucocorticoids    | 1368 (9.8)          | 1099 (9.9)       | 269 (9.1)                                  | 0.78 (0.64 - 0.95)                        | 0.01 a                                    |                                          |                                                          |
| Condition                                                                 | Before vaccine | Lymphocyte-depleting | Persistent positive test (%) | BMI Class (%) | Comorbidities (%) |
|---------------------------------------------------------------------------|----------------|----------------------|-------------------------------|---------------|-------------------|
| Before vaccine Lymphocyte-depleting                                      | 223 (1.6)      | 153 (1.4)            | 70 (2.4)                     | 1.12 (0.73 - 1.70) | 0.61 |
| Persistent positive test (%)                                             | 111 (0.8)      | 74 (0.7)             | 37 (1.3)                     | 1.11 (0.71 - 1.72) | 0.65 |
| BMI Class (%)                                                             |                |                      |                               |               |                   |
| Underweight                                                               | 119 (0.8)      | 60 (0.5)             | 59 (2.0)                     | 1.67 (1.11 - 2.53) | 0.01 |
| Normal                                                                    | 1994 (14.2)    | 1372 (12.4)          | 622 (21.0)                   | 0.65 (0.57 - 0.75) | <1.0E-08 |
| Overweight                                                                | 4085 (29.1)    | 3271 (29.6)          | 814 (27.5)                   | 0.69 (0.60 - 0.80) | 6.7E-07 |
| Obesity I                                                                 | 3883 (27.7)    | 3155 (28.5)          | 728 (24.6)                   | 0.93 (0.77 - 1.12) | 0.44 |
| Obesity II                                                                | 2204 (15.7)    | 1798 (16.3)          | 406 (13.7)                   | 0.55 (0.30 - 1.01) | 0.05 |
| Severe Obesity                                                            | 1568 (11.2)    | 1252 (11.3)          | 316 (10.7)                   | 1.93 (1.11 - 2.53) | 0.01 |
| Unknown                                                                   | 168 (1.2)      | 154 (1.4)            | 14 (0.5)                     | 0.55 (0.30 - 1.01) | 0.05 |
| Comorbidities (%)                                                         |                |                      |                               |               |                   |
| Acquired hypothyroidism                                                   | 834 (5.9)      | 600 (5.4)            | 234 (7.9)                    | 1.07 (0.89 - 1.28) | 0.50 |
| Acute myocardial infarction                                               | 150 (1.1)      | 95 (0.9)             | 55 (1.9)                     | 0.91 (0.61 - 1.35) | 0.64 |
| Alzheimer's disease and related disorders or senile dementia              | 450 (3.2)      | 228 (2.1)            | 222 (7.5)                    | 1.51 (1.21 - 1.88) | 2.0E-04 |
| Anemia                                                                    | 1850 (13.2)    | 1213 (11.0)          | 637 (21.5)                   | 1.19 (1.04 - 1.36) | 0.01 |
| Anxiety disorders                                                         | 3382 (24.1)    | 2827 (25.6)          | 555 (18.8)                   | 0.84 (0.74 - 0.96) | 0.01 |
| Asthma                                                                    | 913 (6.5)      | 756 (6.8)            | 157 (5.3)                    | 1.07 (0.87 - 1.31) | 0.52 |
| Atrial fibrillation                                                       | 1172 (8.4)     | 719 (6.5)            | 453 (15.3)                   | 1.18 (1.01 - 1.37) | 0.04 |
| Bipolar disorder                                                          | 871 (6.2)      | 683 (6.2)            | 188 (6.4)                    | 1.31 (1.06 - 1.61) | 0.01 |
| Chronic kidney disease                                                    | 2285 (16.3)    | 1441 (13.0)          | 844 (28.5)                   | 1.57 (1.38 - 1.78) | <1.0E-08 |
| Chronic obstructive pulmonary disease and bronchiectasis                  | 2489 (17.8)    | 1539 (13.9)          | 950 (32.1)                   | 1.71 (1.52 - 1.92) | <1.0E-08 |
| Colorectal cancer                                                         | 164 (1.2)      | 117 (1.1)            | 47 (1.6)                     | 1.09 (0.74 - 1.59) | 0.67 |
| Depression                                                                | 3113 (22.2)    | 2542 (23.0)          | 571 (19.3)                   | 0.99 (0.86 - 1.14) | 0.89 |
| Diabetes                                                                  | 3931 (28.0)    | 2800 (25.3)          | 1131 (38.2)                  | 1.22 (1.10 - 1.36) | 3.0E-04 |
| Epilepsy                                                                  | 175 (1.2)      | 117 (1.1)            | 58 (2.0)                     | 1.44 (0.99 - 2.08) | 0.05 |
| Heart failure                                                             | 1205 (8.6)     | 675 (6.1)            | 530 (17.9)                   | 1.51 (1.29 - 1.77) | 2.2E-07 |
| Human immunodeficiency virus and/or acquired immunodeficiency syndrome HIV/AIDS | 103 (0.7)    | 83 (0.8)             | 20 (0.7)                     | 0.98 (0.56 - 1.70) | 0.93 |
| Hyperlipidemia                                                            | 4665 (33.3)    | 3510 (31.7)          | 1155 (39.0)                  | 0.84 (0.75 - 0.94) | 0.003 |
| Hypertension                                                              | 6332 (45.2)    | 4642 (42.0)          | 1690 (57.1)                  | 1.04 (0.93 - 1.16) | 0.49 |
| Ischemic heart disease                                                    | 2066 (14.7)    | 1381 (12.5)          | 685 (23.1)                   | 0.92 (0.81 - 1.05) | 0.23 |
| Leukemias and lymphomas                                                   | 1336 (9.5)     | 993 (9.0)            | 343 (11.6)                   | 1.58 (1.33 - 1.88) | 1.7E-07 |
| Liver disease cirrhosis and other liver conditions except viral hepatitis | 785 (5.6)      | 577 (5.2)            | 208 (7.0)                    | 1.29 (1.06 - 1.57) | 0.01 |
| Lung cancer                                                               | 289 (2.1)      | 173 (1.6)            | 116 (3.9)                    | 1.38 (1.05 - 1.80) | 0.02 |
| Mobility impairments                                                      | 166 (1.2)      | 94 (0.8)             | 72 (2.4)                     | 1.73 (1.20 - 2.51) | 0.003 |
| Multiple sclerosis and transverse myelitis                                 | 207 (1.5)      | 166 (1.5)            | 41 (1.4)                     | 2.02 (1.31 - 3.11) | 0.001 |
| Peripheral vascular disease                                               | 558 (4.0)      | 317 (2.9)            | 241 (8.1)                    | 1.26 (1.03 - 1.54) | 0.03 |
| Condition                              | Cases (100,000) | Controls (100,000) | Cases (100,000) | OR (95% CI) | P-value |
|----------------------------------------|-----------------|-------------------|-----------------|-------------|---------|
| Pressure and chronic ulcers            | 235 (1.7)       | 117 (1.1)         | 118 (4.0)       | 1.68 (1.24 - 2.29) | 9.0E-04 a |
| Prostate cancer                        | 774 (5.5)       | 547 (4.9)         | 227 (7.7)       | 0.96 (0.81 - 1.16) | 0.70    |
| Schizophrenia and other psychotic disorders | 327 (2.3)     | 236 (2.1)         | 91 (3.1)        | 1.41 (1.06 - 1.88) | 0.02 a  |
| Tobacco use                            | 1523 (10.9)     | 1105 (10.0)       | 418 (14.1)      | 1.25 (1.07 - 1.45) | 0.004 a |
| Viral hepatitis                        | 271 (1.9)       | 194 (1.8)         | 77 (2.6)        | 0.74 (0.54 - 1.01) | 0.06    |
| Death from breakthrough                | 539 (3.8)       | 0 (0.0)           | 539 (18.2)      |              |         |

a Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.027 in this analysis. OR = odds ratio. CI = 95% confidence interval.
### eTable 7. Immunosuppressive Medications Before and/or After Vaccination

|                  | Before initial vaccination only | After vaccination (before breakthrough) only | Both before and after vaccination (before breakthrough) |
|------------------|---------------------------------|---------------------------------------------|-------------------------------------------------------|
|                  | Non-severe | Severe | Non-severe | Severe | Non-severe | Severe | Non-severe | Severe |
| N                | 1687       | 263    | 6129       | 1767   | 2534       | 730    |
| **Sex (%)**      |            |        |            |        |            |        |
| Male             | 1467 (87.0)| 254 (96.6)| 5320 (86.8)| 1710 (96.8)| 2182 (86.1)| 693 (94.9)|
| Female           | 220 (13.0) | 9 (3.4) | 809 (13.2) | 57 (3.2) | 352 (13.9) | 37 (5.1) |
| **Age ranges (%)**|             |        |            |        |            |        |
| Less than 40     | 143 (8.5)  | 1 (0.4) | 479 (7.8)  | 14 (0.8) | 182 (7.2)  | 2 (0.3) |
| 40-45            | 80 (4.7)   | 2 (0.8) | 291 (4.7)  | 10 (0.6) | 125 (4.9)  | 6 (0.8) |
| 45-50            | 102 (6.0)  | 4 (1.5) | 345 (5.6)  | 9 (0.5)  | 151 (6.0)  | 9 (1.2) |
| 50-55            | 167 (9.9)  | 8 (3.0) | 502 (8.2)  | 47 (2.7) | 220 (8.7)  | 22 (3.0) |
| 55-60            | 157 (9.3)  | 9 (3.4) | 625 (10.2) | 70 (4.0) | 266 (10.5)| 50 (6.8) |
| 60-65            | 264 (15.6) | 20 (7.6) | 790 (12.9) | 156 (8.8) | 339 (13.4)| 77 (10.5)|
| 65-70            | 227 (13.5) | 38 (14.4)| 808 (13.2) | 247 (14.0)| 328 (12.9)| 117 (16.0)|
| 70-75            | 278 (16.5) | 86 (32.7)| 1121 (18.3)| 490 (27.7)| 517 (20.4)| 203 (27.8)|
| 75-80            | 158 (9.4)  | 45 (17.1)| 715 (11.7) | 350 (19.8)| 277 (10.9)| 127 (17.4)|
| 80 or greater    | 111 (6.6)  | 50 (19.0)| 453 (7.4)  | 374 (21.2)| 129 (5.1) | 117 (16.0)|
| **Race (%)**     |            |        |            |        |            |        |
| American Indian or Alaska Native | 12 (0.7) | 0 (0.0) | 43 (0.7) | 9 (0.5) | 21 (0.8) | 4 (0.5) |
| Asian            | 19 (1.1)  | 1 (0.4) | 55 (0.9)  | 10 (0.6) | 24 (0.9)  | 4 (0.5) |
| Black or African American | 460 (27.3)| 57 (21.7)| 1538 (25.1)| 379 (21.4)| 579 (22.8)| 178 (24.4)|
| Native Hawaiian or other Pacific Islander | 22 (1.3) | 1 (0.4) | 58 (0.9) | 11 (0.6) | 23 (0.9) | 7 (1.0) |
| White            | 1082 (64.1)| 193 (73.4)| 4093 (66.8)| 1274 (73.7)| 1710 (67.5)| 503 (68.9)|
| Unknown          | 92 (5.5)  | 11 (4.2) | 342 (5.6) | 84 (4.8) | 177 (7.0) | 34 (4.7) |
| **Ethnicity Hispanic/Latino (%)** |           |        |            |        |            |        |
| Hispanic or Latino | 141 (8.4) | 27 (10.3)| 506 (8.3) | 102 (5.8) | 217 (8.6) | 42 (5.8) |
| Not Hispanic or Latino | 1486 (88.1)| 231 (87.8)| 5358 (87.4)| 1619 (91.6)| 2244 (88.6)| 665 (91.1)|
| Unknown          | 60 (3.6)  | 5 (1.9) | 265 (4.3) | 46 (2.6) | 73 (2.9)  | 23 (3.2) |
| **US Region (%)** |           |        |            |        |            |        |
| Continental      | 287 (17.0) | 35 (13.3)| 1087 (17.7)| 296 (16.8)| 374 (14.8)| 120 (16.4)|
| Midwest          | 335 (19.9) | 67 (25.5)| 1175 (19.2)| 370 (20.9)| 616 (24.3)| 191 (26.2)|
| North Atlantic   | 367 (21.8) | 56 (21.3)| 1342 (21.9)| 379 (21.4)| 560 (22.1)| 147 (20.1)|
| Pacific          | 240 (14.2) | 40 (15.2)| 862 (14.1) | 253 (14.3)| 430 (17.0)| 109 (14.9)|
| Southeast        | 440 (26.1) | 65 (24.7)| 1573 (25.7)| 466 (26.4)| 530 (20.9)| 163 (22.3)|
| Unknown          | 18 (1.1)  | 0 (0.0) | 90 (1.5)  | 3 (0.2)  | 24 (0.9)  | 0 (0.0)  |
| Period of dominant variant (%) | Pre-delta period | Delta period | Omicron period |  
|-------------------------------|-----------------|--------------|---------------|  
| Pre-delta period              | 49 (2.9)        | 15 (5.7)     | 142 (2.3)     |  
| Delta period                  | 399 (23.7)      | 119 (45.2)   | 1834 (29.9)   |  
| Omicron period                | 1239 (73.4)     | 129 (49.0)   | 4153 (67.8)   |  

| Vaccine type (%)              | Janssen         | Moderna      | Pfizer        |  
|-------------------------------|-----------------|--------------|---------------|  
| Janssen                       | 166 (9.8)       | 694 (41.1)   | 827 (49.0)    |  
| Moderna                       | 29 (11.0)       | 117 (44.5)   | 117 (44.5)    |  
| Pfizer                        | 530 (8.6)       | 2763 (45.1)  | 2836 (46.3)   |  

| History of infection before vaccinated (%) | 99 (5.9) | 12 (4.6) | 248 (4.0) | 70 (4.0) | 135 (5.3) | 28 (3.8) |  
| Months since full vax at breakthrough (%) | 4 or less     | 4-5        | 5-6         | 6-7       | 7-8       | 8-9       | 9-10         | 10-11        | 11-12       | 12 or more  | Not boosted | 1 or less | 1-2 | 2-3 | 3-4 | 4-5 | 5-6 | 6 or more |  
|------------------------------------------|-------------|------------|-------------|-----------|----------|-----------|--------------|-------------|-------------|-------------|-------------|-----------|------|-----|-----|-----|-----|---------|  
|                                          | 198 (11.7)  | 115 (6.8)  | 123 (7.3)   | 116 (6.9) | 162 (9.6) | 271 (16.1) | 322 (19.1)   | 281 (16.7)  | 86 (5.1)    | 13 (0.8)    | 1102 (65.3) | 84 (5.0)  | 138 (8.2) | 163 (9.7) | 107 (6.3) | 69 (4.1) | 16 (0.9) | 8 (0.5) |  
|                                          | 47 (17.9)   | 19 (7.2)   | 33 (12.5)   | 26 (9.9)   | 22 (8.4)  | 28 (10.6)  | 35 (13.3)    | 39 (14.8)   | 11 (4.2)    | 3 (1.1)     | 218 (82.9)  | 8 (3.0)   | 5 (1.9)   | 19 (7.2)  | 8 (3.0)   | 3 (1.1)   | 2 (0.8)  | 0 (0.0)  |  
|                                          | 644 (10.5)  | 396 (6.5)  | 463 (7.6)   | 496 (8.1)  | 648 (10.6)| 984 (16.1) | 1103 (18.0)  | 925 (15.1)  | 414 (6.8)   | 56 (0.9)    | 238 (13.5) | 287 (4.7) | 402 (6.6) | 462 (7.5) | 384 (6.3) | 192 (3.1) | 51 (0.8) | 61 (1.0) |  
|                                          | 238 (13.5)  | 138 (7.8)  | 207 (11.7)  | 182 (10.3) | 149 (8.4) | 191 (10.8) | 255 (14.4)   | 265 (15.0)  | 130 (7.4)   | 12 (0.7)    | 304 (12.0) | 70 (4.0)  | 403 (15.9)| 189 (7.5) | 149 (8.4) | 42 (2.5)  | 14 (0.8) |  
|                                          | 304 (12.0)  | 188 (7.4)  | 181 (7.1)   | 195 (7.7)  | 221 (8.7) | 403 (15.9)| 520 (20.5)   | 366 (14.4)  | 149 (5.9)   | 13 (0.5)    | 121 (16.6) | 63 (8.6)  | 66 (9.0)  | 65 (8.9)  | 70 (9.6)  | 66 (16.6) |  
|                                          | 86 (5.1)    | 11 (4.2)   | 248 (4.0)   | 70 (4.0)   | 135 (5.3) | 121 (16.6)| 99 (13.6)    | 114 (15.6)  | 51 (7.0)    | 4 (0.5)     | 1102 (65.3)| 138 (5.4) | 148 (5.8) | 220 (8.7) | 149 (8.4) | 66 (9.0)  |  
|                                          | 13 (0.8)    | 13 (0.5)   | 486 (66.6)  | 34 (4.7)   | 138 (5.4) | 46 (6.3)  | 56 (7.7)     | 46 (6.3)    | 11 (1.5)    |  

| Immune-suppressive medications before breakthrough (%) | Before breakthrough Chemotherapy | Before breakthrough Cytokine-blocking | Before breakthrough Glucocorticoids | Before breakthrough Leukocyte-inhibitory | Before breakthrough Lymphocyte-depleting |  
|----------------------------------------------------|-----------------------------------|-----------------------------------|----------------------------------------|----------------------------------------|-------------------------------|  
| Before breakthrough Chemotherapy                   | 455 (7.4)                         | 207 (11.7)                        | 495 (8.1)                              | 203 (3.3)                              | 237 (9.4)                    |  
| Before breakthrough Cytokine-blocking              | 385 (6.3)                         | 88 (5.0)                          | 4942 (80.6)                            | 208 (11.8)                            | 99 (13.6)                    |  
| Before breakthrough Glucocorticoids                | 1016 (40.1)                       | 112 (15.3)                        | 781 (30.8)                             | 943 (37.2)                            |  
| Before breakthrough Leukocyte-depleting            | 237 (9.4)                         | 99 (13.6)                         | 427 (58.5)                             | 278 (38.1)                            |  
| Immune-suppressive medications before initial vaccination (%) | Before vaccine Chemotherapy |  
| Before vaccine Chemotherapy                        | 79 (4.7)                          | 15 (5.7)                          | 237 (9.4)                              | 99 (13.6)                            |  

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| Before vaccine | Cytokine-blocking | Glucocorticoids | Leukocyte-inhibitory | Lymphocyte-depleting | Persistent positive test (%) | BMI Class (%) | Comorbidities (%) |
|----------------|------------------|----------------|--------------------|---------------------|-------------------------------|---------------|-------------------|
| Before vaccine | 110 (6.5)        | 9 (3.4)        | 986 (38.9)         | 106 (14.5)          | 16 (0.9)                      | 8 (0.5)       | Acquired hypothyroidism 103 (6.1) |
|                | 1363 (80.8)      | 218 (82.9)     | 912 (36.0)         | 236 (32.3)          | 3 (1.1)                       | 209 (12.4)    | Acute myocardial infarction 22 (1.3) |
|                | 187 (11.1)       | 33 (12.5)      | 153 (6.0)          | 70 (9.6)            | 21 (1.2)                      | 761 (12.4)    | Aldermyel degenerative disorders 291 (17.2) |
|                | 0 (0.0)          | 0 (0.0)        | 153 (6.0)          | 70 (9.6)            | 18 (0.7)                      | 139 (19.0)    | Anemia 225 (13.3) |
| Persistent     | 986 (38.9)       | 106 (14.5)     | 912 (36.0)         | 236 (32.3)          | 16 (0.9)                      | 67 (9.2)      | Atrial fibrillation 136 (8.1) |
| positive test  | 106 (14.5)       | 236 (32.3)     | 236 (32.3)         | 139 (19.0)          | 3 (1.1)                       | 209 (12.4)    | Bipolar disorder 123 (7.3) |
| (%)            |                  |                |                    |                     |                               |               | Chronic kidney disease 291 (17.2) |
| Persistent     | 986 (38.9)       | 106 (14.5)     | 912 (36.0)         | 236 (32.3)          | 16 (0.9)                      | 70 (9.6)      | Hypertenison 805 (47.7) |
| positive test  | 106 (14.5)       | 236 (32.3)     | 236 (32.3)         | 139 (19.0)          | 21 (1.2)                      | 139 (19.0)    | Insomnia 123 (7.3) |
| (%)            |                  |                |                    |                     |                               |               | Liver disease 31 (1.8) |
| Persistent     | 986 (38.9)       | 106 (14.5)     | 912 (36.0)         | 236 (32.3)          | 18 (0.7)                      | 139 (19.0)    | Leukemias and lymphomas 31 (1.8) |
| positive test  | 106 (14.5)       | 236 (32.3)     | 236 (32.3)         | 139 (19.0)          | 10 (4.2)                      | 70 (9.6)      | Liver disease 31 (1.8) |
| (%)            |                  |                |                    |                     |                               |               | Liver disease 31 (1.8) |
| Persistent     | 986 (38.9)       | 106 (14.5)     | 912 (36.0)         | 236 (32.3)          | 18 (0.7)                      | 139 (19.0)    | Liver disease 31 (1.8) |
| positive test  | 106 (14.5)       | 236 (32.3)     | 236 (32.3)         | 139 (19.0)          | 10 (4.2)                      | 70 (9.6)      | Liver disease 31 (1.8) |
| (%)            |                  |                |                    |                     |                               |               | Liver disease 31 (1.8) |
| Persistent     | 986 (38.9)       | 106 (14.5)     | 912 (36.0)         | 236 (32.3)          | 18 (0.7)                      | 139 (19.0)    | Liver disease 31 (1.8) |
| positive test  | 106 (14.5)       | 236 (32.3)     | 236 (32.3)         | 139 (19.0)          | 10 (4.2)                      | 70 (9.6)      | Liver disease 31 (1.8) |
| (%)            |                  |                |                    |                     |                               |               | Liver disease 31 (1.8) |
| Condition                                      | Breakthrough (%) | Vaccination (%) |
|-----------------------------------------------|-------------------|-----------------|
| Lung cancer                                   | 32 (1.9)          | 16 (6.1)        |
| Mobility impairments                          | 19 (1.1)          | 4 (1.5)         |
| Multiple sclerosis and transverse myelitis    | 8 (0.5)           | 0 (0.0)         |
| Peripheral vascular disease                   | 58 (3.4)          | 29 (11.0)       |
| Pressure and chronic ulcers                   | 30 (1.8)          | 12 (4.6)        |
| Prostate cancer                               | 88 (5.2)          | 25 (9.5)        |
| Schizophrenia and other psychotic disorders   | 45 (2.7)          | 13 (4.9)        |
| Tobacco use                                   | 218 (12.9)        | 49 (18.6)       |
| Viral hepatitis                                | 31 (1.8)          | 13 (4.9)        |

Medication classes at breakthrough (%)

| Class | Breakthrough (%) | Vaccination (%) |
|-------|-------------------|-----------------|
| 1     | 11479 (94.7)      | 1597 (96.4)     |
| 2     | 593 (4.8)         | 167 (10.5)      |
| 3     | 21 (0.5)          | 10 (0.6)        |
| 4     | 0 (0.0)           | 0 (0.0)         |

Medication classes at vaccination (%)

| Class | Breakthrough (%) | Vaccination (%) |
|-------|-------------------|-----------------|
| 1     | 1637 (97.0)       | 251 (95.4)      |
| 2     | 844 (4.6)         | 12 (0.4)        |
| 3     | 2 (0.1)           | 0 (0.0)         |
| 4     | 0 (0.0)           | 0 (0.0)         |

Death from breakthrough

| Class | Breakthrough (%) | Vaccination (%) |
|-------|-------------------|-----------------|
| 1     | 0 (0.0)           | 36 (13.7)       |
| 2     | 0 (0.0)           | 287 (16.2)      |
| 3     | 0 (0.0)           | 157 (21.5)      |
| 4     | 0 (0.0)           | 0 (0.0)         |
**eTable 8. Subcohort of Immunocompromised Patients, Analysis by Number of Medication Classes**

|                           | Overall  | Non-severe | Severe   | Multivariable OR (CI) number of drug classes | P       |
|---------------------------|----------|------------|----------|---------------------------------------------|---------|
| N                         | 14021    | 11062      | 2959     |                                             |         |
| Sex (%)                   |          |            |          |                                             |         |
| Male                      | 12505    | 9653       | 2852     | 1.0 (referent)                              |         |
| Female                    | 1516     | 1409       | 107      | 0.58 (0.47 - 0.73)                          | 2.3E-06 |
| Age ranges (%)            |          |            |          |                                             |         |
| Less than 40              |          |            |          |                                             |         |
| Male                      | 848      | 829        | 19       | 0.66 (0.35 - 1.24)                          | 0.20    |
| Female                    | 524      | 506        | 18       | 0.97 (0.51 - 1.84)                          | 0.93    |
| 40-45                     | 636      | 613        | 23       | 1.0 (referent)                              |         |
| 50-55                     | 1004     | 925        | 79       | 2.06 (1.27 - 3.35)                          | 0.004   |
| 55-60                     | 1228     | 1093       | 135      | 2.49 (1.56 - 3.96)                          | 1.2E-04 |
| 60-65                     | 1733     | 1467       | 266      | 3.53 (2.26 - 5.53)                          | 3.5E-08 |
| 65-70                     | 1874     | 1452       | 422      | 5.03 (3.22 - 7.85)                          | <1.0E-08|
| 70-75                     | 2955     | 2122       | 833      | 6.79 (4.38 - 10.6)                          | <1.0E-08|
| 75-80                     | 1841     | 1274       | 567      | 7.83 (5.01 - 12.2)                          | <1.0E-08|
| 80 or greater             | 1378     | 781        | 597      | 12.9 (8.22 - 20.3)                          | <1.0E-08|
| Race (%)                  |          |            |          |                                             |         |
| American Indian or Alaska Native | 95     | 81         | 14       | 0.93 (0.50 - 1.72)                          | 0.81    |
| Asian                     | 117      | 102        | 15       | 1.10 (0.60 - 2.01)                          | 0.76    |
| Black or African American | 3339     | 2691       | 648      | 1.10 (0.98 - 1.24)                          | 0.11    |
| Native Hawaiian or other Pacific Islander | 130 | 110     | 20       | 0.93 (0.56 - 1.57)                          | 0.80    |
| White                     | 9554     | 7438       | 2116     | 1.0 (referent)                              |         |
| Unknown                   | 786      | 640        | 146      | 0.99 (0.79 - 1.24)                          | 0.90    |
| Ethnicity Hispanic/Latino (%) |          |            |          |                                             |         |
| Hispanic or Latino        | 1094     | 912        | 182      | 1.07 (0.88 - 1.30)                          | 0.49    |
| Not Hispanic or Latino    | 12426    | 9731       | 2695     | 1.0 (referent)                              |         |
| Unknown                   | 501      | 419        | 82       | 0.94 (0.70 - 1.26)                          | 0.68    |
| US Region (%)             |          |            |          |                                             |         |
| Continental               | 2314     | 1835       | 479      | 1.03 (0.89 - 1.19)                          | 0.67    |
| Midwest                   | 2973     | 2297       | 676      | 0.96 (0.84 - 1.09)                          | 0.51    |
| North Atlantic            | 3047     | 2419       | 628      | 0.88 (0.77 - 1.01)                          | 0.07    |
| Pacific                   | 2096     | 1665       | 431      | 0.96 (0.82 - 1.11)                          | 0.56    |
| Southeast                 | 3449     | 2708       | 741      | 1.0 (referent)                              |         |
| Unknown                   | 142      | 138        | 4        | 0.31 (0.11 - 0.87)                          | 0.03    |
| Period of dominant variant (%) |          |            |          |                                             |         |
| Period                  | Cases       | Controls     | Risk Ratio | 95% CI       | p-value |
|------------------------|-------------|--------------|------------|--------------|---------|
| Pre-delta period       | 501 (3.6)   | 299 (2.7)    | 202 (6.8)  | 1.0 (referent)|         |
| Delta period           | 4422 (31.5) | 3146 (28.4)  | 1276 (43.1)| 0.71 (0.55 - 0.92)| 0.01ᵃ |
| Omicron period         | 9098 (64.9) | 7617 (68.9)  | 1481 (50.1)| 0.42 (0.32 - 0.56)| <1.0E-08ᵃ |
| Vaccine type (%)       |             |              |            |              |         |
| Janssen                | 1172 (8.4)  | 940 (8.5)    | 232 (7.8)  | 1.12 (0.93 - 1.34)| 0.23    |
| Moderna                | 6098 (43.5) | 4860 (43.9)  | 1238 (41.8)| 0.79 (0.71 - 0.87)| 1.1E-06ᵃ |
| Pfizer                 | 6751 (48.1) | 5262 (47.6)  | 1489 (50.3)| 1.0 (referent)   |         |
| History of infection before vaccinated (%) | 636 (4.5)   | 515 (4.7)    | 121 (4.1)  | 0.62 (0.48 - 0.78)| 8.4E-05ᵃ |
| Months since full vax at breakthrough (%) |             |              |            |              |         |
| 4 or less              | 1672 (11.9) | 1225 (11.1)  | 447 (15.1) | 1.0 (referent)   |         |
| 4-5                    | 975 (7.0)   | 743 (6.7)    | 232 (7.8)  | 1.06 (0.84 - 1.33)| 0.62    |
| 5-6                    | 1159 (8.3)  | 831 (7.5)    | 328 (11.1) | 1.12 (0.90 - 1.40)| 0.29    |
| 6-7                    | 1140 (8.1)  | 845 (7.6)    | 295 (10.0) | 1.05 (0.84 - 1.31)| 0.67    |
| 7-8                    | 1336 (9.5)  | 1083 (9.8)   | 253 (8.6)  | 0.94 (0.75 - 1.17)| 0.57    |
| 8-9                    | 2069 (14.8) | 1759 (15.9)  | 310 (10.5) | 0.98 (0.78 - 1.22)| 0.84    |
| 9-10                   | 2488 (17.7) | 2070 (18.7)  | 418 (14.1) | 1.11 (0.88 - 1.40)| 0.37    |
| 10-11                  | 2160 (15.4) | 1709 (15.4)  | 451 (15.2) | 1.33 (1.04 - 1.69)| 0.02ᵃ   |
| 11-12                  | 915 (6.5)   | 710 (6.4)    | 205 (6.9)  | 1.42 (1.07 - 1.88)| 0.02ᵃ   |
| 12 or more             | 107 (0.8)   | 87 (0.8)     | 20 (0.7)   | 0.96 (0.54 - 1.70)| 0.88    |
| Months since boosted at breakthrough (%) |             |              |            |              |         |
| Not boosted            | 9408 (67.1) | 7234 (65.4)  | 2174 (73.5)| 1.0 (referent)   |         |
| 1 or less              | 663 (4.7)   | 541 (4.9)    | 122 (4.1)  | 0.80 (0.64 – 1.00)| 0.05    |
| 1-2                    | 878 (6.3)   | 734 (6.6)    | 144 (4.9)  | 0.64 (0.52 - 0.79)| 3.9E-05ᵃ |
| 2-3                    | 1107 (7.9)  | 903 (8.2)    | 204 (6.9)  | 0.70 (0.58 - 0.85)| 2.2E-04ᵃ |
| 3-4                    | 1040 (7.4)  | 883 (8.0)    | 157 (5.3)  | 0.51 (0.42 - 0.63)| <1.0E-08ᵃ |
| 4-5                    | 670 (4.8)   | 563 (5.1)    | 107 (3.6)  | 0.54 (0.42 - 0.69)| 1.2E-06ᵃ |
| 5-6                    | 141 (1.0)   | 109 (1.0)    | 32 (1.1)   | 0.78 (0.50 - 1.22)| 0.28    |
| 6 or more              | 114 (0.8)   | 95 (0.9)     | 19 (0.6)   | 0.75 (0.44 - 1.30)| 0.30    |
| Immune-suppressive medications before breakthrough (%) |             |              |            |              |         |
| Before breakthrough    | 1006 (7.2)  | 696 (6.3)    | 310 (10.5) |                |         |
| Chemotherapy           |              |              |            |                |         |
| Before breakthrough    | 1601 (11.4) | 1401 (12.7)  | 200 (6.8)  |                |         |
| Cytokine-blocking      |              |              |            |                |         |
| Before breakthrough    | 7544 (53.8) | 5723 (51.7)  | 1821 (61.5)|                |         |
| Glucocorticoids        |              |              |            |                |         |
| Before breakthrough    | 1924 (13.7) | 1438 (13.0)  | 486 (16.4) |                |         |
| Leukocyte-inhibitory   |              |              |            |                |         |
| Before breakthrough    | 585 (4.2)   | 406 (3.7)    | 179 (6.0)  |                |         |
| Lymphocyte-depleting   |              |              |            |                |         |
| Immune-suppressive medications before initial vaccination (%) |             |              |            |              |         |
| Before vaccine         | 430 (3.1)   | 316 (2.9)    | 114 (3.9)  |                |         |
| Chemotherapy           |              |              |            |                |         |
| Before vaccine         | 1211 (8.6)  | 1096 (9.9)   | 115 (3.9)  |                |         |
| Cytokine-blocking      |              |              |            |                |         |
| Before vaccine         | 2754 (19.6) | 2124 (19.2)  | 630 (21.3) |                |         |

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|                                      | Before vaccine Leukocyte-inhibitory | Before vaccine Lymphocyte-depleting | Persistent positive test (%) | BMI Class (%) | Comorbidities (%) |
|--------------------------------------|--------------------------------------|--------------------------------------|------------------------------|---------------|-------------------|
|                                      | 1368 (9.8)                           | 1099 (9.9)                           | 269 (9.1)                   | 111 (0.8)     | 74 (0.7)          |
|                                      |                                      |                                      |                              | 37 (1.3)      | 1.17 (0.75 - 1.81)| 0.48 |
| **Persistent positive test (%)**     |                                      |                                      |                              |               |                   |
| **BMI Class (%)**                    |                                      |                                      |                              |               |                   |
| **Underweight**                      | 119 (0.8)                            | 60 (0.5)                             | 59 (2.0)                    | 1.70 (1.12 - 2.56) | 0.01 |
| **Normal**                           | 1994 (14.2)                          | 1372 (12.4)                          | 622 (21.0)                  | 1.0 (referent) |                   |
| **Overweight**                       | 4085 (29.1)                          | 3271 (29.6)                          | 814 (27.5)                  | 0.65 (0.57 - 0.75) | <1.0E-08 |
| **Obesity I**                        | 3883 (27.7)                          | 3155 (28.5)                          | 728 (24.6)                  | 0.69 (0.60 - 0.80) | 5.0E-07 |
| **Obesity II**                       | 2204 (15.7)                          | 1798 (16.3)                          | 406 (13.7)                  | 0.75 (0.64 - 0.89) | 7.8E-04 |
| **Severe Obesity**                   | 1568 (11.2)                          | 1252 (11.3)                          | 316 (10.7)                  | 0.91 (0.75 - 1.09) | 0.30  |
| **Unknown**                          | 168 (1.2)                            | 154 (1.4)                            | 14 (0.5)                    | 0.57 (0.32 - 1.05) | 0.07  |
| **Comorbidities (%)**                |                                      |                                      |                              |               |                   |
| **Acquired hypothyroidism**          | 834 (5.9)                            | 600 (5.4)                            | 234 (7.9)                   | 1.05 (0.88 - 1.27) | 0.57  |
| **Anemia**                           | 150 (1.1)                            | 95 (0.9)                             | 55 (1.9)                    | 0.91 (0.61 - 1.35) | 0.64  |
| **Alzheimer's disease and related disorders or senile dementia** | 450 (3.2)                            | 228 (2.1)                            | 222 (7.5)                   | 1.52 (1.22 - 1.89) | 2.0E-04 |
| **Anxiety disorders**                | 1850 (13.2)                          | 1213 (11.0)                          | 637 (21.5)                  | 1.21 (1.06 - 1.38) | 0.005 |
| **Atrial fibrillation**              | 3382 (24.1)                          | 2827 (25.6)                          | 555 (18.8)                  | 0.85 (0.74 - 0.96) | 0.01 |
| **Asthma**                           | 913 (6.5)                            | 756 (6.8)                            | 157 (5.3)                   | 1.02 (0.83 - 1.25) | 0.87  |
| **Bipolar disorder**                 | 1172 (8.4)                           | 719 (6.5)                            | 453 (15.3)                  | 1.19 (1.02 - 1.38) | 0.03  |
| **Chronic kidney disease**           | 871 (6.2)                            | 683 (6.2)                            | 188 (6.4)                   | 1.30 (1.06 - 1.60) | 0.01 |
| **Chronic obstructive pulmonary disease and bronchiectasis** | 2285 (16.3)                          | 1441 (13.0)                          | 844 (28.5)                  | 1.61 (1.42 - 1.83) | <1.0E-08 |
| **Colorectal cancer**                | 2489 (17.8)                          | 1539 (13.9)                          | 950 (32.1)                  | 1.76 (1.57 - 1.97) | <1.0E-08 |
| **Depression**                       | 164 (1.2)                            | 117 (1.1)                            | 47 (1.6)                    | 1.12 (0.77 - 1.64) | 0.55  |
| **Diabetes**                         | 3113 (22.2)                          | 2542 (23.0)                          | 571 (19.3)                  | 0.99 (0.86 - 1.13) | 0.88  |
| **Epilepsy**                         | 3931 (28.0)                          | 2800 (25.3)                          | 1131 (38.2)                 | 1.22 (1.10 - 1.36) | 2.8E-04 |
| **Heart failure**                    | 175 (1.2)                            | 117 (1.1)                            | 58 (2.0)                    | 1.45 (1.00 - 2.10) | 0.05  |
| **Liver disease cirrhosis and other liver conditions except viral hepatitis** | 1205 (8.6)                            | 675 (6.1)                            | 530 (17.9)                  | 1.53 (1.31 - 1.78) | 1.1E-07 |
| **Mobility impairments**             | 103 (0.7)                            | 83 (0.8)                             | 20 (0.7)                    | 0.95 (0.54 - 1.66) | 0.85  |
| **Human immunodeficiency virus and/or acquired immunodeficiency syndrome HIV/AIDS** | 4665 (33.3)                          | 3510 (31.7)                          | 1155 (39.0)                 | 0.84 (0.75 - 0.94) | 0.002 |
| **Ischemic heart disease**           | 6332 (45.2)                          | 4642 (42.0)                          | 1690 (57.1)                 | 1.04 (0.93 - 1.17) | 0.44  |
| **Leukemias and lymphomas**          | 2066 (14.7)                          | 1381 (12.5)                          | 685 (23.1)                  | 0.93 (0.81 - 1.06) | 0.29  |
| **Lung cancer**                      | 1336 (9.5)                           | 993 (9.0)                            | 343 (11.6)                  | 1.46 (1.23 - 1.74) | 2.2E-05 |
| **Mobility impairments**             | 103 (0.7)                            | 83 (0.8)                             | 20 (0.7)                    | 0.95 (0.54 - 1.66) | 0.85  |
| **Hyperlipidemia**                   | 4665 (33.3)                          | 3510 (31.7)                          | 1155 (39.0)                 | 0.84 (0.75 - 0.94) | 0.002 |
| **Hypertension**                     | 6332 (45.2)                          | 4642 (42.0)                          | 1690 (57.1)                 | 1.04 (0.93 - 1.17) | 0.44  |
| **Ischemic heart disease**           | 2066 (14.7)                          | 1381 (12.5)                          | 685 (23.1)                  | 0.93 (0.81 - 1.06) | 0.29  |
| **Leukemias and lymphomas**          | 1336 (9.5)                           | 993 (9.0)                            | 343 (11.6)                  | 1.46 (1.23 - 1.74) | 2.2E-05 |
| **Liver disease cirrhosis and other liver conditions except viral hepatitis** | 785 (5.6)                            | 577 (5.2)                            | 208 (7.0)                   | 1.29 (1.06 - 1.56) | 0.01 |
| **Lung cancer**                      | 289 (2.1)                            | 173 (1.6)                            | 116 (3.9)                   | 1.45 (1.11 - 1.89) | 0.006 |
| **Mobility impairments**             | 166 (1.2)                            | 94 (0.8)                             | 72 (2.4)                    | 1.75 (1.21 - 2.52) | 0.003 |

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| Condition                                               | Number of Subjects (%) | Number of Subjects (%) | Number of Subjects (%) | Odds Ratio (95% CI) | P-value |
|---------------------------------------------------------|------------------------|------------------------|------------------------|---------------------|---------|
| Multiple sclerosis and transverse myelitis              | 207 (1.5)              | 166 (1.5)              | 41 (1.4)               | 2.28 (1.51 - 3.42)  | 7.5E-05 |
| Peripheral vascular disease                            | 558 (4.0)              | 317 (2.9)              | 241 (8.1)              | 1.27 (1.04 - 1.56)  | 0.02    |
| Pressure and chronic ulcers                            | 235 (1.7)              | 117 (1.1)              | 118 (4.0)              | 1.69 (1.25 - 2.30)  | 7.7E-04 |
| Prostate cancer                                         | 774 (5.5)              | 547 (4.9)              | 227 (7.7)              | 0.98 (0.82 - 1.17)  | 0.79    |
| Schizophrenia and other psychotic disorders             | 327 (2.3)              | 236 (2.1)              | 91 (3.1)               | 1.44 (1.08 - 1.91)  | 0.01    |
| Tobacco use                                             | 1523 (10.9)            | 1105 (10.0)            | 418 (14.1)             | 1.25 (1.08 - 1.45)  | 0.003   |
| Viral hepatitis                                         | 271 (1.9)              | 194 (1.8)              | 77 (2.6)               | 0.73 (0.54 – 1.00)  | 0.05    |

Number of medication classes after vaccination (%)

| Number of medication classes after vaccination (%) | Number of Subjects (%) | Number of Subjects (%) | Number of Subjects (%) | Odds Ratio (95% CI) | P-value |
|-----------------------------------------------------|------------------------|------------------------|------------------------|---------------------|---------|
| 0                                                   | 2961 (21.1)            | 2399 (21.7)            | 562 (19.0)             | 0.60 (0.51 - 0.69)  | <1.0E-08 |
| 1                                                   | 10007 (71.4)           | 7869 (71.1)            | 2138 (72.3)            | 1.0 (referent)      |         |
| 2                                                   | 934 (6.7)              | 722 (6.5)              | 212 (7.2)              | 1.92 (1.64 - 2.26)  | <1.0E-08 |
| 3                                                   | 114 (0.8)              | 72 (0.7)               | 42 (1.4)               | 2.53 (1.69 - 3.80)  | 7.5E-06 |
| 4                                                   | 5 (0.0)                | 0 (0.0)                | 5 (0.2)                | 20.8 (3.93 - 110)   |         |

Number of medication classes before vaccination (%)

| Number of medication classes before vaccination (%) | Number of Subjects (%) | Number of Subjects (%) | Number of Subjects (%) | Odds Ratio (95% CI) | P-value |
|-----------------------------------------------------|------------------------|------------------------|------------------------|---------------------|---------|
| 0                                                   | 8817 (62.9)            | 6841 (61.8)            | 1966 (66.4)            | 1.16 (1.04 - 1.31)  | 0.009   |
| 1                                                   | 4320 (30.8)            | 3585 (32.4)            | 735 (24.8)             | 1.0 (referent)      |         |
| 2                                                   | 790 (5.6)              | 572 (5.2)              | 228 (7.7)              | 1.16 (0.92 - 1.46)  | 0.21    |
| 3                                                   | 87 (0.6)               | 62 (0.06)              | 25 (0.8)               | 1.09 (0.58 - 2.04)  | 0.80    |
| 4                                                   | 7 (0.0)                | 2 (0.0)                | 5 (0.2)                | ND                  |         |

Death from breakthrough

| Death from breakthrough | Number of Subjects (%) | Number of Subjects (%) | Number of Subjects (%) | Odds Ratio (95% CI) | P-value |
|-------------------------|------------------------|------------------------|------------------------|---------------------|---------|
|                         | 539 (3.8)              | 0 (0.0)                | 539 (18.2)             | ND                  |         |

* Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.025 for this analysis. OR = odds ratio. CI = 95% confidence interval.
### eTable 9. Subcohort of Nonimmunocompromised Patients, Data and Analysis

|                         | Overall  | Non-severe | Severe  | Multivariable OR (CI) | P        |
|-------------------------|----------|------------|---------|-----------------------|----------|
| N                       | 96739    | 89086      | 7653    |                       |          |
| **Sex (%)**             |          |            |         |                       |          |
| Male                    | 85109 (88.0) | 77736 (87.3) | 7373 (96.3) | 1.0 (referent)         |          |
| Female                  | 11630 (12.0) | 11350 (12.7) | 280 (3.7)   | 0.70 (0.62 - 0.80)    | 1.0E-07 a|
| **Age ranges (%)**      |          |            |         |                       |          |
| Less than 40            | 12266 (12.7) | 12175 (13.7) | 91 (1.2)    | 0.55 (0.41 - 0.75)    | 1.0E-04 a|
| 40-45                   | 5717 (5.9)   | 5647 (6.3)   | 70 (0.9)    | 0.86 (0.62 - 1.19)    | 0.36     |
| 45-50                   | 5671 (5.9)   | 5587 (6.3)   | 84 (1.1)    | 1.0 (referent)         |          |
| 50-55                   | 8717 (9.0)   | 8519 (9.6)   | 198 (2.6)   | 1.47 (1.13 - 1.90)    | 0.004 a  |
| 55-60                   | 9706 (10.0)  | 9365 (10.5)  | 341 (4.5)   | 2.15 (1.69 - 2.75)    | <1.0E-08 a|
| 60-65                   | 11238 (11.6) | 10615 (11.9) | 623 (8.1)   | 3.14 (2.49 - 3.97)    | <1.0E-08 a|
| 65-70                   | 10479 (10.8) | 9561 (10.7)  | 918 (12.0)  | 4.70 (3.73 - 5.92)    | <1.0E-08 a|
| 70-75                   | 15372 (15.9) | 13581 (15.2) | 1791 (23.4) | 6.52 (5.19 - 8.18)    | <1.0E-08 a|
| 75-80                   | 9721 (10.0)  | 8272 (9.3)   | 1449 (18.9) | 8.97 (7.13 - 11.3)    | <1.0E-08 a|
| 80 or greater           | 7852 (8.1)   | 5764 (6.5)   | 2088 (27.3) | 17.7 (14.1 - 22.4)    | <1.0E-08 a|
| **Race (%)**            |          |            |         |                       |          |
| American Indian or Alaska Native | 795 (0.8) | 721 (0.8) | 74 (1.0) | 1.40 (1.07 - 1.84) | 0.01 a   |
| Asian                   | 1464 (1.5)  | 1423 (1.6)  | 41 (0.5)   | 0.76 (0.54 - 1.07)    | 0.12     |
| Black or African American | 23614 (24.4) | 22099 (24.8) | 1515 (19.8) | 0.94 (0.88 - 1.01)    | 0.07     |
| Native Hawaiian or other Pacific Islander | 1012 (1.0) | 956 (1.1) | 56 (0.7) | 0.87 (0.65 - 1.16) | 0.34     |
| White                   | 62111 (64.2) | 56580 (63.5) | 5531 (72.3) | 1.0 (referent)         |          |
| Unknown                 | 7743 (8.0)   | 7307 (8.2)  | 436 (5.7)  | 0.89 (0.79 – 1.00)    | 0.05     |
| **Ethnicity Hispanic/Latino (%)** |          |            |         |                       |          |
| Hispanic or Latino      | 10165 (10.5) | 9593 (10.8) | 572 (7.5) | 1.01 (0.91 - 1.12) | 0.84     |
| Not Hispanic or Latino  | 80974 (83.7) | 74210 (83.3) | 6764 (88.4) | 1.0 (referent)         |          |
| Unknown                 | 5600 (5.8)   | 5283 (5.9)  | 317 (4.1)  | 1.0 (0.91 - 1.21)     | 0.50     |
| **US Region (%)**       |          |            |         |                       |          |
| Continental             | 15826 (16.4) | 14408 (16.2) | 1418 (18.5) | 1.20 (1.11 - 1.31)    | 7.4E-06 a|
| Midwest                 | 18916 (19.6) | 17264 (19.4) | 1652 (21.6) | 1.00 (0.92 - 1.08)    | 0.98     |
| North Atlantic          | 20743 (21.4) | 19165 (21.5) | 1578 (20.6) | 0.96 (0.89 - 1.04)    | 0.29     |
| Pacific                 | 18136 (18.7) | 16858 (18.9) | 1278 (16.7) | 0.97 (0.89 - 1.05)    | 0.46     |
| Southeast               | 20955 (21.7) | 19246 (21.6) | 1709 (22.3) | 1.0 (referent)         |          |
| Unknown                 | 2163 (2.2)   | 2145 (2.4)  | 18 (0.2)   | 0.34 (0.21 - 0.55)    | 8.0E-06 a|
| **Period of dominant variant (%)** |          |            |         |                       |          |
| Pre-delta period        | 2387 (2.5)   | 1952 (2.2)  | 435 (5.7)  | 1.0 (referent)         |          |
| Delta period            | 25071 (25.9) | 21616 (24.3) | 3455 (45.1) | 1.04 (0.89 - 1.20)    | 0.65     |
|                              | Unvaccinated (71.6) | Vaccinated (73.5) | Breakthrough (49.2) | p Value | Adjusted p Value |
|------------------------------|---------------------|-------------------|---------------------|---------|-----------------|
| **Omicron period**           |                     |                   |                     |         |                 |
|                              | 69281               | 65518             | 3763                | 0.52    | 0.44 - 0.61     |
| **Vaccine type (%)**         |                     |                   |                     |         |                 |
| Janssen                      | 9894 (10.2)         | 9088 (10.2)       | 806 (10.5)          | 1.35    | 1.24 - 1.48     |
| Moderna                      | 39432 (40.8)        | 36429 (40.9)      | 3003 (39.2)         | 0.80    | 0.75 - 0.84     |
| Pfizer                       | 47413 (49.0)        | 43569 (48.9)      | 3844 (50.2)         | 1.00    |                 |
| **History of infection before vaccinated (%)** |                     |                   |                     |         |                 |
|                              | 3737 (3.9)          | 3444 (3.9)        | 293 (3.8)           | 0.71    | 0.62 - 0.83     |
| **Months since full vax at breakthrough (%)** |                     |                   |                     |         |                 |
| 4 or less                    | 10825 (11.2)        | 9758 (11.0)       | 1067 (13.9)         | 1.00    |                 |
| 4-5                          | 6241 (6.5)          | 5612 (6.3)        | 629 (8.2)           | 1.04    | 0.92 - 1.18     |
| 5-6                          | 6989 (7.2)          | 6208 (7.0)        | 781 (10.2)          | 0.97    | 0.86 - 1.10     |
| 6-7                          | 7762 (8.0)          | 6918 (7.8)        | 844 (11.0)          | 1.09    | 0.96 - 1.23     |
| 7-8                          | 10403 (10.8)        | 9582 (10.8)       | 821 (10.7)          | 1.18    | 1.04 - 1.33     |
| 8-9                          | 17049 (17.6)        | 16114 (18.1)      | 935 (12.2)          | 1.19    | 1.05 - 1.34     |
| 9-10                         | 17509 (18.1)        | 16500 (18.5)      | 1009 (13.2)         | 1.15    | 1.01 - 1.31     |
| 10-11                        | 13571 (14.0)        | 12543 (14.1)      | 1028 (13.4)         | 1.33    | 1.16 - 1.52     |
| 11-12                        | 5604 (5.8)          | 5143 (5.8)        | 461 (6.0)           | 1.48    | 1.26 - 1.74     |
| 12 or more                   | 786 (0.8)           | 708 (0.8)         | 78 (1.0)            | 1.77    | 1.32 - 2.36     |
| **Months since boosted at breakthrough (%)** |                     |                   |                     |         |                 |
| Not boosted                  | 71631 (74.0)        | 65249 (73.2)      | 6382 (83.4)         | 1.00    |                 |
| 1 or less                    | 5092 (5.3)          | 4860 (5.5)        | 232 (3.0)           | 0.50    | 0.43 - 0.57     |
| 1-2                          | 6854 (7.1)          | 6607 (7.4)        | 247 (3.2)           | 0.37    | 0.32 - 0.43     |
| 2-3                          | 7443 (7.7)          | 7093 (8.0)        | 350 (4.6)           | 0.39    | 0.34 - 0.44     |
| 3-4                          | 3593 (3.7)          | 3314 (3.7)        | 279 (3.6)           | 0.55    | 0.48 - 0.64     |
| 4-5                          | 1079 (1.1)          | 980 (1.1)         | 99 (1.3)            | 0.64    | 0.51 - 0.81     |
| 5-6                          | 229 (0.2)           | 211 (0.2)         | 18 (0.2)            | 0.59    | 0.35 - 0.99     |
| 6 or more                    | 818 (0.8)           | 772 (0.9)         | 46 (0.6)            | 0.77    | 0.56 - 1.07     |
| **Persistent positive test (%)** | 351 (0.4)          | 285 (0.3)         | 66 (0.9)            | 1.35    | 1.00 - 1.82     |
| **BMI Class (%)**            |                     |                   |                     |         |                 |
| Underweight                  | 558 (0.6)           | 436 (0.5)         | 122 (1.6)           | 1.47    | 1.16 - 1.87     |
| Normal                       | 12400 (12.8)        | 10927 (12.3)      | 1473 (19.2)         | 1.00    |                 |
| Overweight                   | 28622 (29.6)        | 26521 (29.8)      | 2101 (27.5)         | 0.74    | 0.68 - 0.80     |
| Obesity I                    | 27273 (28.2)        | 25402 (28.5)      | 1871 (24.4)         | 0.81    | 0.75 - 0.88     |
| Obesity II                   | 14658 (15.2)        | 13537 (15.2)      | 1121 (14.6)         | 1.01    | 0.92 - 1.11     |
| Severe Obesity               | 9073 (9.4)          | 8258 (9.3)        | 815 (10.6)          | 1.36    | 1.22 - 1.51     |
| Unknown                      | 4155 (4.3)          | 4005 (4.5)        | 150 (2.0)           | 0.97    | 0.80 - 1.17     |
| **Comorbidities (%)**        |                     |                   |                     |         |                 |
| Acquired hypothyroidism      | 4131 (4.3)          | 3573 (4.0)        | 558 (7.3)           | 1.02    | 0.92 - 1.14     |
| Acute myocardial infarction  | 637 (0.7)           | 478 (0.5)         | 159 (2.1)           | 1.15    | 0.92 - 1.44     |

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| Condition                                      | Cases (1% of Total) | Controls (1% of Total) | OR (95% CI)         | P Value |
|-----------------------------------------------|---------------------|------------------------|---------------------|---------|
| Alzheimers disease and related disorders or senile dementia | 2600 (2.7)          | 1687 (1.9)             | 913 (11.9)          | 2.12 (1.92 - 2.35) | <1.0E-08<sup>a</sup> |
| Anemia                                        | 6284 (6.5)          | 5055 (5.7)             | 1229 (16.1)         | 1.19 (1.09 - 1.29) | 8.6E-05<sup>a</sup>  |
| Anxiety disorders                             | 22899 (23.7)        | 21516 (24.2)           | 1383 (18.1)         | 0.92 (0.85 - 0.99) | 0.03<sup>a</sup>     |
| Asthma                                        | 2605 (2.7)          | 2450 (2.8)             | 155 (2.0)           | 0.79 (0.66 - 0.95) | 0.01<sup>a</sup>     |
| Atrial fibrillation                           | 4627 (4.8)          | 3580 (4.0)             | 1047 (13.7)         | 1.18 (1.08 - 1.29) | 2.4E-04<sup>a</sup>  |
| Bipolar disorder                              | 5426 (5.6)          | 4971 (5.6)             | 455 (5.9)           | 1.22 (1.08 - 1.38) | 0.001<sup>a</sup>    |
| Chronic kidney disease                        | 9547 (9.9)          | 7630 (8.6)             | 1917 (25.0)         | 1.59 (1.47 - 1.71) | <1.0E-08<sup>a</sup> |
| Chronic obstructive pulmonary disease and bronchiectasis | 5848 (6.0)          | 4564 (5.1)             | 1284 (16.8)         | 1.62 (1.50 - 1.76) | <1.0E-08<sup>a</sup> |
| Colorectal cancer                             | 444 (0.5)           | 370 (0.4)              | 74 (1.0)            | 0.99 (0.75 - 1.31) | 0.95                |
| Depression                                    | 19429 (20.1)        | 17975 (20.2)           | 1454 (19.0)         | 1.12 (1.03 - 1.21) | 0.005<sup>a</sup>    |
| Diabetes                                      | 22152 (22.9)        | 19119 (21.5)           | 3033 (39.6)         | 1.26 (1.19 - 1.34) | <1.0E-08<sup>a</sup> |
| Epilepsy                                      | 906 (0.9)           | 753 (0.8)              | 153 (2.0)           | 1.50 (1.22 - 1.84) | 1.0E-04<sup>a</sup>  |
| Heart failure                                 | 4239 (4.4)          | 3006 (3.4)             | 1233 (16.1)         | 1.84 (1.68 - 2.02) | <1.0E-08<sup>a</sup> |
| Human immunodeficiency virus and/or acquired immunodeficiency syndrome HIV/AIDS | 771 (0.8)           | 708 (0.8)              | 63 (0.8)            | 1.40 (1.06 - 1.86) | 0.02<sup>a</sup>     |
| Hyperlipidemia                                | 26846 (27.8)        | 24114 (27.1)           | 2732 (35.7)         | 0.78 (0.73 - 0.83) | <1.0E-08<sup>a</sup> |
| Hypertension                                  | 32577 (33.7)        | 28548 (32.0)           | 4029 (52.6)         | 1.09 (1.03 - 1.17) | 0.006<sup>a</sup>    |
| Ischemic heart disease                        | 8941 (9.2)          | 7339 (8.2)             | 1602 (20.9)         | 1.00 (0.93 - 1.09) | 0.91                |
| Liver disease cirrhosis and other liver conditions except viral hepatitis | 3408 (3.5)          | 2991 (3.4)             | 417 (5.4)           | 1.38 (1.22 - 1.56) | 1.8E-07<sup>a</sup>  |
| Lung cancer                                   | 535 (0.6)           | 400 (0.4)              | 135 (1.8)           | 1.78 (1.43 - 2.22) | 2.9E-07<sup>a</sup>  |
| Mobility impairments                          | 864 (0.9)           | 634 (0.7)              | 230 (3.0)           | 2.00 (1.67 - 2.40) | <1.0E-08<sup>a</sup> |
| Multiple sclerosis and transverse myelitis     | 247 (0.3)           | 196 (0.2)              | 51 (0.7)            | 3.33 (2.32 - 4.78) | <1.0E-08<sup>a</sup> |
| Peripheral vascular disease                   | 2539 (2.6)          | 1924 (2.2)             | 615 (8.0)           | 1.26 (1.12 - 1.41) | 8.1E-05<sup>a</sup>  |
| Pressure and chronic ulcers                   | 1112 (1.1)          | 755 (0.8)              | 357 (4.7)           | 1.53 (1.31 - 1.79) | 9.9E-08<sup>a</sup>  |
| Prostate cancer                               | 3041 (3.1)          | 2635 (3.0)             | 406 (5.3)           | 0.87 (0.77 - 0.98) | 0.02<sup>a</sup>     |
| Schizophrenia and other psychotic disorders   | 2428 (2.5)          | 2084 (2.3)             | 344 (4.5)           | 1.79 (1.56 - 2.05) | <1.0E-08<sup>a</sup> |
| Tobacco use                                   | 7799 (8.1)          | 7009 (7.9)             | 790 (10.3)          | 1.32 (1.21 - 1.45) | <1.0E-08<sup>a</sup> |
| Viral hepatitis                               | 1145 (1.2)          | 986 (1.1)              | 159 (2.1)           | 1.11 (0.91 - 1.35) | 0.30                |
| Death from breakthrough                       | 1016 (1.1)          | 0 (0.0)                | 1016 (13.3)         |                     |                     |

<sup>a</sup> Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.035 for this analysis. OR = odds ratio. CI = 95% confidence interval.
**eTable 10. Subcohort of Patients Aged 50 or Older, Data and Analysis**

|                        | Overall | Non-severe | Severe | Multivariable OR (CI) | P      |
|------------------------|---------|------------|--------|-----------------------|--------|
| N                      | 85098   | 74791      | 10307  |                       |        |
| Sex (%)                |         |            |        |                       |        |
| Male                   | 78268 (92.0) | 68307 (91.3) | 9961 (96.6) | 1.0 (referent)       |        |
| Female                 | 6830 (8.0)   | 6484 (8.7)   | 346 (3.4)   | 0.72 (0.64 - 0.81)   | 5.0E-08 |
| Age ranges (%)         |         |            |        |                       |        |
| 50-55                  | 9721 (11.4)  | 9444 (12.6)  | 277 (2.7)  |                       |        |
| 55-60                  | 10934 (12.8) | 10458 (14.0) | 476 (4.6)  |                       |        |
| 60-65                  | 12971 (15.2)| 12082 (16.2) | 889 (8.6)  |                       |        |
| 65-70                  | 12353 (14.5)| 11013 (14.7)| 1340 (13.0)|                       |        |
| 70-75                  | 18327 (21.5)| 15703 (21.0)| 2624 (25.5)|                       |        |
| 75-80                  | 11562 (13.6)| 9546 (12.8)  | 2016 (19.6)|                       |        |
| 80 or greater          | 9230 (10.8)| 6545 (8.8)   | 2685 (26.1)|                       |        |
| Age (per 5 years)      |         |            |        | 1.42 (1.4 - 1.44)     | <1E-08 |
| Race (%)               |         |            |        |                       |        |
| American Indian or Alaska Native | 626 (0.7) | 546 (0.7) | 80 (0.8) | 1.24 (0.96 - 1.61) | 0.10   |
| Asian                  | 759 (0.9)  | 709 (0.9)  | 50 (0.5)  | 0.81 (0.59 - 1.12)   | 0.20   |
| Black or African American | 21252 (25.0)| 19152 (25.6)| 2100 (20.4)| 0.98 (0.92 - 1.04) | 0.52   |
| Native Hawaiian or other Pacific Islander | 798 (0.9) | 724 (1.0) | 74 (0.7) | 0.89 (0.69 - 1.15) | 0.38   |
| White                  | 56038 (65.9)| 48587 (65.0)| 7451 (72.3)| 1.0 (referent)     |        |
| Unknown                | 5625 (6.6)  | 5073 (6.8)  | 552 (5.4) | 0.90 (0.80 - 1.00)  | 0.05   |
| Ethnicity Hispanic/Latino (%) |         |            |        |                       |        |
| Hispanic or Latino     | 6850 (8.0)  | 6140 (8.2)  | 710 (6.9) | 1.02 (0.93 - 1.12)  | 0.70   |
| Not Hispanic or Latino | 74494 (87.5)| 65272 (87.3)| 9222 (89.5)| 1.0 (referent)     |        |
| Unknown                | 3754 (4.4)  | 3379 (4.5)  | 375 (3.6) | 1.01 (0.89 - 1.16)  | 0.86   |
| US Region (%)          |         |            |        |                       |        |
| Continental            | 13575 (16.0)| 11751 (15.7)| 1824 (17.7)| 1.16 (1.08 - 1.25)  | 3.7E-05|
| Midwest                | 17725 (20.8)| 15448 (20.7)| 2277 (22.1)| 0.99 (0.92 - 1.06)  | 0.70   |
| North Atlantic         | 18426 (21.7)| 16275 (21.8)| 2151 (20.9)| 0.93 (0.87 - 1.00)  | 0.05   |
| Pacific                | 14739 (17.3)| 13082 (17.5)| 1657 (16.1)| 0.97 (0.90 - 1.04)  | 0.41   |
| Southeast              | 19480 (22.9)| 17099 (22.9)| 2381 (23.1)| 1.0 (referent)     |        |
| Unknown                | 1153 (1.4)  | 1136 (1.5)  | 17 (0.2)  | 0.31 (0.19 - 0.50)  | 2.4E-06|
| Period of dominant variant (%) |         |            |        |                       |        |
| Pre-delta period       | 2640 (3.1)  | 2009 (2.7)  | 631 (6.1) | 1.0 (referent)     |        |
| Delta period           | 24712 (29.0)| 20096 (26.9)| 4616 (44.8)| 0.94 (0.83 - 1.08)  | 0.40   |
| Omicron period         | 57746 (67.9)| 52686 (70.4)| 5060 (49.1)| 0.49 (0.43 - 0.57)  | <1E-08 |
| Vaccine type (%) | Janssen | Moderna | Pfizer | Janssen - Moderna (95% CI) | History of infection before vaccinated (%) | Months since full vax at breakthrough (%) | Months since boosted at breakthrough (%) | Immune-suppressive medications before breakthrough (%) | Immune-suppressive medications before initial vaccination (%) | Persistent positive test (%) |
|------------------|---------|---------|--------|---------------------------|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------------|------------------------------------------------|-----------------------------|
| Janssen          | 7503 (8.8) | 6532 (8.7) | 971 (9.4) | 1.29 (1.19 - 1.41) | <1.0E-08                                  | 3172 (3.7) | 2772 (3.7) | 400 (3.9) | 0.69 (0.61 - 0.79) | 1.8E-08                             |
| Moderna          | 36379 (42.7) | 32230 (43.1) | 4149 (40.3) | 0.78 (0.75 - 0.82) | <1.0E-08                                  | 1.0 (referent) | 4 or less | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 | 9-10 | 10-11 | 11-12 | 12 or more | 6 or more |
| Pfizer           | 41216 (48.4) | 36029 (48.2) | 5187 (50.3) | 1.0 (referent) | <1.0E-08                                  | 41216 (48.4) | 36029 (48.2) | 5187 (50.3) | 1.0 (referent) | 4 or less | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 | 9-10 | 10-11 | 11-12 | 12 or more | 6 or more |
| History of infection before vaccinated (%) | 3172 (3.7) | 2772 (3.7) | 400 (3.9) | 0.69 (0.61 - 0.79) | 1.8E-08 | 4 or less | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 | 9-10 | 10-11 | 11-12 | 12 or more | 6 or more |
| Months since full vax at breakthrough (%) | 3172 (3.7) | 2772 (3.7) | 400 (3.9) | 0.69 (0.61 - 0.79) | 1.8E-08 | 4 or less | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 | 9-10 | 10-11 | 11-12 | 12 or more | 6 or more |
| Months since boosted at breakthrough (%) | 3172 (3.7) | 2772 (3.7) | 400 (3.9) | 0.69 (0.61 - 0.79) | 1.8E-08 | 4 or less | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 | 9-10 | 10-11 | 11-12 | 12 or more | 6 or more |
| Immune-suppressive medications before breakthrough (%) | 3172 (3.7) | 2772 (3.7) | 400 (3.9) | 0.69 (0.61 - 0.79) | 1.8E-08 | 4 or less | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 | 9-10 | 10-11 | 11-12 | 12 or more | 6 or more |
| Immune-suppressive medications before initial vaccination (%) | 3172 (3.7) | 2772 (3.7) | 400 (3.9) | 0.69 (0.61 - 0.79) | 1.8E-08 | 4 or less | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 | 9-10 | 10-11 | 11-12 | 12 or more | 6 or more |
| Persistent positive test (%) | 3172 (3.7) | 2772 (3.7) | 400 (3.9) | 0.69 (0.61 - 0.79) | 1.8E-08 | 4 or less | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 | 9-10 | 10-11 | 11-12 | 12 or more | 6 or more |
### BMI Class (%)

| BMI Class          | Underweight  | Normal       | Overweight   | Obesity I     | Obesity II    | Severe Obesity | Unknown  |
|--------------------|--------------|--------------|--------------|---------------|---------------|----------------|----------|
|                    | 591 (0.7)    | 413 (0.6)    | 178 (1.7)    | 1.44 (1.17 - 1.78) | 5.4E-04       |                |          |
|                    | 11472 (13.5) | 9409 (12.6)  | 2063 (20.0)  | 0.9 (referent) |               |                |          |
|                    | 25795 (30.3) | 22941 (30.7) | 2854 (27.7)  | 0.73 (0.68 - 0.79) | <1.0E-08      |                |          |
|                    | 24261 (28.5) | 21759 (29.1) | 2502 (24.3)  | 0.80 (0.75 - 0.86) | <1.0E-08      |                |          |
|                    | 12843 (15.1) | 11357 (15.2) | 1486 (14.4)  | 1 (0.92 - 1.08)  | 0.95          |                |          |
|                    | 7870 (9.2)   | 6795 (9.1)   | 1075 (10.4)  | 1.29 (1.17 - 1.42) | 1.3E-07       |                |          |
|                    | 2266 (2.7)   | 2117 (2.8)   | 149 (1.4)    | 0.92 (0.76 - 1.11) | 0.38          |                |          |

### Comorbidities (%)

| Comorbidity                                                      | Underweight  | Normal       | Overweight   | Obesity I     | Obesity II    | Severe Obesity | Unknown  |
|-----------------------------------------------------------------|--------------|--------------|--------------|---------------|---------------|----------------|----------|
| Acquired hypothyroid                                            | 4393 (5.2)   | 3612 (4.8)   | 781 (7.6)    | 1.02 (0.92 - 1.12) | 0.75          |                |          |
| Acute myocardial infarction                                     | 749 (0.9)    | 542 (0.7)    | 207 (2.0)    | 1.05 (0.86 - 1.28) | 0.63          |                |          |
| Alzheimers disease and related disorders or senile dementia     | 3005 (3.5)   | 1876 (2.5)   | 1129 (11.0)  | 1.89 (1.72 - 2.07) | <1.0E-08      |                |          |
| Anemia                                                          | 7295 (8.6)   | 5458 (7.3)   | 1837 (17.8)  | 1.18 (1.10 - 1.27) | 5.4E-06       |                |          |
| Anxiety disorders                                               | 16675 (19.6)| 14868 (19.9)| 1807 (17.5)  | 0.88 (0.82 - 0.94) | 2.3E-04       |                |          |
| Asthma                                                          | 2524 (3.0)   | 2233 (3.0)   | 291 (2.8)    | 0.87 (0.75 - 1.00) | 0.05          |                |          |
| Atrial fibrillation                                             | 5701 (6.7)   | 4203 (5.6)   | 1498 (14.5)  | 1.17 (1.09 - 1.27) | 5.0E-05       |                |          |
| Bipolar disorder                                                | 4288 (5.0)   | 3685 (4.9)   | 603 (5.9)    | 1.24 (1.11 - 1.38) | 1.1E-04       |                |          |
| Chronic kidney disease                                          | 11069 (13.0)| 8356 (11.2)  | 2713 (26.3)  | 1.58 (1.48 - 1.68) | <1.0E-08      |                |          |
| Chronic obstructive pulmonary disease and bronchiectasis        | 8150 (9.6)   | 5926 (7.9)   | 2224 (21.6)  | 1.67 (1.56 - 1.78) | <1.0E-08      |                |          |
| Colorectal cancer                                               | 589 (0.7)    | 468 (0.6)    | 121 (1.2)    | 1.05 (0.83 - 1.31) | 0.70          |                |          |
| Depression                                                      | 15229 (17.9)| 13311 (17.8)| 1918 (18.6)  | 1.09 (1.02 - 1.17) | 0.01          |                |          |
| Diabetes                                                        | 24430 (28.7)| 20324 (27.2)| 4106 (39.8)  | 1.26 (1.19 - 1.33) | <1.0E-08      |                |          |
| Epilepsy                                                        | 891 (1.0)    | 687 (0.9)    | 204 (2.0)    | 1.49 (1.24 - 1.79) | 2.1E-05       |                |          |
| Heart failure                                                   | 5322 (6.3)   | 3571 (4.8)   | 1751 (17.0)  | 1.72 (1.59 - 1.86) | <1.0E-08      |                |          |
| Human immunodeficiency virus and/or acquired immunodeficiency syndrome HIV/AIDS | 688 (0.8)    | 607 (0.8)    | 81 (0.8)     | 1.37 (1.06 - 1.77) | 0.02          |                |          |
| Hyperlipidemia                                                  | 27594 (32.4)| 23772 (31.8)| 3822 (37.1)  | 0.80 (0.76 - 0.85) | <1.0E-08      |                |          |
| Hypertension                                                    | 35573 (41.8)| 29939 (40.0)| 5634 (54.7)  | 1.07 (1.01 - 1.13) | 0.02          |                |          |
| Ischemic heart disease                                          | 10764 (12.6)| 8492 (11.4)  | 2272 (22.0)  | 0.98 (0.92 - 1.05) | 0.63          |                |          |
| Leukemias and lymphomas                                         | 1268 (1.5)   | 932 (1.2)    | 336 (3.3)    | 1.86 (1.60 - 2.17) | <1.0E-08      |                |          |
| Liver disease cirrhosis and other liver conditions except viral hepatitis | 3386 (4.0)   | 2792 (3.7)   | 594 (5.8)    | 1.34 (1.20 - 1.49) | 7.9E-08       |                |          |
| Lung cancer                                                     | 820 (1.0)    | 569 (0.8)    | 251 (2.4)    | 1.67 (1.41 - 1.98) | <1.0E-08      |                |          |
| Mobility impairments                                            | 939 (1.1)    | 648 (0.9)    | 291 (2.8)    | 1.89 (1.61 - 2.24) | <1.0E-08      |                |          |
| Multiple sclerosis and transverse myelitis                      | 326 (0.4)    | 244 (0.3)    | 82 (0.8)     | 2.80 (2.08 - 3.76) | <1.0E-08      |                |          |
| Peripheral vascular disease                                     | 3050 (3.6)   | 2200 (2.9)   | 850 (8.2)    | 1.25 (1.13 - 1.38) | 1.0E-05       |                |          |
| Pressure and chronic ulcers                                     | 1306 (1.5)   | 837 (1.1)    | 469 (4.6)    | 1.58 (1.37 - 1.81) | <1.0E-08      |                |          |
| Prostate cancer                                                 | 3803 (4.5)   | 3170 (4.2)   | 633 (6.1)    | 0.89 (0.81 - 0.98) | 0.02          |                |          |
| Condition                                      | Cases (N=100) | Controls (N=100) | Difference (Mean ± Standard Deviation) | OR (95% CI) | p Value |
|-----------------------------------------------|---------------|------------------|---------------------------------------|------------|---------|
| Schizophrenia and other psychotic disorders   | 2148 (2.5)    | 1730 (2.3)       | 418 (4.1)                             | 1.75 (1.54 - 1.98) | <1.0E-08<sup>a</sup> |
| Tobacco use                                   | 7134 (8.4)    | 5974 (8.0)       | 1160 (11.3)                           | 1.33 (1.23 - 1.45) | <1.0E-08<sup>a</sup> |
| Viral hepatitis                               | 1310 (1.5)    | 1079 (1.4)       | 231 (2.2)                             | 0.99 (0.84 - 1.18)  | 0.94    |
| Death from breakthrough                       | 1546 (1.8)    | 0 (0.0)          | 1546 (15.0)                           |             |         |

<sup>a</sup> Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.035 for this analysis. OR = odds ratio. CI = 95% confidence interval.
### eTable 11. Subcohort of Nonimmunocompromised Patients Younger Than 65 Years With No Booster, Data and Analysis

|                        | Overall | Non-severe | Severe | Multivariable OR (CI) | P       |
|------------------------|---------|------------|--------|-----------------------|---------|
| **N**                  | 16996   | 16595      | 401    |                       |         |
| **Sex (%)**            |         |            |        |                       |         |
| Male                   | 13626 (80.2) | 13265 (79.9) | 361 (90.0) | 1.0 (referent) | 0.008   |
| Female                 | 3370 (19.8) | 3330 (20.1) | 40 (10.0) | 0.62 (0.44 - 0.89) |         |
| **Age ranges (%)**     |         |            |        |                       |         |
| Less than 40           | 5644 (33.2) | 5602 (33.8) | 42 (10.5) | 0.78 (0.46 - 1.31) | 0.35    |
| 40-45                  | 2226 (13.1) | 2194 (13.2) | 32 (8.0)  | 1.25 (0.72 - 2.16) | 0.43    |
| 45-50                  | 1905 (11.2) | 1882 (11.3) | 23 (5.7)  | 1.0 (referent)      |         |
| 50-55                  | 2483 (14.6) | 2429 (14.6) | 54 (13.5) | 1.59 (0.96 - 2.63) | 0.07    |
| 55-60                  | 2279 (13.4) | 2183 (13.2) | 96 (23.9) | 2.99 (1.86 - 4.81) | 5.6E-06*|
| 60-65                  | 2240 (13.2) | 2114 (12.7) | 126 (31.4) | 3.28 (2.05 - 5.25) | 7.4E-07*|
| 65-70                  | 219 (1.3)  | 191 (1.2)  | 28 (7.0)  | 7.41 (3.98 - 13.8) | <1.0E-08*|
| **Race (%)**           |         |            |        |                       |         |
| American Indian or Alaska Native | 146 (0.9) | 137 (0.8)  | 9 (2.2)  | 3.89 (1.87 - 8.09) | 2.7E-04*|
| Asian                  | 319 (1.9)  | 313 (1.9)  | 6 (1.5)  | 1.77 (0.75 - 4.17) | 0.19    |
| Black or African American | 4674 (27.5) | 4556 (27.5) | 118 (29.4) | 1.15 (0.89 - 1.48) | 0.28    |
| Native Hawaiian or other Pacific Islander | 196 (1.2) | 193 (1.2)  | 3 (0.7)  | 0.91 (0.28 - 2.92) | 0.87    |
| White                  | 9878 (58.1) | 9638 (58.1) | 240 (59.9) | 1.0 (referent)      |         |
| Unknown                | 1783 (10.5) | 1758 (10.6) | 25 (6.2)  | 0.71 (0.45 - 1.14) | 0.16    |
| **Ethnicity Hispanic/Latino (%)** |         |            |        |                       |         |
| Hispanic or Latino     | 2203 (13.0) | 2169 (13.1) | 34 (8.5)  | 0.96 (0.65 - 1.42) | 0.84    |
| Not Hispanic or Latino | 13288 (78.2) | 12948 (78.0) | 340 (84.8) | 1.0 (referent)      |         |
| Unknown                | 1505 (8.9)  | 1478 (8.9)  | 27 (6.7)  | 1.45 (0.90 - 2.32) | 0.13    |
| **US Region (%)**      |         |            |        |                       |         |
| Continental            | 2984 (17.6) | 2893 (17.4) | 91 (22.7) | 1.30 (0.96 - 1.77) | 0.09    |
| Midwest                | 2842 (16.7) | 2769 (16.7) | 73 (18.2) | 0.81 (0.58 - 1.13) | 0.22    |
| North Atlantic         | 3623 (21.3) | 3565 (21.5) | 58 (14.5) | 0.63 (0.45 - 0.89) | 0.009   |
| Pacific                | 3352 (19.7) | 3275 (19.7) | 77 (19.2) | 0.97 (0.70 - 1.35) | 0.85    |
| Southeast              | 3549 (20.9) | 3450 (20.8) | 99 (24.7) | 1.0 (referent)      |         |
| Unknown                | 646 (3.8)  | 643 (3.9)  | 3 (0.7)  | 0.30 (0.09 - 0.96) | 0.04    |
| **Period of dominant variant (%)** |         |            |        |                       |         |
| Pre-delta period       | 90 (0.5)  | 83 (0.5)   | 7 (1.7)  | 1.0 (referent)      |         |
| Delta period           | 2841 (16.7) | 2698 (16.3) | 143 (35.7) | 0.93 (0.38 - 2.27) | 0.88    |
| Omicron period         | 14065 (82.8) | 13814 (83.2) | 251 (62.6) | 0.37 (0.15 - 0.90) | 0.03    |
| **Vaccine type (%)**   |         |            |        |                       |         |
|                      | Janssen | Moderna | Pfizer | 1.70 (1.32 - 2.17) | 2.9E-05 \(a\) |
|----------------------|---------|---------|--------|--------------------|----------------|
| History of infection before vaccinated (%) | 833 (4.9) | 823 (5.0) | 10 (2.5) | 0.44 (0.22 - 0.85) | 0.01 |
| Months since full vax at breakthrough (%) | 833 (4.9) | 823 (5.0) | 10 (2.5) | 0.44 (0.22 - 0.85) | 0.01 |
| 4 or less | 4762 (28.0) | 4621 (27.8) | 141 (35.2) | 1.0 (referent) | 0.98 |
| 4-5 | 1871 (11.0) | 1818 (11.0) | 53 (13.2) | 1.00 (0.70 - 1.42) | 0.98 |
| 5-6 | 1574 (9.3) | 1538 (9.3) | 36 (9.0) | 0.81 (0.54 - 1.21) | 0.31 |
| 6-7 | 2260 (13.3) | 2210 (13.3) | 50 (12.5) | 1.08 (0.76 - 1.55) | 0.66 |
| 7-8 | 3916 (23.0) | 3849 (23.2) | 67 (16.7) | 1.02 (0.72 - 1.44) | 0.90 |
| 8-9 | 2258 (13.3) | 2214 (13.3) | 44 (11.0) | 1.22 (0.82 - 1.82) | 0.32 |
| 9-10 | 341 (2.0) | 331 (2.0) | 10 (2.5) | 1.29 (0.63 - 2.63) | 0.48 |
| 10-11 | 14 (0.1) | 14 (0.1) | 0 (0.0) | ND | ND |
| 11-12 | 0 | 0 | 0 | ND | ND |
| 12 or more | 0 | 0 | 0 | ND | ND |
| Persistent positive test (%) | 36 (0.2) | 35 (0.2) | 1 (0.2) | 0.29 (0.02 - 3.85) | 0.35 |
| BMI Class (%) | 59 (0.3) | 57 (0.3) | 2 (0.5) | 1.23 (0.27 - 5.63) | 0.79 |
| Normal | 1912 (11.2) | 1858 (11.2) | 54 (13.5) | 1.0 (referent) | 0.10 |
| Overweight | 4474 (26.3) | 4400 (26.5) | 74 (18.5) | 0.64 (0.44 - 0.94) | 0.02 |
| Obesity I | 4793 (28.2) | 4679 (28.2) | 114 (28.4) | 0.93 (0.65 - 1.34) | 0.70 |
| Obesity II | 2696 (15.9) | 2617 (15.8) | 79 (19.7) | 1.15 (0.78 - 1.70) | 0.49 |
| Severe Obesity | 1882 (11.1) | 1818 (11.0) | 64 (16.0) | 1.19 (0.78 - 1.81) | 0.41 |
| Unknown | 1180 (6.9) | 1166 (7.0) | 14 (3.5) | 0.90 (0.47 - 1.74) | 0.76 |
| Comorbidities (%) | 592 (3.5) | 563 (3.4) | 29 (7.2) | 1.32 (0.85 - 2.05) | 0.22 |
| Acute myocardial infarction | 91 (0.5) | 79 (0.5) | 12 (3.0) | 1.40 (0.63 - 3.12) | 0.41 |
| Alzheimers disease and related disorders or senile dementia | 75 (0.4) | 58 (0.3) | 17 (4.2) | 2.28 (1.16 - 4.49) | 0.02 |
| Anemia | 796 (4.7) | 750 (4.5) | 46 (11.5) | 0.97 (0.65 - 1.45) | 0.89 |
| Anxiety disorders | 5909 (34.8) | 5766 (34.7) | 143 (35.7) | 0.99 (0.77 - 1.28) | 0.95 |
| Asthma | 647 (3.8) | 626 (3.8) | 21 (5.2) | 1.23 (0.75 - 2.02) | 0.41 |
| Atrial fibrillation | 233 (1.4) | 214 (1.3) | 19 (4.7) | 0.80 (0.44 - 1.45) | 0.46 |
| Bipolar disorder | 1411 (8.3) | 1353 (8.2) | 58 (14.5) | 1.35 (0.96 - 1.90) | 0.09 |
| Chronic kidney disease | 991 (5.8) | 904 (5.4) | 87 (21.7) | 1.46 (1.05 - 2.03) | 0.02 |
| Chronic obstructive pulmonary disease and bronchiectasis | 458 (2.7) | 406 (2.4) | 52 (13.0) | 1.52 (1.04 - 2.23) | 0.03 |
| Colorectal cancer | 38 (0.2) | 34 (0.2) | 4 (1.0) | 1.38 (0.39 - 4.85) | 0.62 |
| Depression | 4867 (28.6) | 4712 (28.4) | 155 (38.7) | 1.38 (1.06 - 1.80) | 0.02 |
| Condition                                                                 | A (N) (%) | B (N) (%) | C (N) (%) | OR (95% CI) | P-value |
|--------------------------------------------------------------------------|----------|----------|----------|-------------|---------|
| Diabetes                                                                 | 2280 (13.4) | 2135 (12.9) | 145 (36.2) | 1.68 (1.28 - 2.22) | 1.9E-04<sup>a</sup> |
| Epilepsy                                                                 | 170 (1.0) | 152 (0.9) | 18 (4.5) | 2.38 (1.31 - 4.31) | 0.004<sup>a</sup> |
| Heart failure                                                            | 263 (1.5) | 219 (1.3) | 44 (11.0) | 2.63 (1.66 - 4.17) | 3.8E-05<sup>a</sup> |
| Human immunodeficiency virus and/or acquired immunodeficiency syndrome HIV/AIDS | 113 (0.7) | 107 (0.6) | 6 (1.5) | 1.24 (0.46 - 3.32) | 0.67 |
| Hyperlipidemia                                                           | 4322 (25.4) | 4167 (25.1) | 155 (38.7) | 0.73 (0.57 - 0.94) | 0.02 |
| Hypertension                                                             | 4270 (25.1) | 4067 (25.1) | 203 (50.6) | 1.16 (0.90 - 1.51) | 0.26 |
| Ischemic heart disease                                                  | 620 (3.6) | 571 (3.4) | 49 (12.2) | 0.94 (0.62 - 1.43) | 0.78 |
| Liver disease cirrhosis and other liver conditions except viral hepatitis | 691 (4.1) | 645 (3.9) | 46 (11.5) | 1.55 (1.07 - 2.25) | 0.02 |
| Lung cancer                                                              | 12 (0.1) | 8 (0.0) | 4 (1.0) | 10.8 (2.69 - 43.5) | 8.1E-04<sup>a</sup> |
| Mobility impairments                                                    | 82 (0.5) | 74 (0.4) | 8 (2.0) | 0.80 (0.34 - 1.90) | 0.62 |
| Multiple sclerosis and transverse myelitis                               | 34 (0.2) | 31 (0.2) | 3 (0.7) | 5.17 (1.45 - 18.4) | 0.01 |
| Peripheral vascular disease                                              | 153 (0.9) | 133 (0.8) | 20 (5.0) | 1.09 (0.59 - 2.01) | 0.78 |
| Pressure and chronic ulcers                                              | 87 (0.5) | 69 (0.4) | 18 (4.5) | 2.81 (1.40 - 5.65) | 0.004<sup>a</sup> |
| Prostate cancer                                                          | 116 (0.7) | 109 (0.7) | 7 (1.7) | 1.17 (0.51 - 2.68) | 0.71 |
| Schizophrenia and other psychotic disorders                              | 447 (2.6) | 414 (2.5) | 33 (8.2) | 1.73 (1.11 - 2.70) | 0.02 |
| Tobacco use                                                              | 2058 (12.1) | 1956 (11.8) | 102 (25.4) | 1.42 (1.07 - 1.88) | 0.01 |
| Viral hepatitis                                                          | 155 (0.9) | 137 (0.8) | 18 (4.5) | 1.69 (0.93 - 3.09) | 0.09 |
| Death from breakthrough                                                  | 42 (0.2) | 0 (0.0) | 42 (8.6) |               |         |

<sup>a</sup> Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.007 for this analysis. OR = odds ratio. CI = 95% confidence interval.
eTable 12. Subcohort of Nonimmunocompromised Patients Aged 65 Years or Older With No Booster, Data and Analysis

|                          | Overall | Non-severe | Severe | Multivariable OR (CI) | P       |
|--------------------------|---------|------------|--------|------------------------|---------|
| N                        | 17756   | 14428      | 3328   |                        |         |
| **Sex (%)**              |         |            |        |                        |         |
| Male                     | 17210 (96.9) | 13946 (96.7) | 3264 (98.1) | 1.0 (referent) |         |
| Female                   | 546 (3.1)  | 482 (3.3)  | 64 (1.9) | 0.75 (0.57 – 1.00)     | 0.05    |
| **Age ranges (%)**       |         |            |        |                        |         |
| 65-70                    | 3815 (21.5) | 3407 (23.6) | 408 (12.3) | 1.0 (referent) |         |
| 70-75                    | 6389 (36.0) | 5443 (37.7) | 946 (28.4) | 1.50 (1.32 - 1.71)    | <1.0E-08 |
| 75-80                    | 4017 (22.6) | 3273 (22.7) | 744 (22.4) | 2.07 (1.79 - 2.38)    | <1.0E-08 |
| 80 or greater            | 3535 (19.9) | 2305 (16.0) | 1230 (37.0) | 4.58 (3.97 - 5.28)    | <1.0E-08 |
| **Race (%)**             |         |            |        |                        |         |
| American Indian or Alaska Native | 129 (0.7)  | 104 (0.7)  | 25 (0.8) | 1.03 (0.63 - 1.66)     | 0.92    |
| Asian                    | 110 (0.6)  | 94 (0.7)   | 16 (0.5) | 0.91 (0.51 - 1.63)     | 0.75    |
| Black or African American| 2744 (15.5) | 2207 (15.3) | 537 (16.1) | 1.12 (1.00 - 1.27)     | 0.06    |
| Native Hawaiian or other Pacific Islander | 141 (0.8)  | 115 (0.8)  | 26 (0.8) | 1.13 (0.71 - 1.81)     | 0.60    |
| White                    | 13512 (76.1) | 10966 (76.0) | 2546 (76.5) | 1.0 (referent)         |         |
| Unknown                  | 1120 (6.3)  | 942 (6.5)  | 178 (5.3) | 0.83 (0.68 - 1.01)     | 0.06    |
| **Ethnicity Hispanic/Latino (%)** |         |            |        |                        |         |
| Hispanic or Latino       | 1187 (6.7)  | 967 (6.7)  | 220 (6.6) | 1.13 (0.95 - 1.34)     | 0.17    |
| Not Hispanic or Latino   | 15826 (89.1) | 12852 (89.1) | 2974 (89.4) | 1.0 (referent)         |         |
| Unknown                  | 743 (4.2)   | 609 (4.2)  | 134 (4.0) | 1.09 (0.86 - 1.38)     | 0.46    |
| **US Region (%)**        |         |            |        |                        |         |
| Continental              | 2972 (16.7) | 2334 (16.2) | 638 (19.2) | 1.21 (1.07 - 1.37)     | 0.003 a |
| Midwest                  | 3660 (20.6) | 2964 (20.5) | 696 (20.9) | 1.03 (0.91 - 1.17)     | 0.59    |
| North Atlantic           | 3628 (20.4) | 2955 (20.5) | 673 (20.2) | 1.02 (0.90 - 1.16)     | 0.74    |
| Pacific                  | 3243 (18.3) | 2700 (18.7) | 543 (16.3) | 0.94 (0.83 - 1.07)     | 0.37    |
| Southeast                | 4188 (23.6) | 3415 (23.7) | 773 (23.2) | 1.0 (referent)         |         |
| Unknown                  | 65 (0.4)    | 60 (0.4)   | 5 (0.2)   | 0.51 (0.20 - 1.31)     | 0.16    |
| **Period of dominant variant (%)** |         |            |        |                        |         |
| Pre-delta period         | 634 (3.6)  | 442 (3.1)  | 192 (5.8) | 1.0 (referent)         |         |
| Delta period             | 5775 (32.5) | 4311 (29.9) | 1464 (44.0) | 0.99 (0.78 - 1.26)     | 0.94    |
| Omicron period           | 11347 (63.9) | 9675 (67.1) | 1672 (50.2) | 0.51 (0.40 - 0.66)     | 2.1E-07 a|
| **Vaccine type (%)**     |         |            |        |                        |         |
| Janssen                  | 1684 (9.5)  | 1315 (9.1) | 369 (11.1) | 1.21 (1.05 - 1.40)     | 0.008 a |
| Moderna                  | 8379 (47.2) | 6963 (48.3) | 1416 (42.5) | 0.81 (0.75 - 0.89)     | 3.6E-06 a|

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| Pfizer | 7693 (43.3) | 6150 (42.6) | 1543 (46.4) | 1.0 (referent) |
| History of infection before vaccinated (%) | 552 (3.1) | 451 (3.1) | 101 (3.0) | 0.58 (0.45 - 0.75) | 3.3E-05a |
| Months since full vax at breakthrough (%) |  |  |  |  |  |
| 4 or less | 1975 (11.1) | 1488 (10.3) | 487 (14.6) | 1.0 (referent) | 0.75 |
| 4-5 | 1188 (6.7) | 930 (6.4) | 258 (7.8) | 1.03 (0.84 - 1.27) | 0.23 |
| 5-6 | 1450 (8.2) | 1106 (7.7) | 344 (10.3) | 1.13 (0.93 - 1.37) | 0.08 |
| 6-7 | 1500 (8.4) | 1132 (7.8) | 368 (11.1) | 1.19 (0.98 - 1.44) | 0.37 |
| 7-8 | 1706 (9.6) | 1355 (9.4) | 351 (10.5) | 1.09 (0.90 - 1.32) | 0.12 |
| 8-9 | 2350 (13.2) | 1929 (13.4) | 421 (12.7) | 1.16 (0.96 - 1.40) | 0.67 |
| 9-10 | 3514 (19.6) | 3034 (21.0) | 480 (14.4) | 1.03 (0.85 - 1.25) | 0.76 |
| 10-11 | 3019 (17.0) | 2570 (17.8) | 449 (13.5) | 1.11 (0.91 - 1.36) | 0.31 |
| 11-12 | 958 (5.4) | 807 (5.7) | 151 (4.5) | 1.06 (0.82 - 1.36) | 0.42 |
| 12 or more | 96 (0.5) | 77 (0.5) | 19 (0.6) | 1.26 (0.72 - 2.18) | 0.61 |
| Persistent positive test (%) | 101 (0.6) | 78 (0.5) | 23 (0.7) | 0.88 (0.53 - 1.45) | 0.002a |
| BMI Class (%) | 181 (1.0) | 107 (0.7) | 74 (2.2) | 1.73 (1.23 - 2.44) | 3.7E-08a |
| Underweight | 3028 (17.1) | 2282 (15.8) | 746 (22.4) | 1.0 (referent) | 0.41 |
| Normal | 5903 (33.2) | 4941 (34.2) | 962 (28.9) | 0.72 (0.64 - 0.81) | 0.001a |
| Overweight | 4731 (26.6) | 3959 (27.4) | 772 (23.2) | 0.81 (0.72 - 0.92) | 0.15 |
| Obesity I | 2266 (12.8) | 1837 (12.7) | 429 (12.9) | 1.02 (0.88 - 1.19) | 0.67 |
| Obesity II | 1229 (6.9) | 946 (6.6) | 283 (8.5) | 1.38 (1.16 - 1.65) | 0.56 |
| Severe Obesity | 418 (2.4) | 356 (2.5) | 62 (1.9) | 0.91 (0.67 - 1.24) | 0.002a |
| Unknown | 1087 (6.1) | 816 (5.7) | 271 (8.1) | 1.01 (0.86 - 1.19) | 0.002a |
| Comorbidities (%) | 119 (0.8) | 69 (2.1) | 69 (2.1) | 1.09 (0.76 - 1.56) | 0.15 |
| Acute myocardial infarction | 1557 (8.9) | 1135 (8.1) | 422 (12.3) | 1.27 (1.11 - 1.45) | 0.41 |
| Alzheimers disease and related disorders or senile dementia | 1057 (6.0) | 593 (4.1) | 464 (13.9) | 2.01 (1.73 - 2.33) | <1.0E-08a |
| Anemia | 1717 (9.7) | 1135 (7.9) | 582 (17.5) | 1.27 (1.11 - 1.45) | 0.001a |
| Anxiety disorders | 2637 (14.9) | 2152 (14.9) | 485 (14.6) | 0.95 (0.83 - 1.08) | 0.15 |
| Asthma | 316 (1.8) | 266 (1.8) | 50 (1.5) | 0.68 (0.49 - 0.96) | 0.04 |
| Atrial fibrillation | 1676 (9.4) | 1161 (8.0) | 515 (15.5) | 1.15 (1.01 - 1.32) | 0.15 |
| Bipolar disorder | 634 (3.6) | 490 (3.4) | 144 (4.3) | 1.18 (0.94 - 1.48) | 0.41 |
| Chronic kidney disease | 2600 (14.6) | 1745 (12.1) | 855 (25.7) | 1.60 (1.42 - 1.80) | <1.0E-08a |
| Chronic obstructive pulmonary disease and bronchiectasis | 1922 (10.8) | 1328 (9.2) | 594 (17.8) | 1.60 (1.42 - 1.82) | <1.0E-08a |
| Colorectal cancer | 136 (0.8) | 103 (0.7) | 33 (1.0) | 0.94 (0.61 - 1.46) | 0.002a |
| Depression | 2345 (13.2) | 1853 (12.8) | 492 (14.8) | 1.03 (0.90 - 1.19) | 0.002a |
| Diabetes | 5514 (31.1) | 4220 (29.2) | 1294 (38.9) | 1.21 (1.10 - 1.34) | 0.002a |
| Epilepsy | 172 (1.0) | 121 (0.8) | 51 (1.5) | 1.23 (0.85 - 1.78) | 0.002a |
| Heart failure | 1472 (8.3) | 882 (6.1) | 590 (17.7) | 1.88 (1.63 - 2.16) | 3.3E-05a |
| Condition                                                                 | Group 1 | Group 2 | Group 3 | Odds Ratio (95% CI) | P-value |
|---------------------------------------------------------------------------|---------|---------|---------|---------------------|---------|
| Human immunodeficiency virus and/or acquired immunodeficiency syndrome HIV/AIDS | 66 (0.4) | 50 (0.3) | 16 (0.5) | 1.76 (0.96 - 3.24) | 0.07    |
| Hyperlipidemia                                                             | 6055 (34.1) | 4836 (33.5) | 1219 (36.6) | 0.78 (0.71 - 0.87) | 4.3E-06^a |
| Hypertension                                                               | 8009 (45.1) | 6205 (43.0) | 1804 (54.2) | 1.10 (0.99 - 1.22) | 0.07    |
| Ischemic heart disease                                                     | 2995 (16.9) | 2247 (15.6) | 748 (22.5) | 0.91 (0.80 - 1.02) | 0.10    |
| Liver disease cirrhosis and other liver conditions except viral hepatitis | 609 (3.4) | 463 (3.2) | 146 (4.4) | 1.17 (0.94 - 1.45) | 0.16    |
| Lung cancer                                                                | 173 (1.0) | 114 (0.8) | 59 (1.8) | 1.64 (1.16 - 2.33) | 0.005^a |
| Mobility impairments                                                       | 223 (1.3) | 137 (0.9) | 86 (2.6) | 1.70 (1.24 - 2.33) | 0.001^a |
| Multiple sclerosis and transverse myelitis                                  | 35 (0.2) | 21 (0.1) | 14 (0.4) | 3.45 (1.61 - 7.37) | 0.001^a |
| Peripheral vascular disease                                                | 866 (4.9) | 580 (4.0) | 286 (8.6) | 1.20 (1.01 - 1.43) | 0.04    |
| Pressure and chronic ulcers                                                | 359 (2.0) | 205 (1.4) | 154 (4.6) | 1.31 (1.02 - 1.69) | 0.04    |
| Prostate cancer                                                            | 926 (5.2) | 740 (5.1) | 286 (5.6) | 0.80 (0.67 - 0.97) | 0.02    |
| Schizophrenia and other psychotic disorders                                 | 376 (2.1) | 271 (1.9) | 105 (3.2) | 1.54 (1.19 - 1.99) | 9.4E-04^a |
| Tobacco use                                                                | 1215 (6.8) | 923 (6.4) | 292 (8.8) | 1.28 (1.09 - 1.51) | 0.003^a |
| Viral hepatitis                                                             | 246 (1.4) | 193 (1.3) | 53 (1.6) | 1.00 (0.70 - 1.42) | 1.00    |
| Death from breakthrough                                                    | 786 (4.4) | 0 (0.0)  | 786 (23.6) |

^a Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.015 in this analysis. OR = odds ratio. CI = 95% confidence interval.
eFigure. Age Distributions of Male and Female Patients

The X-axis indicates percentages within the group indicated. The male patients in the VA cohort are older than the female patients and than the general US male population.
### eTable 13. Subcohort of Female Patients, Data and Analysis

| Overall | Non-severe | Severe | Multivariable OR (CI) | P (multi) |
|---------|------------|--------|-----------------------|-----------|
| N       | 13146      | 12759  | 387                   |           |
| Age ranges (%) |       |        |                       |           |
| Less than 40 | 3314 (25.2) | 3299 (25.9) | 15 (3.9) | 0.83 (0.38 - 1.83) | 0.65 |
| 40-45   | 1553 (11.8) | 1539 (12.1) | 14 (3.6) | 1.41 (0.63 - 3.12) | 0.40 |
| 45-50   | 1449 (11.0) | 1437 (11.3) | 12 (3.1) | 1.0 (referent) |          |
| 50-55   | 1706 (13.0) | 1667 (13.1) | 39 (10.1) | 3.01 (1.53 - 5.91) | 0.001 a |
| 55-60   | 1721 (13.1) | 1677 (13.1) | 44 (11.4) | 2.86 (1.46 - 5.60) | 0.002 a |
| 60-65   | 1593 (12.1) | 1520 (11.9) | 73 (18.9) | 4.72 (2.46 - 9.05) | 3.0E-06 a |
| 65-70   | 1024 (7.8)  | 955 (7.5)  | 69 (17.8) | 5.32 (2.73 - 10.4) | 9.0E-07 a |
| 70-75   | 489 (3.7)   | 428 (3.4)  | 61 (15.8) | 9.40 (4.72 - 18.7) | <1.0E-08 a |
| 75-80   | 171 (1.3)   | 145 (1.1)  | 26 (6.7)  | 14.9 (6.80 - 32.8) | <1.0E-08 a |
| 80 or greater | 126 (1.0) | 92 (0.7) | 34 (8.8) | 43.5 (19.8 - 95.5) | <1.0E-08 a |
| Race (%) |           |        |                       |           |
| American Indian or Alaska Native | 155 (1.2) | 153 (1.2) | 2 (0.5) | 0.46 (0.10 - 2.04) | 0.31 |
| Asian   | 252 (1.9)  | 251 (2.0) | 1 (0.3) | 0.26 (0.03 - 1.97) | 0.19 |
| Black or African American | 4537 (34.5) | 4409 (34.6) | 128 (33.1) | 0.76 (0.58 - 1.01) | 0.06 |
| Native Hawaiian or other Pacific Islander | 164 (1.2) | 159 (1.2) | 5 (1.3) | 0.78 (0.27 - 2.29) | 0.65 |
| White   | 6713 (51.1) | 6482 (50.8) | 231 (59.7) | 1.0 (referent) |          |
| Unknown | 1325 (10.1) | 1305 (10.2) | 20 (5.2) | 0.68 (0.38 - 1.21) | 0.19 |
| Ethnicity Hispanic/Latino (%) |       |        |                       |           |
| Hispanic or Latino | 1397 (10.6) | 1377 (10.8) | 20 (5.2) | 0.64 (0.38 - 1.09) | 0.10 |
| Not Hispanic or Latino | 10671 (81.2) | 10318 (80.9) | 353 (91.2) | 1.0 (referent) |          |
| Unknown | 1078 (8.2)  | 1064 (8.3) | 14 (3.6) | 1.40 (0.73 - 2.72) | 0.31 |
| US Region (%) |      |        |                       |           |
| Continental | 2340 (17.8) | 2259 (17.7) | 81 (20.9) | 1.33 (0.96 - 1.86) | 0.09 |
| Midwest  | 2119 (16.1) | 2053 (16.1) | 66 (17.1) | 0.85 (0.60 - 1.22) | 0.39 |
| North Atlantic | 2754 (20.9) | 2688 (21.1) | 66 (17.1) | 0.82 (0.57 - 1.16) | 0.26 |
| Pacific  | 2169 (16.5) | 2106 (16.5) | 63 (16.3) | 1.11 (0.77 - 1.59) | 0.59 |
| Southeast | 3220 (24.5) | 3111 (24.4) | 109 (28.2) | 1.0 (referent) |          |
| Unknown  | 544 (4.1)   | 542 (4.2) | 2 (0.5)  | 0.33 (0.08 - 1.36) | 0.13 |
| Period of dominant variant (%) |       |        |                       |           |
| Pre-delta period |       |        |                       | 1.0 (referent) |          |
| Delta period | 2712 (20.6) | 2556 (20.0) | 156 (40.3) | 0.89 (0.44 - 1.80) | 0.75 |
| Omicron period | 10251 (78.0) | 10036 (78.7) | 215 (55.6) | 0.41 (0.20 - 0.86) | 0.02 |
| Vaccine type (%) |       |        |                       |           |
|                | Janssen   | Moderna   | Pfizer   | Risk Ratio | p-value |
|----------------|-----------|-----------|----------|------------|---------|
|                | 1317 (10.0) | 1273 (10.0) | 44 (11.4) | 1.08 (0.74 - 1.56) | 0.69    |
| History of infection before vaccinated (%) | 4813 (36.6) | 4703 (36.9) | 110 (28.4) | 0.58 (0.45 - 0.76) | 5.4E-05* |
| Months since full vax at breakthrough (%) | 7016 (53.4) | 6783 (53.2) | 233 (60.2) | 1.0 (referent) |         |
| 4 or less      | 1694 (12.9) | 1632 (12.8) | 62 (16.0) | 1.0 (referent) |         |
| 4-5            | 963 ( 7.3)  | 924 ( 7.2)  | 39 (10.1) | 1.08 (0.66 - 1.77) | 0.76    |
| 5-6            | 909 ( 6.9)  | 879 ( 6.9)  | 30 ( 7.8) | 0.79 (0.46 - 1.34) | 0.37    |
| 6-7            | 1036 ( 7.9) | 1001 ( 7.8) | 35 ( 9.0) | 0.98 (0.58 - 1.65) | 0.94    |
| 7-8            | 1616 (12.3) | 1573 (12.3) | 43 (11.1) | 1.40 (0.87 - 2.28) | 0.17    |
| 8-9            | 2671 (20.3) | 2616 (20.5) | 55 (14.2) | 1.17 (0.72 - 1.89) | 0.52    |
| 9-10           | 2191 (16.7) | 2140 (16.8) | 51 (13.2) | 1.06 (0.63 - 1.78) | 0.84    |
| 10-11          | 1278 ( 9.7) | 1230 ( 9.6) | 48 (12.4) | 1.63 (0.93 - 2.85) | 0.09    |
| 11-12          | 685 ( 5.2)  | 665 ( 5.2)  | 20 ( 5.2) | 1.77 (0.89 - 3.53) | 0.10    |
| 12 or more     | 103 ( 0.8)  | 99 ( 0.8)   | 4 ( 1.0)  | 2.58 (0.77 - 8.71) | 0.13    |
| Months since boosted at breakthrough (%) | 10214 (77.7) | 9905 (77.6) | 309 (79.8) | 1.0 (referent) |         |
| Not boosted    | 656 ( 5.0)  | 640 ( 5.0)  | 16 ( 4.1) | 0.71 (0.39 - 1.31) | 0.28    |
| 1 or less      | 790 ( 6.0)  | 783 ( 6.1)  | 7 ( 1.8)  | 0.17 (0.07 - 0.41) | 1.1E-04* |
| 1-2            | 790 ( 6.0)  | 769 ( 6.0)  | 21 ( 5.4) | 0.63 (0.37 - 1.07) | 0.09    |
| 2-3            | 361 ( 2.7)  | 342 ( 2.7)  | 19 ( 4.9) | 0.95 (0.53 - 1.71) | 0.87    |
| 3-4            | 155 ( 1.2)  | 144 ( 1.1)  | 11 ( 2.8) | 1.18 (0.57 - 2.44) | 0.66    |
| 4-5            | 23 ( 0.2)   | 21 ( 0.2)   | 2 ( 0.5)  | 2.16 (0.40 - 11.8) | 0.37    |
| 6 or more      | 157 ( 1.2)  | 155 ( 1.2)  | 2 ( 0.5)  | 0.53 (0.12 - 2.38) | 0.40    |
| Immune-suppressive medications before breakthrough (%) | Before breakthrough Chemotherapy | 49 ( 0.4) | 42 ( 0.3) | 7 ( 1.8) | 4.55 (1.25 - 16.5) | 0.02    |
| Before breakthrough Cytokine-blocking | 212 (1.6) | 199 (1.6) | 13 ( 3.4) | 0.97 (0.38 - 2.50) | 0.96    |
| Before breakthrough Glucocorticoids | 819 (6.2) | 762 (6.0) | 57 (14.7) | 1.64 (1.16 - 2.33) | 0.005*  |
| Before breakthrough Leukocyte-inhibitory | 256 (1.9) | 227 (1.8) | 29 ( 7.5) | 2.62 (1.24 - 5.53) | 0.01    |
| Before breakthrough Lymphocyte-depleting | 69 (0.5) | 59 (0.5) | 10 ( 2.6) | 2.37 (0.69 - 8.11) | 0.17    |
| Immune-suppressive medications before initial vaccination (%) | Before vaccine Chemotherapy | 27 ( 0.2) | 24 ( 0.2) | 3 ( 0.8) | 0.44 (0.07 - 2.82) | 0.39    |
| Before vaccine Cytokine-blocking | 176 (1.3) | 166 (1.3) | 10 ( 2.6) | 0.96 (0.32 - 2.90) | 0.94    |
| Before vaccine Glucocorticoids | 283 (2.2) | 264 (2.1) | 19 ( 4.9) | 1.34 (0.76 - 2.35) | 0.31    |
| Before vaccine Leukocyte-inhibitory | 202 (1.5) | 181 (1.4) | 21 ( 5.4) | 1.13 (0.49 - 2.62) | 0.77    |
| Before vaccine Lymphocyte-depleting | 28 ( 0.2) | 24 ( 0.2) | 4 ( 1.0)  | 0.31 (0.04 - 2.45) | 0.27    |
| Persistent positive test (%) | 32 ( 0.2) | 27 ( 0.2) | 5 ( 1.3)  | 3.37 (1.07 - 10.7) | 0.04    |

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| BMI Class (%) | Underweight | Normal | Overweight | Obesity I | Obesity II | Severe Obesity | Unknown |
|--------------|-------------|--------|------------|-----------|------------|----------------|---------|
|              | 77 (0.6)    | 67 (0.5)| 10 (2.6)   | 2.04 (0.86 - 4.82) | 0.10       |
|              | 1752 (13.3) | 1685 (13.2)| 67 (17.3)  | 1.0 (referent)     |            |
|              | 3175 (24.2) | 3111 (24.4)| 64 (16.5)  | 0.49 (0.33 - 0.74) | 05.4E-04a  |
|              | 3364 (25.6) | 3276 (25.7)| 88 (22.7)  | 0.74 (0.51 - 1.08) | 0.11       |
|              | 2216 (16.9) | 2147 (16.8)| 69 (17.8)  | 0.87 (0.58 - 1.29) | 0.48       |
|              | 1688 (12.8) | 1602 (12.6)| 86 (22.2)  | 1.31 (0.88 - 1.95) | 0.18       |
|              | 874 (6.6)   | 871 (6.8)  | 3 (0.8)    | 0.27 (0.08 - 0.92) | 0.04       |
| Comorbidities (%) |            |        |            |            |            |                |         |
| Acquired hypothyroidism | 943 (7.2) | 897 (7.0) | 46 (11.9)  | 0.76 (0.52 - 1.12) | 0.16       |
| Acute myocardial infarction | 32 (0.2) | 27 (0.2)  | 5 (1.3)    | 0.92 (0.28 - 3.00) | 0.89       |
| Alzheimers disease and related disorders or senile dementia | 95 (0.7) | 76 (0.6)  | 19 (4.9)   | 1.57 (0.83 - 2.97) | 0.17       |
| Anemia | 923 (7.0) | 852 (6.7) | 71 (18.3)  | 1.24 (0.85 - 1.79) | 0.26       |
| Anxiety disorders | 4862 (37.0)| 4729 (37.1)| 133 (34.4) | 1.02 (0.77 - 1.34) | 0.92       |
| Asthma | 825 (6.3) | 785 (6.2) | 40 (10.3)  | 1.35 (0.91 - 1.99) | 0.13       |
| Atrial fibrillation | 141 (1.1) | 123 (1.0) | 18 (4.7)   | 0.61 (0.33 - 1.16) | 0.13       |
| Bipolar disorder | 1202 (9.1) | 1152 (9.0)| 50 (12.9)  | 1.53 (1.07 - 2.19) | 0.02       |
| Chronic kidney disease | 625 (4.8) | 530 (4.2) | 95 (24.5)  | 2.14 (1.51 - 3.02) | 1.7E-05a  |
| Chronic obstructive pulmonary disease and bronchiectasis | 414 (3.1) | 343 (2.7) | 71 (18.3)  | 2.27 (1.57 - 3.29) | 1.3E-05a  |
| Colorectal cancer | 27 (0.2) | 26 (0.2)  | 1 (0.3)    | 0.46 (0.05 - 3.89) | 0.47       |
| Depression | 4579 (34.8)| 4428 (34.7)| 151 (39.0) | 1.04 (0.79 - 1.37) | 0.78       |
| Diabetes | 1624 (12.4)| 1489 (11.7)| 135 (34.9) | 1.38 (1.03 - 1.85) | 0.03       |
| Epilepsy | 113 (0.9) | 102 (0.8) | 11 (2.8)   | 2.10 (0.94 - 4.72) | 0.07       |
| Heart failure | 166 (1.3) | 130 (1.0) | 36 (9.3)   | 2.04 (1.21 - 3.47) | 0.008      |
| HIV/AIDS | 35 (0.3) | 30 (0.2) | 5 (1.3)    | 5.60 (1.85 - 16.9) | 0.002a     |
| Hyperlipidemia | 2329 (17.7)| 2190 (17.2)| 139 (35.9) | 0.96 (0.72 - 1.27) | 0.77       |
| Hypertension | 2749 (20.9)| 2556 (20.0)| 193 (49.9) | 1.26 (0.95 - 1.66) | 0.11       |
| Ischemic heart disease | 305 (2.3) | 259 (2.0) | 46 (11.9)  | 1.14 (0.71 - 1.82) | 0.60       |
| Leukemias and lymphomas | 44 (0.3) | 38 (0.3)  | 6 (1.6)    | 1.37 (0.44 - 4.25) | 0.58       |
| Liver disease: cirrhosis and other liver conditions except viral hepatitis | 347 (2.6) | 326 (2.6) | 21 (5.4)   | 1.07 (0.62 - 1.83) | 0.81       |
| Lung cancer | 33 (0.3) | 27 (0.2) | 6 (1.6)    | 1.68 (0.57 - 4.98) | 0.34       |
| Mobility impairments | 59 (0.4) | 49 (0.4) | 10 (2.6)   | 2.61 (1.08 - 6.31) | 0.03       |
| Multiple sclerosis and transverse myelitis | 121 (0.9) | 111 (0.9) | 10 (2.6)   | 3.01 (1.35 - 6.73) | 0.007a     |
| Peripheral vascular disease | 101 (0.8) | 84 (0.7) | 17 (4.4)   | 0.93 (0.47 - 1.83) | 0.84       |
| Pressure and chronic ulcers | 42 (0.3) | 30 (0.2) | 12 (3.1)   | 2.33 (0.95 - 5.75) | 0.07       |
| Prostate cancer | 1 (0.0) | 1 (0.0) | 0 (0.0)    | ND         | ND         |
| Condition                                    | Cases 1 | Cases 2 | Cases 3 | OR (95% CI)          | P-value |
|----------------------------------------------|---------|---------|---------|----------------------|---------|
| Schizophrenia and other psychotic disorders | 307 (2.3) | 284 (2.2) | 23 (5.9) | 1.61 (0.94 - 2.74) | 0.08    |
| Tobacco use                                  | 897 (6.8) | 842 (6.6) | 55 (14.2) | 1.28 (0.88 - 1.86) | 0.20    |
| Viral hepatitis                              | 57 (0.4)  | 52 (0.4)  | 5 (1.3)   | 1.11 (0.34 - 3.65) | 0.86    |
| Death from breakthrough                      | 21 (0.2)  | 0 (0.0)   | 21 (5.4)  |                      |         |

*Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.008 for this analysis. OR = odds ratio. CI = 95% confidence interval.*
eTable 14. Subcohort of Male Patients, Data and Analysis

|                      | Overall  | Non-severe | Severe  | Multivariable OR (CI) | P (multi) |
|----------------------|----------|------------|---------|-----------------------|-----------|
| N                    | 97614    | 87389      | 10225   |                       |           |
| Age ranges (%)       |          |            |         |                       |           |
| Less than 40         | 9800 (10.0) | 9705 (11.1) | 95 (0.9) | 0.55 (0.41 - 0.74)    | 6.4E-05 a |
| 40-45                | 4688 (4.8)  | 4614 (5.3)  | 74 (0.7) | 0.83 (0.60 - 1.13)    | 0.24      |
| 45-50                | 4858 (5.0)  | 4763 (5.5)  | 95 (0.9) | 1.0 (referent)        |           |
| 50-55                | 8015 (8.2)  | 7777 (8.9)  | 238 (2.3) | 1.41 (1.10 - 1.80)    | 0.007 a   |
| 55-60                | 9213 (9.4)  | 8781 (10.0) | 432 (4.2) | 2.04 (1.62 - 2.57)    | <1.0E-08 a|
| 60-65                | 11378 (11.7) | 10562 (12.1) | 816 (8.0) | 2.85 (2.28 - 3.56)    | <1.0E-08 a|
| 65-70                | 11329 (11.6) | 10058 (11.5) | 1271 (12.4) | 4.17 (3.35 - 5.19)    | <1.0E-08 a|
| 70-75                | 17838 (18.3) | 15275 (17.5) | 2563 (25.1) | 5.56 (4.48 - 6.90)    | <1.0E-08 a|
| 75-80                | 11391 (11.7) | 9401 (10.8)  | 1990 (19.5) | 7.13 (5.72 - 8.87)    | <1.0E-08 a|
| 80 or greater        | 9104 (9.3)  | 6453 (7.4)  | 2651 (25.9) | 12.5 (10.1 - 15.6)    | <1.0E-08 a|
| Race (%)             |          |            |         |                       |           |
| American Indian or Alaska Native | 735 (0.8)   | 649 (0.7)   | 86 (0.8) | 1.37 (1.05 - 1.79)    | 0.02 a    |
| Asian                | 1329 (1.4)  | 1274 (1.5)  | 55 (0.5) | 0.88 (0.64 - 1.20)    | 0.43      |
| Black or African American | 22416 (23.0) | 20381 (23.3) | 2035 (19.9) | 0.98 (0.92 - 1.05)    | 0.63      |
| Native Hawaiian or other Pacific Islander | 978 (1.0)   | 907 (1.0)   | 71 (0.7) | 0.81 (0.61 - 1.08)    | 0.15      |
| White                | 64952 (66.5) | 57536 (65.8)| 7416 (72.5) | 1.0 (referent)        |           |
| Unknown              | 7204 (7.4)  | 6642 (7.6)  | 562 (5.5) | 0.92 (0.82 - 1.03)    | 0.16      |
| Ethnicity Hispanic/Latino (%) |          |            |         |                       |           |
| Hispanic or Latino   | 9862 (10.1) | 9128 (10.4) | 734 (7.2) | 1.06 (0.97 - 1.17)    | 0.21      |
| Not Hispanic or Latino | 82729 (84.8) | 73623 (84.2) | 9106 (89.1) | 1.0 (referent)        |           |
| Unknown              | 5023 (5.1)  | 4638 (5.3)  | 385 (3.8) | 1.07 (0.94 - 1.23)    | 0.32      |
| US Region (%)        |          |            |         |                       |           |
| Continental          | 15800 (16.2) | 13984 (16.0) | 1816 (17.8) | 1.16 (1.07 - 1.25)    | 2.2E-04 a |
| Midwest              | 19770 (20.3) | 17508 (20.0) | 2262 (22.1) | 0.98 (0.91 - 1.06)    | 0.67      |
| North Atlantic       | 21036 (21.6) | 18896 (21.6) | 2140 (20.9) | 0.94 (0.87 - 1.01)    | 0.09      |
| Pacific              | 18063 (18.5) | 16417 (18.8) | 1646 (16.1) | 0.95 (0.88 - 1.03)    | 0.24      |
| Southeast            | 21184 (21.7) | 18843 (21.6) | 2341 (22.9) | 1.0 (referent)        |           |
| Unknown              | 1761 (1.8)  | 1741 (2.0)  | 20 (0.2)  | 0.29 (0.18 - 0.48)    | 1.5E-06 a |
| Period of dominant variant (%) |          |            |         |                       |           |
| Pre-delta period     |          |            |         |                       |           |
| Delta period         | 26781 (27.4) | 22206 (25.4) | 4575 (44.7) | 0.93 (0.81 - 1.07)    | 0.32      |
| Omicron period       | 68128 (69.8) | 63099 (72.2) | 5029 (49.2) | 0.48 (0.42 - 0.56)    | <1.0E-08 a|
| Vaccine type (%)     |          |            |         |                       |           |

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|                          | Janssen       | Moderna       | Pfizer        |                 |                 |
|--------------------------|---------------|---------------|---------------|----------------|----------------|
|                          | 9749 (10.0)   | 40717 (41.7)  | 47148 (48.3)  | 8755 (10.0)    | 42048 (48.1)   |
|                          | 994 ( 9.7)    | 36586 (41.9)  | 5100 (49.9)   | 1.29 (1.19 - 1.41) | 1.0 (referent) |
| History of infection before vaccinated (%) | 3849 ( 3.9)   | 3446 ( 3.9)   | 403 ( 3.9)    | 0.76 (0.67 - 0.86) | 3.1E-05*       |
| Months since full vax at breakthrough (%) | 3849 ( 3.9)   | 3446 ( 3.9)   | 403 ( 3.9)    | 0.76 (0.67 - 0.86) | 3.1E-05*       |
| 4 or less                | 10803 (11.1)  | 9351 (10.7)   | 1452 (14.2)   | 1.0 (referent)  |                 |
| 4-5                      | 6253 ( 6.4)   | 5431 ( 6.2)   | 822 ( 8.0)    | 1.07 (0.95 - 1.21) | 0.26           |
| 5-6                      | 7239 ( 7.4)   | 6160 ( 7.0)   | 1079 (10.6)   | 1.01 (0.90 - 1.13) | 0.91           |
| 6-7                      | 7866 ( 8.1)   | 6762 ( 7.7)   | 1104 (10.8)   | 1.07 (0.95 - 1.20) | 0.24           |
| 7-8                      | 10123 (10.4)  | 9092 (10.4)   | 1031 (10.1)   | 1.13 (1.01 - 1.27) | 0.03*          |
| 8-9                      | 16447 (16.8)  | 15277 (16.4)  | 1376 (13.5)   | 1.14 (1.01 - 1.28) | 0.04           |
| 9-10                     | 17806 (18.2)  | 16430 (18.8)  | 1431 (14.0)   | 1.31 (1.15 - 1.49) | 4.6E-05*       |
| 10-11                    | 14453 (14.8)  | 13022 (14.9)  | 1079 (10.6)   | 1.01 (0.90 - 1.13) | 0.91           |
| 11-12                    | 5834 ( 6.0)   | 5188 ( 5.9)   | 646 ( 6.3)    | 1.31 (1.15 - 1.49) | 4.6E-05*       |
| 12 or more               | 790 ( 0.8)    | 696 ( 0.8)    | 94 ( 0.9)     | 1.58 (1.19 - 2.08) | 0.001*         |
| Months since boosted at breakthrough (%) | 70825 (72.6)  | 62578 (71.6)  | 8247 (80.7)   | 1.0 (referent)  |                 |
| Not boosted              | 5099 ( 5.2)   | 4761 ( 5.4)   | 338 ( 3.3)    | 0.57 (0.50 - 0.65) | <1.0E-08*      |
| 1 or less                | 6942 ( 7.1)   | 6558 ( 7.5)   | 384 ( 3.8)    | 0.46 (0.40 - 0.52) | <1.0E-08*      |
| 1-2                      | 7760 ( 7.9)   | 7227 ( 8.3)   | 533 ( 5.2)    | 0.46 (0.41 - 0.51) | <1.0E-08*      |
| 2-3                      | 4272 ( 4.4)   | 3855 ( 4.4)   | 417 ( 4.1)    | 0.55 (0.48 - 0.62) | <1.0E-08*      |
| 3-4                      | 1594 ( 1.6)   | 1399 ( 1.6)   | 195 ( 1.9)    | 0.59 (0.49 - 0.71) | <1.0E-08*      |
| 4-5                      | 347 ( 0.4)    | 299 ( 0.3)    | 48 ( 0.5)     | 0.72 (0.50 - 1.02) | 0.07           |
| 5-6                      | 775 ( 0.8)    | 712 ( 0.8)    | 63 ( 0.6)     | 0.79 (0.59 - 1.07) | 0.13           |
| Immune-suppressive medications before breakthrough (%) | 957 ( 1.0)    | 654 ( 0.7)    | 303 ( 3.0)    | 2.46 (2.03 - 2.99) | <1.0E-08*      |
| Before breakthrough      | 1389 ( 1.4)   | 1202 ( 1.4)   | 187 ( 1.8)    | 1.62 (1.25 - 2.10) | 2.3E-04*       |
| Before breakthrough      | 6725 ( 6.9)   | 4961 ( 5.7)   | 1764 (17.3)   | 2.36 (2.20 - 2.54) | <1.0E-08*      |
| Before breakthrough      | 1668 ( 1.7)   | 1211 ( 1.4)   | 457 ( 4.5)    | 2.48 (2.08 - 2.97) | <1.0E-08*      |
| Before breakthrough      | 516 ( 0.5)    | 347 ( 0.4)    | 169 ( 1.7)    | 1.77 (1.30 - 2.40) | 2.9E-04*       |
| Immune-suppressive       | 403 ( 0.4)    | 292 ( 0.3)    | 111 ( 1.1)    | 0.61 (0.44 - 0.84) | 0.003*         |
| medications before initial vaccination (%) | 1035 ( 1.1)   | 930 ( 1.1)    | 105 ( 1.0)    | 1.31 (1.16 - 1.48) | 2.0E-05*       |
| Before vaccine           | 2471 ( 2.5)   | 1860 ( 2.1)   | 611 ( 6.0)    | 0.76 (0.60 - 0.95) | 0.02*          |
| Before vaccine           | 1166 ( 1.2)   | 918 ( 1.1)    | 248 ( 2.4)    | 1.24 (0.76 - 2.01) | 0.39           |
| Before vaccine           | 195 ( 0.2)    | 129 ( 0.1)    | 66 ( 0.6)     | 1.47 (1.14 - 1.89) | 0.003*         |
| Persistent positive test (%) | 430 ( 0.4)    | 332 ( 0.4)    | 98 ( 1.0)     | 2.46 (2.03 - 2.99) | <1.0E-08*      |

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| BMI Class (%) | 600 (0.6) | 429 (0.5) | 171 (1.7) | 1.43 (1.14 - 1.79) | 0.002* |
|---------------|-----------|-----------|-----------|---------------------|--------|
| Normal        | 12642 (13.0) | 10614 (12.1) | 2028 (19.8) | 1.0 (referent)     |        |
| Overweight    | 29532 (30.3) | 26681 (30.5) | 2851 (27.9) | 0.76 (0.70 - 0.82) | <1.0E-08* |
| Obesity I     | 27792 (28.5) | 25281 (28.9) | 2511 (24.6) | 0.82 (0.76 - 0.89) | 9.5E-07* |
| Obesity II    | 14646 (15.0) | 13188 (15.1) | 1458 (14.3) | 1.01 (0.92 - 1.10) | 0.84    |
| Severe Obesity| 8953 (9.2)   | 7908 (9.0)   | 1045 (10.2) | 1.30 (1.17 - 1.43) | 3.3E-07* |
| Unknown       | 3449 (3.5)   | 3288 (3.8)   | 161 (1.6)   | 0.95 (0.78 - 1.16) | 0.62    |

| Comorbidities (%) | 4022 (4.1) | 3276 (3.7) | 746 (7.3) | 1.03 (0.93 - 1.14) | 0.60    |
|-------------------|-----------|-----------|-----------|---------------------|--------|
| Acquired hypothyroidism | 755 (0.8) | 546 (0.6) | 209 (2.0) | 1.14 (0.93 - 1.40) | 0.21    |
| Acute myocardial infarction | 2955 (3.0) | 1839 (2.1) | 1116 (10.9) | 1.93 (1.75 - 2.13) | <1.0E-08* |
| Alzheimers disease and related disorders or senile dementia | 7211 (7.4) | 5416 (6.2) | 1795 (17.7) | 0.90 (0.78 - 1.05) | 0.19    |
| Anemia | 21419 (21.9) | 19614 (22.4) | 1805 (17.7) | 0.90 (0.78 - 1.05) | 0.19    |
| Anxiety disorders | 6568 (5.8) | 4176 (4.8) | 1482 (14.5) | 1.21 (1.12 - 1.32) | 3.5E-06* |
| Asthma | 5095 (5.2) | 4502 (5.2) | 593 (5.8) | 1.23 (1.10 - 1.37) | 3.4E-04* |
| Atrial fibrillation | 11207 (11.5) | 8541 (9.8) | 2666 (26.1) | 1.52 (1.42 - 1.63) | <1.0E-08* |
| Hypertension | 7923 (8.1) | 5760 (6.6) | 2163 (21.2) | 1.72 (1.60 - 1.84) | <1.0E-08* |
| Colorectal cancer | 581 (0.6) | 461 (0.5) | 120 (1.2) | 1.01 (0.79 - 1.29) | 0.94    |
| Depression | 17963 (18.4) | 16089 (18.4) | 1874 (18.3) | 1.10 (1.02 - 1.18) | 0.02*   |
| Diabetes | 24459 (25.1) | 20430 (23.4) | 4029 (39.4) | 1.24 (1.17 - 1.31) | <1.0E-08* |
| Epilepsy | 2693 (2.8) | 2421 (2.8) | 272 (2.7) | 0.90 (0.78 - 1.05) | 0.19    |
| Heart failure | 5278 (5.4) | 3551 (4.1) | 1727 (16.9) | 1.70 (1.56 - 1.85) | <1.0E-08* |
| HIV/AIDS | 839 (0.9) | 761 (0.9) | 78 (0.8) | 1.22 (0.93 - 1.60) | 0.16    |
| Hyperlipidemia | 29182 (29.9) | 25434 (29.1) | 3748 (36.7) | 0.81 (0.76 - 0.86) | <1.0E-08* |
| Hypertension | 36160 (37.0) | 30634 (35.1) | 5526 (54.0) | 1.07 (1.01 - 1.14) | 0.02*   |
| Ischemic heart disease | 10702 (11.0) | 8461 (9.7) | 2241 (21.9) | 0.97 (0.90 - 1.04) | 0.37    |
| Leukemias and lymphomas | 1292 (1.3) | 955 (1.1) | 337 (3.3) | 1.60 (1.36 - 1.90) | 3.7E-08* |
| Liver disease: cirrhosis and other liver conditions except viral hepatitis | 3846 (3.9) | 3242 (3.7) | 604 (5.9) | 1.30 (1.16 - 1.46) | 4.3E-06* |
| Lung cancer | 791 (0.8) | 546 (0.6) | 245 (2.4) | 1.53 (1.27 - 1.84) | 8.0E-06* |
| Mobility impairments | 971 (1.0) | 679 (0.8) | 292 (2.9) | 1.97 (1.66 - 2.34) | <1.0E-08* |
| Multiple sclerosis and transverse myelitis | 333 (0.3) | 251 (0.3) | 82 (0.8) | 3.13 (2.30 - 4.26) | <1.0E-08* |
| Peripheral vascular disease | 2996 (3.1) | 2157 (2.5) | 839 (8.2) | 1.22 (1.10 - 1.36) | 2.0E-04* |
| Pressure and chronic ulcers | 1305 (1.3) | 842 (1.0) | 463 (4.5) | 1.52 (1.31 - 1.76) | 3.6E-08* |
| Prostate cancer | 3814 (3.9) | 3181 (3.6) | 633 (6.2) | 0.92 (0.83 - 1.02) | 0.11    |
| Condition                                      | Cases 1 | Cases 2 | Cases 3 | OR (95% CI)      | P-value |
|-----------------------------------------------|---------|---------|---------|------------------|---------|
| Schizophrenia and other psychotic disorders   | 2448 (2.5) | 2036 (2.3) | 412 (4.0) | 1.68 (1.47 - 1.92) | <1.0E-08 * |
| Tobacco use                                   | 8425 (8.6) | 7272 (8.3) | 1153 (11.3) | 1.37 (1.26 - 1.49) | <1.0E-08 * |
| Viral hepatitis                                | 1359 (1.4) | 1128 (1.3) | 231 (2.3) | 0.98 (0.82 - 1.17) | 0.79 |
| Death from breakthrough                       | 1534 (1.6) | 0 (0.0) | 1534 (15.0) |                  |         |

*Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.033 for this analysis. OR = odds ratio. CI = 95% confidence interval.*
# eTable 15. Subcohorts of Female and Male, Comparison of Analyses

| Age ranges (%) | Female | | | Male | | |
|----------------|--------|---|---|--------|---|---|
|                | Non-severe | Severe | Multivariable OR (CI) | Non-severe | Severe | Multivariable OR (CI) |
| N              | 12759  | 387 |  | 87389  | 10225  |  |
| Age ranges (%) | | | | | | |
| Less than 40   | 3299 (25.9) | 15 (3.9) | 0.83 (0.38 - 1.83) | 9705 (11.1) | 95 (0.9) | 0.55 (0.41 - 0.74) |
| 40-45          | 1539 (12.1) | 14 (3.6) | 1.41 (0.63 - 3.12) | 4614 (5.3) | 74 (0.7) | 0.83 (0.60 - 1.13) |
| 45-50          | 1437 (11.3) | 12 (3.1) | 1.0 (referent) | 4763 (5.5) | 95 (0.9) | 1.0 (referent) |
| 50-55          | 1667 (13.1) | 39 (10.1) | 3.01 (1.53 - 5.91) | 7777 (8.9) | 238 (2.3) | 1.41 (1.10 - 1.80) |
| 55-60          | 1677 (13.1) | 44 (11.4) | 2.86 (1.46 - 5.60) | 8781 (10.0) | 432 (4.2) | 2.04 (1.62 - 2.57) |
| 60-65          | 1520 (11.9) | 73 (18.9) | 4.72 (2.46 - 9.05) | 10562 (12.1) | 816 (8.0) | 2.85 (2.28 - 3.56) |
| 65-70          | 955 (7.5) | 69 (17.8) | 5.32 (2.73 - 10.4) | 10058 (11.5) | 1271 (12.4) | 4.17 (3.35 - 5.19) |
| 70-75          | 428 (3.4) | 61 (15.8) | 9.40 (4.72 - 18.7) | 15275 (17.5) | 2563 (25.1) | 5.56 (4.48 - 6.90) |
| 75-80          | 145 (1.1) | 26 (6.7) | 14.9 (6.80 - 32.8) | 9401 (10.8) | 1990 (19.5) | 7.13 (5.72 - 8.87) |
| 80 or greater  | 92 (0.7) | 34 (8.8) | 43.5 (19.8 - 95.5) | 6453 (7.4) | 2651 (25.9) | 12.5 (10.1 - 15.6) |
| Race (%)       | | | | | | |
| American Indian or Alaska Native | 153 (1.2) | 2 (0.5) | 0.46 (0.10 - 2.04) | 649 (0.7) | 86 (0.8) | 1.37 (1.05 - 1.79) |
| Asian          | 251 (2.0) | 1 (0.3) | 0.26 (0.03 - 1.97) | 1274 (1.5) | 55 (0.5) | 0.88 (0.64 - 1.20) |
| Black or African American | 4409 (34.6) | 128 (33.1) | 0.76 (0.58 - 1.01) | 20381 (23.3) | 2035 (19.9) | 0.98 (0.92 - 1.05) |
| Native Hawaiian or other Pacific Islander | 159 (1.2) | 5 (1.3) | 0.78 (0.27 - 2.29) | 907 (1.0) | 71 (0.7) | 0.81 (0.61 - 1.08) |
| White          | 6482 (50.8) | 231 (59.7) | 1.0 (referent) | 57536 (65.8) | 7416 (72.5) | 1.0 (referent) |
| Unknown        | 1305 (10.2) | 20 (5.2) | 0.68 (0.38 - 1.21) | 6642 (7.6) | 562 (5.5) | 0.92 (0.82 - 1.03) |
| Ethnicity Hispanic/Latino (%) | | | | | | |
| Hispanic or Latino | 1377 (10.8) | 20 (5.2) | 0.64 (0.38 - 1.09) | 9128 (10.4) | 734 (7.2) | 1.06 (0.97 - 1.17) |
| Not Hispanic or Latino | 10318 (80.9) | 353 (91.2) | 1.0 (referent) | 73623 (84.2) | 9106 (89.1) | 1.0 (referent) |
| Unknown        | 1064 (8.3) | 14 (3.6) | 1.40 (0.73 - 2.72) | 4638 (5.3) | 385 (3.8) | 1.07 (0.94 - 1.23) |
| US Region (%)  | | | | | | |
| Continental    | 2259 (17.7) | 81 (20.9) | 1.33 (0.96 - 1.86) | 13984 (16.0) | 1816 (17.8) | 1.16 (1.07 - 1.25) |
| Midwest        | 2053 (16.1) | 66 (17.1) | 0.85 (0.60 - 1.22) | 17508 (20.0) | 2262 (22.1) | 0.98 (0.91 - 1.06) |
| North Atlantic | 2688 (21.1) | 66 (17.1) | 0.82 (0.57 - 1.16) | 18896 (21.6) | 2140 (20.9) | 0.94 (0.87 - 1.01) |
| Pacific        | 2106 (16.5) | 63 (16.3) | 1.11 (0.77 - 1.59) | 16417 (18.8) | 1646 (16.1) | 0.95 (0.88 - 1.03) |
| Southeast      | 3111 (24.4) | 109 (28.2) | 1.0 (referent) | 18843 (21.6) | 2341 (22.9) | 1.0 (referent) |
| Unknown        | 542 (4.2) | 2 (0.5) | 0.33 (0.08 - 1.36) | 1741 (2.0) | 20 (0.2) | 0.29 (0.18 - 0.48) |
| Period of dominant variant (%) | | | | | | |
| Pre-delta period | 1.0 (referent) | | | 1.0 (referent) | | |
| Delta period   | 2556 (20.0) | 156 (40.3) | 0.89 (0.44 - 1.80) | 22206 (25.4) | 4575 (44.7) | 0.93 (0.81 - 1.07) |
| Omicron period | 10036 (78.7) | 215 (55.6) | 0.41 (0.20 - 0.86) | 63099 (72.2) | 5029 (49.2) | 0.48 (0.42 - 0.56) |
| Vaccine type (%) | Janssen | Moderna | Pfizer |
|------------------|---------|---------|---------|
|                  | 1273 (10.0) | 4703 (36.9) | 6783 (53.2) |
|                  | 44 (11.4) | 110 (28.4) | 233 (60.2) |
|                  | 1.08 (0.74 - 1.56) | 0.58 (0.45 - 0.76) | 1.0 (referent) |
|                  | 8755 (10.0) | 36586 (41.9) | 42048 (48.1) |
|                  | 994 (9.7) | 4131 (40.4) | 5100 (49.9) |
|                  | 1.29 (1.19 - 1.41) | 0.80 (0.76 - 0.84) | 1.0 (referent) |
| History of infection before vaccinated (%) | 513 (4.0) | 110 (2.8) | 0.60 (0.30 - 1.19) |
| Months since full vax at breakthrough (%) | 1632 (12.8) | 924 (7.2) | 9905 (77.6) |
|                  | 62 (16.0) | 39 (10.1) | 309 (79.8) |
|                  | 1.0 (referent) | 1.08 (0.66 - 1.77) | 1.0 (referent) |
| Months since boosted at breakthrough (%) | 1230 (9.6) | 2140 (16.8) | 1230 (9.6) |
|                  | 48 (12.4) | 51 (13.2) | 48 (12.4) |
|                  | 1.63 (0.93 - 2.85) | 0.71 (0.39 - 1.31) | 1.0 (referent) |
| Immune-suppressive medications before breakthrough (%) | 99 (0.8) | 155 (1.2) | 42 (0.3) |
|                  | 4 (1.0) | 2 (0.5) | 7 (1.8) |
|                  | 2.58 (0.77 - 8.71) | 0.53 (0.12 - 2.38) | 4.55 (1.25 - 16.5) |
| Immune-suppressive medications before initial vaccination (%) | 0.79 (0.57 - 1.10) | 0.44 (0.07 - 2.82) | 0.96 (0.32 - 2.90) |
|                  | 24 (0.2) | 166 (1.3) | 264 (2.1) |
|                  | 0.44 (0.07 - 2.82) | 0.96 (0.32 - 2.90) | 1.34 (0.76 - 2.35) |
|                  | 292 (0.3) | 930 (1.1) | 1860 (2.1) |
|                  | 111 (1.1) | 105 (1.0) | 611 (6.0) |
|                  | 0.61 (0.44 - 0.84) | 1.31 (1.16 - 1.48) | 0.76 (0.60 - 0.95) |
|                  | 24 (0.2) | 21 (5.4) | 113 (4.9) |
|                  | 0.31 (0.04 - 2.45) | 1.13 (0.49 - 2.62) | 1.34 (0.76 - 2.35) |
|                  | 129 (0.1) | 918 (1.1) | 1860 (2.1) |
|                  | 66 (0.6) | 248 (2.4) | 611 (6.0) |
|                  | 1.47 (1.14 - 1.89) | 1.24 (0.76 - 2.01) | 0.76 (0.60 - 0.95) |
| Persistent positive test (%) | 27 (0.2) | 5 (1.3) | 3.37 (1.07 - 10.7) | 332 (0.4) | 98 (1.0) | 2.46 (2.03 - 2.99) |
|-----------------------------|----------|---------|-------------------|-----------|----------|-------------------|
| BMI Class (%)               |          |         |                   |           |          |                   |
| Underweight                 | 67 (0.5) | 10 (2.6) | 2.04 (0.86 - 4.82) | 429 (0.5) | 171 (1.7) | 1.43 (1.14 - 1.79) |
| Normal                       | 1685 (13.2) | 67 (17.3) | 1.0 (referent) | 10614 (12.1) | 2028 (19.8) | 1.0 (referent) |
| Overweight                   | 3111 (24.4) | 64 (16.5) | 0.49 (0.33 - 0.74) | 26681 (30.5) | 2851 (27.9) | 0.76 (0.70 - 0.82) |
| Obesity I                    | 3276 (25.7) | 88 (22.7) | 0.74 (0.51 - 1.08) | 25281 (28.9) | 2511 (24.6) | 0.82 (0.76 - 0.89) |
| Obesity II                   | 2147 (16.8) | 69 (17.8) | 0.87 (0.58 - 1.29) | 13188 (15.1) | 1458 (14.3) | 1.01 (0.92 - 1.10) |
| Severe Obesity               | 1602 (12.6) | 86 (22.2) | 1.31 (0.88 - 1.95) | 7908 (9.0) | 1045 (10.2) | 1.30 (1.17 - 1.43) |
| Unknown                      | 871 (6.8) | 3 (0.8) | 0.27 (0.08 - 0.92) | 3288 (3.8) | 161 (1.6) | 0.95 (0.78 - 1.16) |
| Comorbidities (%)            |          |         |                   |           |          |                   |
| Acquired hypothyroidism      | 897 (7.0) | 46 (11.9) | 0.76 (0.52 - 1.12) | 3276 (3.7) | 746 (7.3) | 1.03 (0.93 - 1.14) |
| Acute myocardial infarction  | 27 (0.2) | 5 (1.3) | 0.92 (0.28 - 3.00) | 546 (0.6) | 209 (2.0) | 1.14 (0.93 - 1.40) |
| Alzheimer's disease and related disorders or senile dementia | 76 (0.6) | 19 (4.9) | 1.57 (0.83 - 2.97) | 1839 (2.1) | 1116 (10.9) | 1.93 (1.75 - 2.13) |
| Anemia                       | 852 (6.7) | 71 (18.3) | 1.24 (0.85 - 1.79) | 5416 (6.2) | 1795 (17.6) | 1.18 (1.09 - 1.27) |
| Anxiety disorders            | 4729 (37.1) | 133 (34.4) | 1.02 (0.77 - 1.34) | 19614 (22.4) | 1805 (17.7) | 0.90 (0.84 - 0.96) |
| Asthma                       | 785 (6.2) | 40 (10.3) | 1.35 (0.91 - 1.99) | 2421 (2.8) | 272 (2.7) | 0.90 (0.78 - 1.05) |
| Atrial fibrillation          | 123 (1.0) | 18 (4.7) | 0.61 (0.33 - 1.16) | 4176 (4.8) | 1482 (14.5) | 1.21 (1.12 - 1.32) |
| Bipolar disorder             | 1152 (9.0) | 50 (12.9) | 1.53 (1.07 - 2.19) | 4502 (5.2) | 593 (5.8) | 1.23 (1.10 - 1.37) |
| Chronic kidney disease       | 530 (4.2) | 95 (24.5) | 2.14 (1.51 - 3.02) | 8541 (9.8) | 2666 (26.1) | 1.52 (1.42 - 1.63) |
| Chronic obstructive pulmonary disease and bronchiectasis | 343 (2.7) | 71 (18.3) | 2.27 (1.57 - 3.29) | 5760 (6.6) | 2163 (21.2) | 1.72 (1.60 - 1.84) |
| Colorectal cancer            | 26 (0.2) | 1 (0.3) | 0.46 (0.05 - 3.89) | 461 (0.5) | 120 (1.2) | 1.01 (0.79 - 1.29) |
| Depression                   | 4428 (34.7) | 151 (39.0) | 1.04 (0.79 - 1.37) | 16089 (18.4) | 1874 (18.3) | 1.10 (1.02 - 1.18) |
| Diabetes                     | 1489 (11.7) | 135 (34.9) | 1.38 (1.03 - 1.85) | 20430 (23.4) | 4029 (39.4) | 1.24 (1.17 - 1.31) |
| Epilepsy                     | 102 (0.8) | 11 (2.8) | 2.10 (0.94 - 4.72) | 768 (0.9) | 200 (2.0) | 1.48 (1.22 - 1.79) |
| Heart failure                | 130 (1.0) | 36 (9.3) | 2.04 (1.21 - 3.47) | 3551 (4.1) | 1727 (16.9) | 1.70 (1.56 - 1.85) |
| HIV/AIDS                     | 30 (0.2) | 5 (1.3) | 5.60 (1.85 - 16.9) | 761 (0.9) | 78 (0.8) | 1.22 (0.93 - 1.60) |
| Hyperlipidemia               | 2190 (17.2) | 139 (35.9) | 0.96 (0.72 - 1.27) | 25434 (29.1) | 3748 (36.7) | 0.81 (0.76 - 0.86) |
| Hypertension                 | 2556 (20.0) | 193 (49.9) | 1.26 (0.95 - 1.66) | 30634 (35.1) | 5526 (54.0) | 1.07 (1.01 - 1.14) |
| Ischemic heart disease       | 259 (2.0) | 46 (11.9) | 1.14 (0.71 - 1.82) | 8461 (9.7) | 2241 (21.9) | 0.97 (0.90 - 1.04) |
| Leukemias and lymphomas      | 38 (0.3) | 6 (1.6) | 1.37 (0.44 - 4.25) | 955 (1.1) | 337 (3.3) | 1.60 (1.36 - 1.90) |
| Liver disease: cirrhosis and other liver conditions except viral hepatitis | 326 (2.6) | 21 (5.4) | 1.07 (0.62 - 1.83) | 3242 (3.7) | 604 (5.9) | 1.30 (1.16 - 1.46) |
| Lung cancer                  | 27 (0.2) | 6 (1.6) | 1.68 (0.57 - 4.98) | 546 (0.6) | 245 (2.4) | 1.53 (1.27 - 1.84) |
| Mobility impairments         | 49 (0.4) | 10 (2.6) | 2.61 (1.08 - 6.31) | 679 (0.8) | 292 (2.9) | 1.97 (1.66 - 2.34) |
| Multiple sclerosis and transverse myelitis | 111 (0.9) | 10 (2.6) | 3.01 (1.35 - 6.73) | 251 (0.3) | 82 (0.8) | 3.13 (2.30 - 4.26) |
| Peripheral vascular disease  | 84 (0.7) | 17 (4.4) | 0.93 (0.47 - 1.83) | 2157 (2.5) | 839 (8.2) | 1.22 (1.10 - 1.36) |
| Pressure and chronic ulcers  | 30 (0.2) | 12 (3.1) | 2.33 (0.95 - 5.75) | 842 (1.0) | 463 (4.5) | 1.52 (1.31 - 1.76) |
| Condition                          | Cases | Controls | OR (95% CI) | Cases | Controls | OR (95% CI) |
|-----------------------------------|-------|----------|-------------|-------|----------|-------------|
| Prostate cancer                   | 1 (0.0) | 0 (0.0) | ND | 3181 (3.6) | 633 (6.2) | 0.92 (0.83 - 1.02) |
| Schizophrenia and other psychotic disorders | 284 (2.2) | 23 (5.9) | 1.61 (0.94 - 2.74) | 2036 (2.3) | 412 (4.0) | 1.68 (1.47 - 1.92) |
| Tobacco use                       | 842 (6.6) | 55 (14.2) | 1.28 (0.88 - 1.86) | 7272 (8.3) | 1153 (11.3) | 1.37 (1.26 - 1.49) |
| Viral hepatitis                    | 52 (0.4) | 5 (1.3) | 1.11 (0.34 - 3.65) | 1128 (1.3) | 231 (2.3) | 0.98 (0.82 - 1.17) |
| Death from breakthrough            | 0 (0.0) | 21 (5.4) | ND | 0 (0.0) | 1534 (15.0) |  |

OR = odds ratio. CI = 95% confidence interval.
# eTable 16. Subcohort During Delta Period, Data and Analysis

|                      | Overall   | Non-severe | Severe | Multivariable OR (CI) | P (multi) |
|----------------------|-----------|------------|--------|-----------------------|-----------|
| **N**                | 29493     | 24762      | 4731   |                       |           |
| **Sex (%)**          |           |            |        |                       |           |
| Male                 | 26781 (90.8) | 22066 (89.7) | 4575 (96.7) | 1.0 (referent)         |           |
| Female               | 2712 (9.2) | 2556 (10.3) | 156 (3.3) | 0.66 (0.55 - 0.8)     | 1.2E-05*  |
| **Age ranges (%)**   |           |            |        |                       |           |
| Less than 40         | 2306 (7.8) | 2276 (9.2)  | 30 (0.6) | 0.37 (0.23 - 0.59)    | 2.6E-05*  |
| 40-45                | 1201 (4.1) | 1169 (4.7)  | 32 (0.7) | 0.64 (0.40 - 1.02)    | 0.06      |
| 45-50                | 1274 (4.3) | 1221 (4.9)  | 53 (1.1) | 1.0 (referent)        |           |
| 50-55                | 2082 (7.1) | 1957 (7.9)  | 125 (2.6) | 1.38 (0.98 - 1.95)    | 0.06      |
| 55-60                | 2654 (9.0) | 2465 (10.0) | 189 (4.0) | 1.53 (1.11 - 2.12)    | 0.01*     |
| 60-65                | 3411 (11.6)| 3025 (12.0) | 386 (8.2) | 2.32 (1.71 - 3.16)    | 8.4E-08   |
| 65-70                | 3550 (12.0)| 2986 (12.1) | 564 (11.9)| 3.20 (2.36 - 4.34)    | <1.0E-08* |
| 70-75                | 6141 (20.8)| 4908 (19.8) | 1233 (26.1)| 4.61 (3.43 - 6.21)    | <1.0E-08* |
| 75-80                | 3656 (12.4)| 2757 (11.1) | 899 (19.0)| 6.06 (4.47 - 8.20)    | <1.0E-08* |
| 80 or greater        | 3218 (10.9)| 1998 (8.1)  | 1220 (25.8)| 10.9 (8.06 - 14.9)    | <1.0E-08* |
| **Race (%)**         |           |            |        |                       |           |
| American Indian or Alaska Native | 231 (0.8) | 193 (0.8)  | 38 (0.8) | 1.13 (0.74 - 1.71)    | 0.57      |
| Asian                | 245 (0.8) | 222 (0.9)  | 23 (0.5) | 1.05 (0.63 - 1.74)    | 0.86      |
| Black or African American | 5322 (18.0) | 4485 (18.1) | 837 (17.7) | 1.14 (1.03 - 1.26)    | 0.01*     |
| Native Hawaiian or other Pacific Islander | 242 (0.8) | 205 (0.8)  | 37 (0.8) | 1.24 (0.82 - 1.85)    | 0.31      |
| White                | 21418 (72.6)| 17885 (72.2)| 3533 (74.7)| 1.0 (referent)       |           |
| Unknown              | 2035 (6.9) | 1772 (7.2)  | 263 (5.6) | 0.92 (0.78 - 1.09)    | 0.34      |
| **Ethnicity Hispanic/Latino (%)** |           |            |        |                       |           |
| Hispanic or Latino   | 2322 (7.9) | 1986 (8.0)  | 336 (7.1) | 1.25 (1.08 - 1.45)    | 0.003*    |
| Not Hispanic or Latino| 25769 (87.4)| 21567 (87.1)| 4202 (88.8)| 1.0 (referent)       |           |
| Unknown              | 1402 (4.8) | 1209 (4.9)  | 193 (4.1) | 1.26 (1.03 - 1.54)    | 0.03      |
| **US Region (%)**    |           |            |        |                       |           |
| Continental          | 4864 (16.5)| 3944 (15.9) | 920 (19.4) | 1.31 (1.16 - 1.46)    | 5.0E-06*  |
| Midwest              | 6765 (22.9)| 5682 (22.9) | 1083 (22.9)| 0.96 (0.86 - 1.07)    | 0.45      |
| North Atlantic       | 6073 (20.6)| 5182 (20.9) | 891 (18.8)| 0.90 (0.81 - 1.01)    | 0.09      |
| Pacific              | 5028 (17.0)| 4261 (17.2) | 767 (16.2)| 1.05 (0.93 - 1.19)    | 0.39      |
| Southeast            | 6368 (21.6)| 5305 (21.4) | 1063 (22.5)| 1.0 (referent)       |           |
| Unknown              | 395 (1.3)  | 388 (1.6)   | 7 (0.1)  | 0.26 (0.12 - 0.60)    | 0.001*    |
| **Vaccine type (%)** |           |            |        |                       |           |
| Janssen              | 3449 (11.7)| 2969 (12.0) | 480 (10.1)| 1.24 (1.09 - 1.41)    | 9.3E-04*  |

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|                | Moderna          | Pfizer           | 11869 (40.0) | 9968 (40.3) | 1841 (38.9) | 0.72 (0.67 - 0.78) | <1.0E-08       |
|----------------|-----------------|------------------|--------------|-------------|--------------|-------------------|----------------|
| History of infection before vaccinated (%) | 598 (2.0)       | 487 (2.0)        | 111 (2.3)    | 0.85 (0.66 - 1.09) | 0.20
| Months since full vax at breakthrough (%) | 4 or less        | 5400 (18.3)      | 4697 (19.0)  | 703 (14.9)   | 1.0 (referent)    | 0.85
|                | 4-5             | 4750 (16.1)      | 4062 (16.4)  | 688 (14.5)   | 0.99 (0.86 - 1.13) | 0.31
|                | 5-6             | 5901 (20.0)      | 4942 (20.0)  | 959 (20.3)   | 0.93 (0.82 - 1.06) | 0.31
|                | 6-7             | 5506 (18.7)      | 4546 (18.4)  | 960 (20.3)   | 1.04 (0.91 - 1.19) | 0.54
|                | 7-8             | 4263 (14.5)      | 3539 (14.3)  | 724 (15.3)   | 1.08 (0.94 - 1.25) | 0.26
|                | 8-9             | 2569 (8.7)       | 2092 (8.4)   | 477 (10.1)   | 1.10 (0.94 - 1.29) | 0.24
|                | 9-10            | 1007 (3.4)       | 803 (3.2)    | 204 (4.3)    | 1.23 (0.99 - 1.53) | 0.06
|                | 10-11           | 95 (0.3)         | 79 (0.3)     | 16 (0.3)     | 1.92 (1.00 - 3.68) | 0.05
|                | 11-12           | 2 (0.0)          | 2 (0.0)      | 0 (0.0)      | ND            | ND
|                | 12 or more       | 0               | 0            | 0            | ND            | ND
| Months since boosted at breakthrough (%)  | Not boosted      | 28142 (95.4)    | 23636 (95.5) | 4506 (95.2)  | 1.0 (referent)   | 0.85
|                | 1 or less        | 653 (2.2)        | 542 (2.2)    | 111 (2.3)    | 0.69 (0.54 - 0.88) | 0.003
|                | 1-2             | 251 (0.9)        | 206 (0.8)    | 45 (1.0)     | 0.62 (0.42 - 0.91) | 0.01
|                | 2-3             | 158 (0.5)        | 129 (0.5)    | 29 (0.6)     | 0.46 (0.27 - 0.77) | 0.004
|                | 3-4             | 49 (0.2)         | 44 (0.2)     | 5 (0.1)      | 0.36 (0.12 - 1.08) | 0.07
|                | 4-5             | 39 (0.1)         | 32 (0.1)     | 7 (0.1)      | 2.25 (0.95 - 5.36) | 0.07
|                | 5-6             | 59 (0.2)         | 52 (0.2)     | 7 (0.1)      | 0.98 (0.41 - 2.36) | 0.96
|                | 6 or more        | 142 (0.5)        | 121 (0.5)    | 21 (0.4)     | 1.22 (0.73 - 2.04) | 0.45
| Immune-suppressive medications before breakthrough (%) | Before breakthrough Chemotherapy | 304 (1.0) | 186 (0.8) | 118 (2.5) | 2.40 (1.72 - 3.36) | 3.1E-07
|                | Before breakthrough Cytokine-blocking | 506 (1.7) | 395 (1.6) | 111 (2.3) | 1.61 (1.09 - 2.38) | 0.02
|                | Before breakthrough Glucocorticoids | 2595 (8.8) | 1812 (7.3) | 783 (16.6) | 1.93 (1.73 - 2.16) | <1.0E-08
|                | Before breakthrough Leukocyte-inhibitory | 568 (1.9) | 356 (1.4) | 212 (4.5) | 2.77 (2.06 - 3.71) | <1.0E-08
|                | Before breakthrough Lymphocyte-depleting | 167 (0.6) | 106 (0.4) | 61 (1.3) | 1.26 (0.73 - 2.18) | 0.40
| Immune-suppressive medications before initial vaccination (%) | Before vaccine Chemotherapy | 150 (0.5) | 100 (0.4) | 50 (1.1) | 0.75 (0.45 - 1.26) | 0.29
|                | Before vaccine Cytokine-blocking | 375 (1.3) | 308 (1.2) | 67 (1.4) | 0.78 (0.48 - 1.25) | 0.30
|                | Before vaccine Glucocorticoids | 846 (2.9) | 570 (2.3) | 276 (5.8) | 1.37 (1.13 - 1.65) | 0.001
|                | Before vaccine Leukocyte-inhibitory | 393 (1.3) | 277 (1.1) | 116 (2.5) | 0.68 (0.47 - 0.98) | 0.04
|                | Before vaccine Lymphocyte-depleting | 66 (0.2) | 40 (0.2) | 26 (0.5) | 1.05 (0.45 - 2.45) | 0.91
| Persistent positive test (%) | 231 (0.8) | 182 (0.7) | 49 (1.0) | 1.12 (0.79 - 1.59) | 0.52
| BMI Class (%) |
| Health Condition                                      | Underweight | Normal | Overweight | Obesity I | Obesity II | Severe Obesity | Unknown |
|-------------------------------------------------------|-------------|--------|------------|-----------|------------|----------------|---------|
| **BMI**                                               | 193 (0.7)   | 119 (0.5) | 74 (1.6)  | 1.60 (1.10 - 2.32) | 1.60 (1.10 - 2.32) |
| **Comorbidities (%)**                                 |             |        |            |           |            |                |         |
| Acquired hypothyroidia                                | 1499 (5.1)  | 1143 (4.6) | 356 (7.5) | 1.10 (0.95 - 1.28) | 1.10 (0.95 - 1.28) |
| Acute myocardial infarction                           | 231 (0.8)   | 150 (0.6)  | 81 (1.7)  | 1.15 (0.89 - 1.35) | 1.15 (0.89 - 1.35) |
| Alzheimer's disease and related disorders or senile dementia | 937 (3.2)  | 485 (2.0)  | 452 (9.6) | 1.96 (1.67 - 2.30) | 1.96 (1.67 - 2.30) |
| Anemia                                                | 2352 (8.0)  | 1612 (6.5) | 740 (15.6) | 1.15 (1.02 - 1.30) | 1.15 (1.02 - 1.30) |
| Anxiety disorders                                     | 6171 (20.9) | 5354 (21.6) | 817 (17.3) | 0.90 (0.81 - 1.01) | 0.90 (0.81 - 1.01) |
| Asthma                                                | 902 (3.1)   | 746 (3.0)  | 156 (3.3) | 1.09 (0.89 - 1.35) | 1.09 (0.89 - 1.35) |
| Atrial fibrillation                                   | 1946 (6.6)  | 1305 (5.3) | 641 (13.5) | 1.16 (1.02 - 1.32) | 1.16 (1.02 - 1.32) |
| Bipolar disorder                                      | 1549 (5.3)  | 1280 (5.2) | 269 (5.7) | 1.26 (1.06 - 1.50) | 1.26 (1.06 - 1.50) |
| Chronic kidney disease                               | 3457 (11.7) | 2329 (9.4) | 1128 (23.8) | 1.44 (1.30 - 1.61) | 1.44 (1.30 - 1.61) |
| Chronic obstructive pulmonary disease and bronchiectasis | 2668 (9.0) | 1741 (7.0) | 927 (19.6) | 1.64 (1.47 - 1.83) | 1.64 (1.47 - 1.83) |
| Colorectal cancer                                     | 185 (0.6)   | 136 (0.5)  | 49 (1.0)  | 0.98 (0.66 - 1.45) | 0.98 (0.66 - 1.45) |
| Depression                                            | 5496 (18.6) | 4634 (18.7) | 862 (18.2) | 1.15 (1.03 - 1.28) | 1.15 (1.03 - 1.28) |
| Diabetes                                              | 7862 (26.7) | 5971 (21.6) | 1891 (40.0) | 1.31 (1.20 - 1.43) | 1.31 (1.20 - 1.43) |
| Epilepsy                                              | 287 (1.0)   | 195 (0.8)  | 92 (1.9)  | 1.81 (1.33 - 2.45) | 1.81 (1.33 - 2.45) |
| Heart failure                                         | 1707 (5.8)  | 1002 (4.0) | 705 (14.9) | 1.54 (1.35 - 1.77) | 1.54 (1.35 - 1.77) |
| HIV/AIDS                                              | 253 (0.9)   | 212 (0.9)  | 41 (0.9)  | 1.43 (0.97 - 2.12) | 1.43 (0.97 - 2.12) |
| Hyperlipidemia                                        | 8677 (29.4) | 6994 (28.2) | 1683 (35.6) | 0.83 (0.76 - 0.91) | 0.83 (0.76 - 0.91) |
| Hypertension                                          | 11170 (37.9)| 8678 (35.0) | 2492 (52.7) | 1.07 (0.98 - 1.17) | 1.07 (0.98 - 1.17) |
| Ischemic heart disease                                | 3494 (11.8) | 2507 (10.1) | 987 (20.9) | 0.99 (0.89 - 1.11) | 0.99 (0.89 - 1.11) |
| Leukemias and lymphomas                               | 394 (1.3)   | 272 (1.1)  | 122 (2.6) | 1.23 (0.93 - 1.64) | 1.23 (0.93 - 1.64) |
| Liver disease: cirrhosis and other liver conditions except viral hepatitis | 1173 (4.0) | 916 (3.7)  | 257 (5.4) | 1.24 (1.04 - 1.47) | 1.24 (1.04 - 1.47) |
| Lung cancer                                           | 250 (0.8)   | 149 (0.6)  | 101 (2.1) | 1.69 (1.25 - 2.29) | 1.69 (1.25 - 2.29) |
| Mobility impairments                                  | 319 (1.1)   | 186 (0.8)  | 133 (2.8) | 2.06 (1.56 - 2.73) | 2.06 (1.56 - 2.73) |
| Multiple sclerosis and transverse myelitis            | 111 (0.4)   | 78 (0.3)   | 33 (0.7)  | 3.19 (1.96 - 5.20) | 3.19 (1.96 - 5.20) |
| Peripheral vascular disease                           | 985 (3.3)   | 638 (2.6)  | 347 (7.3) | 1.13 (0.96 - 1.34) | 1.13 (0.96 - 1.34) |
| Pressure and chronic ulcers                           | 428 (1.5)   | 240 (1.0)  | 188 (4.0) | 1.38 (1.07 - 1.77) | 1.38 (1.07 - 1.77) |
| Prostate cancer                                       | 1127 (3.8)  | 874 (3.5)  | 253 (5.3) | 0.85 (0.72 - 1.00) | 0.85 (0.72 - 1.00) |
| Schizophrenia and other psychotic disorders           | 677 (2.3)   | 514 (2.1)  | 163 (3.4) | 1.64 (1.32 - 2.03) | 1.64 (1.32 - 2.03) |
| Condition                                | Count (Percent) | Count (Percent) | Count (Percent) | Odds Ratio (95% CI) | P-Value |
|-----------------------------------------|-----------------|-----------------|-----------------|---------------------|---------|
| Tobacco use                             | 2399 (8.1)      | 1930 (7.8)      | 469 (9.9)       | 1.22 (1.07 - 1.40)  | 0.004*  |
| Viral hepatitis                          | 374 (1.3)       | 279 (1.1)       | 95 (2.0)        | 1.07 (0.80 - 1.42)  | 0.65    |
| Death from breakthrough infection        | 736 (2.5)       | 0 (0.0)         | 736 (15.6)      |                     |         |

*Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.024 in this analysis. OR = odds ratio. CI = 95% confidence interval.
### eTable 17. Subcohort During Omicron Period, Data and Analysis

|                        | Overall | Non-severe | Severe | Multivariable OR (CI) | P (multi) |
|------------------------|---------|------------|--------|-----------------------|-----------|
| **N**                  | 78379   | 73135      | 5244   |                       |           |
| **Sex (%)**            |         |            |        |                       |           |
| Male                   | 68128 (86.9) | 63099 (86.3) | 5029 (95.9) | 1.0 (referent)      |           |
| Female                 | 11251 (13.1) | 10036 (13.7) | 215 (4.1)   | 0.73 (0.63 - 0.86)  | 7.6E-05   |
| **Age ranges (%)**     |         |            |        |                       |           |
| Less than 40           | 10702 (13.7) | 10626 (14.5) | 76 (1.4)    | 0.70 (0.49 - 1.00)  | 0.05      |
| 40-45                  | 4968 (6.3)  | 4914 (6.7)  | 54 (1.0)   | 1.04 (0.71 - 1.53)  | 0.85      |
| 45-50                  | 4963 (6.3)  | 4909 (6.7)  | 54 (1.0)   | 1.0 (referent)      |           |
| 50-55                  | 7489 (9.6)  | 7344 (10.0) | 145 (2.8)  | 1.69 (1.23 - 2.33)  | 0.001     |
| 55-60                  | 8088 (10.3) | 7827 (10.7) | 261 (5.0)  | 2.59 (1.92 - 3.50)  | <1.0E-08  |
| 60-65                  | 9247 (11.8) | 8791 (12.0) | 456 (8.7)  | 3.61 (2.70 - 4.83)  | <1.0E-08  |
| 65-70                  | 8441 (10.8) | 7747 (10.6) | 694 (13.2) | 5.43 (4.07 - 7.25)  | <1.0E-08  |
| 70-75                  | 11485 (14.7) | 10256 (14.0) | 1229 (23.4) | 7.26 (5.46 - 9.65)  | <1.0E-08  |
| 75-80                  | 7449 (9.5)  | 6457 (8.8)  | 992 (18.9) | 9.20 (6.91 - 12.3)  | <1.0E-08  |
| 80 or greater          | 5547 (7.1)  | 4264 (5.8)  | 1283 (24.5) | 16.6 (12.4 - 22.2)  | <1.0E-08  |
| **Race (%)**           |         |            |        |                       |           |
| American Indian or Alaska Native | 642 (0.8)  | 596 (0.8)  | 46 (0.9)   | 1.42 (1.00 - 2.01)  | 0.05      |
| Asian                  | 1321 (1.7) | 1289 (1.8) | 32 (0.6)   | 0.77 (0.52 - 1.15)  | 0.21      |
| Black or African American | 21032 (26.8) | 19824 (27.1) | 1208 (23.0) | 0.88 (0.81 - 0.95)  | 0.002     |
| Native Hawaiian or other Pacific Islander | 868 (1.1)  | 835 (1.1)  | 33 (0.6)   | 0.59 (0.38 - 0.89)  | 0.01      |
| White                  | 48203 (61.5) | 44563 (60.9) | 3640 (69.4) | 1.0 (referent)      |           |
| Unknown                | 6313 (8.1)  | 6028 (8.2)  | 285 (5.4)  | 0.87 (0.74 - 1.01)  | 0.07      |
| **Ethnicity Hispanic/Latino (%)** |         |            |        |                       |           |
| Hispanic or Latino     | 8679 (11.1) | 8305 (11.4) | 374 (7.1)  | 0.94 (0.83 - 1.07)  | 0.32      |
| Not Hispanic or Latino | 65094 (83.1) | 60413 (82.6) | 4681 (89.3) | 1.0 (referent)      |           |
| Unknown                | 4606 (5.9)  | 4417 (6.0)  | 189 (3.6)  | 0.99 (0.82 - 1.19)  | 0.91      |
| **US Region (%)**      |         |            |        |                       |           |
| Continental            | 12828 (16.4) | 11945 (16.3) | 883 (16.8) | 1.04 (0.94 - 1.16)  | 0.41      |
| Midwest                | 14506 (18.5) | 13418 (18.3) | 1088 (20.7) | 0.95 (0.86 - 1.05)  | 0.34      |
| North Atlantic         | 17017 (21.7) | 15850 (21.7) | 1167 (22.3) | 0.95 (0.86 - 1.05)  | 0.30      |
| Pacific                | 14756 (18.8) | 13915 (19.0) | 841 (16.0)  | 0.87 (0.78 - 0.97)  | 0.01      |
| Southeast              | 17381 (22.2) | 16131 (22.1) | 1250 (23.8) | 1.0 (referent)      |           |
| Unknown                | 1891 (2.4)  | 1876 (2.6)  | 15 (0.3)   | 0.33 (0.18 - 0.59)  | 1.7E-04   |
| **Vaccine type (%)**   |         |            |        |                       |           |
| Janssen                | 7406 (9.4)  | 6884 (9.4)  | 522 (10.0) | 1.27 (1.13 - 1.44)  | 7.6E-05   |

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|                          | Moderna | Pfizer | History of infection before vaccinated (%) | Months since full vax at breakthrough (%) | Immune-suppressive medications before breakthrough (%) | Immune-suppressive medications before initial vaccination (%) |
|--------------------------|---------|--------|---------------------------------------------|-------------------------------------------|------------------------------------------------------|---------------------------------------------------------------|
|                          | 32604 (41.6) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 1.2E-06<sup>a</sup> |                                                                |
|                          | 38369 (49.0) | 35802 (49.0) | 2567 (49.0) | 1.0 (referent) | 2.6E-08<sup>a</sup> |                                                                |
| History of infection before vaccinated (%) | 3152 (4.0) | 3015 (4.1) | 137 (2.6) | 0.56 (0.46 - 0.69) | 2.6E-08<sup>a</sup> |                                                                |
| Months since full vax at breakthrough (%) | 32604 (41.6) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 1.2E-06<sup>a</sup> |                                                                |
| Months since boosted at breakthrough (%) | 32604 (41.6) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 1.2E-06<sup>a</sup> |                                                                |
| Immune-suppressive medications before breakthrough (%) | 32604 (41.6) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 1.2E-06<sup>a</sup> |                                                                |
| Immune-suppressive medications before initial vaccination (%) | 32604 (41.6) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 1.2E-06<sup>a</sup> |                                                                |
| BMI Class (%) | 32604 (41.6) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 1.2E-06<sup>a</sup> |                                                                |

<sup>a</sup> Significance level: p < 0.05.
| Comorbidities (%)                                                                 | N   | N | N | Odds Ratio (95% CI) | P Value |
|-----------------------------------------------------------------------------------|-----|---|---|--------------------|---------|
| Underweight                                                                       | 452 (0.6) | 357 (0.5) | 95 (1.8) | 1.48 (1.11 - 1.97) | 0.007 <sup>a</sup> |
| Normal                                                                            | 10055 (12.8) | 8927 (12.2) | 1128 (21.5) | 1.0 (referent) | <sup>a</sup> |
| Overweight                                                                        | 23253 (29.7) | 21802 (29.8) | 1451 (27.7) | 0.71 (0.64 - 0.78) | <1.0E-08 <sup>a</sup> |
| Obesity I                                                                          | 22054 (28.1) | 20848 (28.5) | 1206 (23.0) | 0.75 (0.68 - 0.83) | 5.1E-08 <sup>a</sup> |
| Obesity II                                                                         | 11774 (15.0) | 11010 (15.1) | 764 (14.6) | 1.00 (0.89 - 1.13) | 0.99 <sup>a</sup> |
| Severe Obesity                                                                     | 7335 (9.4) | 6819 (9.3) | 516 (9.8) | 1.17 (1.02 - 1.34) | 0.02 <sup>a</sup> |
| Unknown                                                                           | 3456 (4.4) | 3372 (4.6) | 84 (1.6) | 0.79 (0.61 - 1.02) | 0.08 <sup>a</sup> |
| Comorbidities (%)                                                                 |
| Acquired hypothyroidism                                                           | 3296 (4.2) | 2917 (4.0) | 379 (7.2) | 0.94 (0.82 - 1.08) | 0.38 <sup>a</sup> |
| Acute myocardial infarction                                                        | 506 (0.6) | 394 (0.5) | 112 (2.1) | 1.05 (0.80 - 1.39) | 0.71 <sup>a</sup> |
| Alzheimer’s disease and related disorders or senile dementia                      | 1885 (2.4) | 1293 (1.8) | 592 (11.3) | 2.00 (1.75 - 2.27) | <1.0E-08 <sup>a</sup> |
| Anemia                                                                            | 5305 (6.8) | 4359 (6.0) | 946 (18.0) | 1.20 (1.08 - 1.33) | 7.2E-04 <sup>a</sup> |
| Anxiety disorders                                                                  | 19505 (24.9) | 18500 (25.3) | 1005 (19.2) | 0.90 (0.82 - 0.98) | 0.02 <sup>a</sup> |
| Asthma                                                                            | 2525 (3.2) | 2381 (3.3) | 144 (2.7) | 0.92 (0.76 - 1.12) | 0.42 <sup>a</sup> |
| Atrial fibrillation                                                                | 3516 (4.5) | 2779 (3.8) | 737 (14.1) | 1.22 (1.09 - 1.37) | 0.02 <sup>a</sup> |
| Bipolar disorder                                                                   | 4603 (5.9) | 4255 (5.8) | 348 (6.6) | 1.25 (1.09 - 1.44) | 0.002 <sup>a</sup> |
| Chronic kidney disease                                                             | 7772 (9.9) | 6357 (8.7) | 1415 (27.0) | 1.66 (1.51 - 1.82) | <1.0E-08 <sup>a</sup> |
| Chronic obstructive pulmonary disease and bronchiectasis                            | 5299 (6.8) | 4145 (5.7) | 1154 (22.0) | 1.75 (1.59 - 1.92) | <1.0E-08 <sup>a</sup> |
| Colorectal cancer                                                                  | 389 (0.5) | 329 (0.4) | 60 (1.1) | 0.95 (0.68 - 1.34) | 0.79 <sup>a</sup> |
| Depression                                                                         | 16534 (21.1) | 15478 (21.2) | 1056 (20.1) | 1.08 (0.98 - 1.19) | 0.12 <sup>a</sup> |
| Diabetes                                                                          | 17226 (22.0) | 15250 (20.9) | 1976 (37.7) | 1.18 (1.09 - 1.28) | 2.7E-05 <sup>a</sup> |
| Epilepsy                                                                          | 744 (0.9) | 639 (0.8) | 105 (2.0) | 1.38 (1.07 - 1.77) | 0.01 <sup>a</sup> |
| Heart failure                                                                      | 3379 (4.3) | 2477 (3.4) | 902 (17.2) | 1.84 (1.65 - 2.07) | <1.0E-08 <sup>a</sup> |
| Hypertension                                                                       | 600 (0.8) | 561 (0.8) | 39 (0.7) | 1.23 (0.84 - 1.80) | 0.29 <sup>a</sup> |
| Hyperlipidemia                                                                    | 21819 (27.8) | 19890 (27.2) | 1929 (36.8) | 0.79 (0.73 - 0.85) | <1.0E-08 <sup>a</sup> |
| Ischemic heart disease                                                             | 26365 (33.6) | 23518 (32.2) | 2847 (54.3) | 1.10 (1.01 - 1.19) | 0.02 <sup>a</sup> |
| Leukemias and lymphomas                                                            | 6967 (8.9) | 5843 (8.0) | 1124 (21.4) | 0.97 (0.87 - 1.07) | 0.49 <sup>a</sup> |
| Liver disease: cirrhosis and other liver conditions except viral hepatitis         | 853 (1.1) | 675 (0.9) | 178 (3.4) | 1.81 (1.45 - 2.25) | 1.5E-07 <sup>a</sup> |
| Lung cancer                                                                        | 2512 (3.2) | 2186 (3.0) | 326 (6.2) | 0.95 (0.82 - 1.09) | 0.45 <sup>a</sup> |
| Multiple sclerosis and transverse myelitis                                         | 1989 (2.5) | 1736 (2.4) | 253 (4.8) | 1.79 (1.52 - 2.11) | <1.0E-08 <sup>a</sup> |

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| Category                              | Cases    | Controls  | OR       | 95% CI        | p-value |
|---------------------------------------|----------|-----------|----------|---------------|---------|
| Tobacco use                           | 6718 (8.6) | 6023 (8.2) | 695 (13.3) | 1.49 (1.34 - 1.66) | <1.0E-08$^a$ |
| Viral hepatitis                        | 980 (1.3)  | 858 (1.2)  | 122 (2.3)  | 0.89 (0.70 - 1.13) | 0.34    |
| Death from breakthrough infection      | 728 (0.9)  | 0 (0.0)    | 728 (13.9) |               |         |

$^a$ Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.044 in this analysis. OR = odds ratio. CI = 95% confidence interval.
eTable 18. Subcohorts During Delta and Omicron, Comparison of Analyses

|                  | Non-severe | Severe | Multivariable OR (CI) | Non-severe | Severe | Multivariable OR (CI) |
|------------------|------------|--------|-----------------------|------------|--------|-----------------------|
| **N**            | 24762      | 4731   |                       | 73135      | 5244   |                       |
| **Sex (%)**      |            |        |                       |            |        |                       |
| Male             | 22206 (89.7) | 4575 (96.7) | 1.0 (referent) | 63099 (86.3) | 5029 (95.9) | 1.0 (referent) |
| Female           | 2556 (10.3) | 156 (3.3) | 0.66 (0.55 - 0.8)     | 10036 (13.7) | 215 (4.1) | 0.73 (0.63 - 0.86)   |
| **Age ranges (%)** |            |        |                       |            |        |                       |
| Less than 40     | 2276 (9.2) | 30 (0.6) | 0.37 (0.23 - 0.59)    | 10626 (14.5) | 76 (1.4) | 0.70 (0.49 - 1.00)   |
| 40-45            | 1169 (4.7) | 32 (0.7) | 0.64 (0.40 - 1.02)    | 4914 (6.7) | 54 (1.0) | 1.04 (0.71 - 1.53)   |
| 45-50            | 1221 (4.9) | 53 (1.1) | 1.0 (referent)        | 4909 (6.7) | 54 (1.0) | 1.0 (referent)        |
| 50-55            | 1957 (7.9) | 125 (2.6) | 1.38 (0.98 - 1.95)   | 7344 (10.0) | 145 (2.8) | 1.69 (1.23 - 2.33)   |
| 55-60            | 2465 (10.0) | 189 (4.0) | 1.53 (1.11 - 2.12)   | 7827 (10.7) | 261 (5.0) | 2.59 (1.92 - 3.50)   |
| 60-65            | 3025 (12.2) | 386 (8.2) | 2.32 (1.71 - 3.16)   | 8791 (12.0) | 456 (8.7) | 3.61 (2.70 - 4.83)   |
| 65-70            | 2986 (12.1) | 564 (11.9) | 3.20 (2.36 - 4.34)   | 7747 (10.6) | 694 (13.2) | 5.43 (4.07 - 7.25)   |
| 70-75            | 4908 (19.8) | 1233 (26.1) | 4.61 (3.43 - 6.21) | 10256 (14.0) | 1229 (23.4) | 7.26 (5.46 - 9.65)   |
| 75-80            | 2757 (11.1) | 899 (19.0) | 6.06 (4.47 - 8.20)   | 6457 (8.8) | 992 (18.9) | 9.20 (6.91 - 12.3)   |
| 80 or greater    | 1998 (8.1) | 1220 (25.8) | 10.9 (8.06 - 14.9)  | 4264 (5.8) | 1283 (24.5) | 16.6 (12.4 - 22.2)   |
| **Race (%)**     |            |        |                       |            |        |                       |
| American Indian or Alaska Native | 193 (0.8) | 38 (0.8) | 1.13 (0.74 - 1.71)   | 596 (0.8) | 46 (0.9) | 1.42 (1.00 - 2.01)   |
| Asian            | 222 (0.9) | 23 (0.5) | 1.05 (0.63 - 1.74)   | 1289 (1.8) | 32 (0.6) | 0.77 (0.52 - 1.15)   |
| Black or African American | 4485 (18.1) | 837 (17.7) | 1.14 (1.03 - 1.26) | 19824 (27.1) | 1208 (23.0) | 0.88 (0.81 - 0.95)   |
| Native Hawaiian or other Pacific Islander | 205 (0.8) | 37 (0.8) | 1.24 (0.82 - 1.85) | 835 (1.1) | 33 (0.6) | 0.59 (0.38 - 0.89)   |
| White            | 17885 (72.2) | 3533 (74.7) | 1.0 (referent)      | 44563 (60.9) | 3640 (69.4) | 1.0 (referent)        |
| Unknown          | 1772 (7.2) | 263 (5.6) | 0.92 (0.78 - 1.09)   | 6028 (8.2) | 285 (5.4) | 0.87 (0.74 - 1.01)   |
| **Ethnicity Hispanic/Latino (%)** |            |        |                       |            |        |                       |
| Hispanic or Latino | 1986 (8.0) | 336 (7.1) | 1.25 (1.08 - 1.45)   | 8305 (11.4) | 374 (7.1) | 0.94 (0.83 - 1.07)   |
| Not Hispanic or Latino | 21567 (87.1) | 4202 (88.8) | 1.0 (referent)      | 60413 (82.6) | 4681 (89.3) | 1.0 (referent)        |
| Unknown          | 1209 (4.9) | 193 (4.1) | 1.26 (1.03 - 1.54)   | 4417 (6.0) | 189 (3.6) | 0.99 (0.82 - 1.19)   |
| **US Region (%)** |            |        |                       |            |        |                       |
| Continental      | 3944 (15.9) | 920 (19.4) | 1.31 (1.16 - 1.46)   | 11945 (16.3) | 883 (16.8) | 1.04 (0.94 - 1.16)   |
| Midwest          | 5682 (22.9) | 1083 (22.9) | 0.96 (0.86 - 1.07) | 13418 (18.3) | 1088 (20.7) | 0.95 (0.86 - 1.05)   |
| North Atlantic   | 5182 (20.9) | 891 (18.8) | 0.90 (0.81 - 1.01)   | 15850 (21.7) | 1167 (22.3) | 0.95 (0.86 - 1.05)   |
| Pacific          | 4261 (17.2) | 767 (16.2) | 1.05 (0.93 - 1.19)   | 13915 (19.0) | 841 (16.0) | 0.87 (0.78 - 0.97)   |
| Southeast        | 5305 (21.4) | 1063 (22.5) | 1.0 (referent)      | 16131 (22.1) | 1250 (23.8) | 1.0 (referent)        |
| Unknown          | 388 (1.6) | 7 (0.1) | 0.26 (0.12 - 0.60)   | 1876 (2.6) | 15 (0.3) | 0.33 (0.18 - 0.59)   |
| **Vaccine type (%)** |            |        |                       |            |        |                       |
| Janssen          | 2969 (12.0) | 480 (10.1) | 1.24 (1.09 - 1.41)   | 6884 (9.4) | 522 (10.0) | 1.27 (1.13 - 1.44)   |

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| Moderna | Pfizer | History of infection before vaccinated (%) | Months since full vax at breakthrough (%) | Months since boosted at breakthrough (%) | Immune-suppressive medications before breakthrough (%) | Immune-suppressive medications before initial vaccination (%) | Persistent positive test (%) | BMI Class (%) |
|---------|--------|------------------------------------------|-----------------------------------------|------------------------------------------|-------------------------------------------------------|--------------------------------------------------------|-----------------------------|----------------|
| 9968 (40.3) | 11825 (47.8) | 487 (2.0) | 4697 (19.0) | 23636 (95.5) | 186 (0.8) | 100 (0.4) | 182 (0.7) | 182 (0.7) |
| 1841 (38.9) | 2410 (50.9) | 111 (2.3) | 703 (14.9) | 4506 (95.2) | 118 (2.5) | 50 (1.1) | 50 (1.1) | 50 (1.1) |
| 0.72 (0.67 - 0.78) | 1.0 (referent) | 0.85 (0.66 - 1.09) | 4079 (5.6) | 46630 (63.8) | 2.40 (1.72 - 3.36) | 2.40 (1.72 - 3.36) | 0.75 (0.45 - 1.26) | 0.75 (0.45 - 1.26) |
| 30449 (41.6) | 35802 (49.0) | 3015 (4.1) | 193 (3.7) | 3417 (65.2) | 4843 (6.6) | 242 (4.6) | 165 (3.1) | 165 (3.1) |
| 2155 (41.1) | 2567 (49.0) | 137 (2.6) | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) |
| 0.84 (0.78 - 0.90) | | 0.56 (0.46 - 0.69) | | | | | | |
| 0.72 (0.67 - 0.78) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 2567 (49.0) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) |
| 0.72 (0.67 - 0.78) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 2567 (49.0) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) |
| 0.72 (0.67 - 0.78) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 2567 (49.0) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) |
| 0.72 (0.67 - 0.78) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 2567 (49.0) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) |
| 0.72 (0.67 - 0.78) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 2567 (49.0) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) |
| 0.72 (0.67 - 0.78) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 2567 (49.0) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) |
| 0.72 (0.67 - 0.78) | 30449 (41.6) | 2155 (41.1) | 0.84 (0.78 - 0.90) | 2567 (49.0) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) | 0.84 (0.78 - 0.90) |

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| Comorbidities (%)                                                                 | Underweight   | Normal          | Overweight     | Obesity I      | Obesity II     | Severe Obesity | Unknown     | Comorbidities (%)                                                                 |
|----------------------------------------------------------------------------------|--------------|----------------|---------------|----------------|----------------|----------------|-------------|----------------------------------------------------------------------------------|
| Acquired hypothyroidism                                                          | 119 (0.5)    | 74 (1.6)       | 1.60 (1.10 - 2.32) | 357 (0.5)      | 95 (1.8)       | 1.48 (1.11 - 1.97) | 747 (3.0)   | Acquired hypothyroidism                                                          |
| Acute myocardial infarction                                                       | 3044 (12.3)  | 814 (17.2)     | 1.0 (referent) | 8927 (12.2)    | 1128 (21.5)    | 1.0 (referent)   | 3044 (12.3) | Acute myocardial infarction                                                       |
| Alzheimer disease and related disorders or senile dementia                       | 7261 (29.3)  | 1284 (27.1)    | 0.82 (0.73 - 0.92) | 21802 (29.8)   | 1451 (27.7)    | 0.71 (0.64 - 0.78) | 7261 (29.3) | Alzheimer disease and related disorders or senile dementia                       |
| Anxiety disorders                                                                | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Anxiety disorders                                                                |
| Atrial fibrillation                                                              | 7120 (28.8)  | 1246 (26.3)    | 0.94 (0.83 - 1.06) | 20848 (28.5)   | 1206 (23.0)    | 0.75 (0.68 - 0.83) | 7120 (28.8) | Atrial fibrillation                                                              |
| Bipolar disorder                                                                 | 1815 (7.2)   | 20 (0.4)       | 0.82 (0.73 - 0.92) | 4356 (6.0)     | 285 (5.3)      | 0.71 (0.64 - 0.78) | 1815 (7.2)  | Bipolar disorder                                                                 |
| Chronic kidney disease                                                            | 3984 (16.1)  | 688 (14.5)     | 1.07 (0.93 - 1.23) | 11010 (15.1)   | 764 (14.6)     | 1.00 (0.89 - 1.13) | 3984 (16.1) | Chronic kidney disease                                                            |
| Chronic obstructive pulmonary disease and bronchiectasis                         | 7261 (29.3)  | 1284 (27.1)    | 0.82 (0.73 - 0.92) | 21802 (29.8)   | 1451 (27.7)    | 0.71 (0.64 - 0.78) | 7261 (29.3) | Chronic obstructive pulmonary disease and bronchiectasis                         |
| Colorectal cancer                                                                 | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Colorectal cancer                                                                 |
| Depression                                                                       | 7120 (28.8)  | 1246 (26.3)    | 0.94 (0.83 - 1.06) | 20848 (28.5)   | 1206 (23.0)    | 0.75 (0.68 - 0.83) | 7120 (28.8) | Depression                                                                       |
| Diabetes                                                                         | 1815 (7.2)   | 20 (0.4)       | 0.82 (0.73 - 0.92) | 4356 (6.0)     | 285 (5.3)      | 0.71 (0.64 - 0.78) | 1815 (7.2)  | Diabetes                                                                         |
| Epilepsy                                                                         | 1815 (7.2)   | 20 (0.4)       | 0.82 (0.73 - 0.92) | 4356 (6.0)     | 285 (5.3)      | 0.71 (0.64 - 0.78) | 1815 (7.2)  | Epilepsy                                                                         |
| Heart failure                                                                    | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Heart failure                                                                    |
| HIV/AIDS                                                                         | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | HIV/AIDS                                                                         |
| Hyperlipidemia                                                                   | 7261 (29.3)  | 1284 (27.1)    | 0.82 (0.73 - 0.92) | 21802 (29.8)   | 1451 (27.7)    | 0.71 (0.64 - 0.78) | 7261 (29.3) | Hyperlipidemia                                                                   |
| Hypertension                                                                     | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Hypertension                                                                     |
| Ischemic heart disease                                                            | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Ischemic heart disease                                                            |
| Leukemias and lymphomas                                                           | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Leukemias and lymphomas                                                           |
| Liver disease: cirrhosis and other liver conditions except viral hepatitis       | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Liver disease: cirrhosis and other liver conditions except viral hepatitis       |
| Lung cancer                                                                       | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Lung cancer                                                                       |
| Mobility impairments                                                             | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Mobility impairments                                                             |
| Multiple sclerosis and transverse myelitis                                       | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Multiple sclerosis and transverse myelitis                                       |
| Peripheral vascular disease                                                       | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Peripheral vascular disease                                                       |
| Pressure and chronic ulcers                                                      | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Pressure and chronic ulcers                                                      |
| Prostate cancer                                                                  | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Prostate cancer                                                                  |
| Schizophrenia and other psychotic disorders                                      | 2487 (10.0)  | 550 (11.6)     | 1.57 (1.36 - 1.82) | 6819 (9.3)     | 516 (9.8)      | 1.17 (1.02 - 1.34) | 2487 (10.0) | Schizophrenia and other psychotic disorders                                      |
| Condition                      | Event 1 | Event 2 | Odds Ratio (95% CI) |
|-------------------------------|---------|---------|--------------------|
| Tobacco use                   | 1930 (7.8) | 469 (9.9) | 1.22 (1.07 - 1.40) |
| Viral hepatitis               | 279 (1.1) | 95 (2.0)  | 1.07 (0.80 - 1.42) |
| Death from breakthrough infection | 0 (0.0)  | 736 (15.6)  |                     |

OR = odds ratio. CI = 95% confidence interval.
# Table 19. Subcohort of Patients Who Received the Pfizer Vaccine, Data and Analysis

|                  | Overall | Non-severe | Severe | Multivariable OR (CI) | P (multi) |
|------------------|---------|------------|--------|-----------------------|-----------|
| **N**            | 54164   | 48831      | 5333   |                       |           |
| **Sex (%)**      |         |            |        |                       |           |
| Male             | 47148 (87.0) | 42048 (86.1) | 5100 (95.6) | 1.0 (referent) |           |
| Female           | 7016 (13.0)  | 6783 (13.9)  | 233 (4.4)  | 0.81 (0.69 - 0.94)  | 0.007 *   |
| **Age ranges (%)** |       |            |        |                       |           |
| Less than 40     | 6643 (12.3)  | 6597 (13.5)  | 46 (0.9)  | 0.41 (0.28 - 0.61)   | 1.3E-05 * |
| 40-45            | 3122 (5.8)   | 3082 (6.3)   | 40 (0.8)  | 0.68 (0.45 - 1.04)   | 0.07      |
| 45-50            | 3183 (5.9)   | 3123 (6.4)   | 60 (1.1)  | 1.0 (referent)       |           |
| 50-55            | 4745 (8.8)   | 4615 (9.5)   | 130 (2.4) | 1.38 (1.00 - 1.89)   | 0.05      |
| 55-60            | 5281 (9.8)   | 5040 (10.3)  | 241 (4.5) | 2.02 (1.50 - 2.71)   | 3.2E-06 * |
| 60-65            | 6181 (11.4)  | 5758 (11.8)  | 423 (7.9) | 2.80 (2.11 - 3.72)   | <1.0E-08 *|
| 65-70            | 6110 (11.3)  | 5414 (11.1)  | 696 (13.1)| 4.15 (3.14 - 5.48)   | <1.0E-08 *|
| 70-75            | 9020 (16.7)  | 7665 (15.7)  | 1355 (25.4)| 5.63 (4.28 - 7.41)   | <1.0E-08 *|
| 75-80            | 5677 (10.5)  | 4629 (9.5)   | 1048 (19.7)| 7.14 (5.40 - 9.44)   | <1.0E-08 *|
| 80 or greater    | 4202 (7.8)   | 2908 (6.0)   | 1294 (24.3)| 13.1 (9.85 - 17.3)   | <1.0E-08 *|
| **Race (%)**     |         |            |        |                       |           |
| American Indian or Alaska Native | 436 (0.8)  | 396 (0.8)   | 40 (0.8) | 1.06 (0.71 - 1.56)   | 0.78     |
| Asian            | 859 (1.6)   | 824 (1.7)   | 35 (0.7) | 0.88 (0.59 - 1.32)   | 0.54     |
| Black or African American | 15308 (28.3) | 14009 (28.7) | 1299 (24.4)| 0.96 (0.89 - 1.05)   | 0.39     |
| Native Hawaiian or other Pacific Islander | 580 (1.1)  | 536 (1.1)   | 44 (0.8) | 0.93 (0.65 - 1.34)   | 0.71     |
| White            | 32713 (60.4) | 29112 (59.6) | 3601 (67.5)| 1.0 (referent)       |           |
| Unknown          | 4268 (7.9)  | 3954 (8.1)  | 314 (5.9) | 0.95 (0.82 - 1.11)   | 0.54     |
| **Ethnicity Hispanic/Latino (%)** |       |            |        |                       |           |
| Hispanic or Latino | 5442 (10.0) | 5030 (10.3) | 412 (7.7) | 1.13 (1.00 - 1.29)   | 0.05     |
| Not Hispanic or Latino | 45641 (84.3) | 40919 (83.8) | 4722 (88.5)| 1.0 (referent)       |           |
| Unknown          | 3081 (5.7)  | 2882 (5.9)  | 199 (3.7) | 1.01 (0.83 - 1.22)   | 0.94     |
| **US Region (%)** |       |            |        |                       |           |
| Continental      | 8636 (15.9) | 7663 (15.7) | 973 (18.2)| 1.26 (1.13 - 1.40)   | 2.0E-05 *|
| Midwest          | 10398 (19.2) | 9298 (19.0) | 1100 (20.6)| 1.01 (0.91 - 1.12)   | 0.83     |
| North Atlantic   | 11767 (21.7) | 10654 (21.8) | 1113 (20.9)| 1.05 (0.95 - 1.16)   | 0.37     |
| Pacific          | 10037 (18.5) | 9178 (18.8) | 859 (16.1)| 0.99 (0.89 - 1.11)   | 0.92     |
| Southeast        | 11891 (22.0) | 10618 (21.7) | 1273 (23.9)| 1.0 (referent)       |           |
| Unknown          | 1435 (2.6)  | 1420 (2.9)  | 15 (0.3)  | 0.29 (0.16 - 0.53)   | 6.7E-05 *|
| **Period of dominant variant (%)** |       |            |        |                       |           |
| Pre-delta period | 1560 (2.9)  | 1204 (2.5)  | 356 (6.7) | 1.0 (referent)       |           |

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| Delta period | 14235 (26.3)  | 11825 (24.2)  | 2410 (45.2)  | 0.97 (0.80 - 1.18) | 0.78 |
|-------------|--------------|--------------|------------|------------------|-----|
| Omicron period | 38369 (70.8)  | 35802 (73.3)  | 2567 (48.1)  | 0.45 (0.37 - 0.56) | <1.0E-08 |
| History of infection before vaccinated (%) | 2122 (3.9)  | 1915 (3.9)  | 207 (3.9)  | 0.73 (0.61 - 0.88) | 8.5E-04 |
| Months since full vax at breakthrough (%) | 6089 (11.2)  | 5375 (11.0)  | 714 (13.4)  | 1.0 (referent) | 0.01 |
| 4 or less | 3473 (6.4)  | 3016 (6.2)  | 457 (8.6)  | 1.33 (1.12 - 1.57) | 0.001 |
| 5-6 | 3934 (7.3)  | 3346 (6.9)  | 588 (11.0)  | 1.09 (0.93 - 1.29) | 0.29 |
| 6-7 | 4244 (7.8)  | 3657 (7.5)  | 587 (11.0)  | 1.15 (0.97 - 1.36) | 0.10 |
| 7-8 | 5464 (10.1)  | 4951 (10.1)  | 513 (9.6)  | 1.29 (1.09 - 1.53) | 0.003 |
| 8-9 | 9310 (17.2)  | 8736 (17.9)  | 574 (10.8)  | 1.35 (1.14 - 1.60) | 4.3E-04 |
| 9-10 | 9193 (17.0)  | 8511 (17.4)  | 682 (12.8)  | 1.41 (1.18 - 1.68) | 1.2E-04 |
| 10-11 | 8167 (15.1)  | 7395 (15.1)  | 772 (14.5)  | 1.50 (1.25 - 1.80) | 1.3E-05 |
| 11-12 | 3710 (6.8)  | 3328 (6.8)  | 382 (7.2)  | 1.75 (1.42 - 2.15) | 1.1E-07 |
| 12 or more | 580 (1.1)  | 516 (1.1)  | 64 (1.2)  | 1.81 (1.27 - 2.58) | 0.001 |
| Months since boosted at breakthrough (%) | 38038 (70.2)  | 33869 (69.4)  | 4169 (78.2)  | 1.0 (referent) | 0.01 |
| Not boosted | 2595 (4.8)  | 2422 (5.0)  | 174 (3.3)  | 0.55 (0.46 - 0.66) | <1.0E-08 |
| 1 or less | 3113 (5.7)  | 2942 (6.0)  | 171 (3.2)  | 0.45 (0.38 - 0.55) | <1.0E-08 |
| 1-2 | 5230 (9.7)  | 4907 (10.0)  | 323 (6.1)  | 0.43 (0.37 - 0.50) | <1.0E-08 |
| 2-3 | 3410 (6.3)  | 3097 (6.3)  | 313 (5.9)  | 0.54 (0.46 - 0.63) | <1.0E-08 |
| 3-4 | 1078 (2.0)  | 957 (2.0)  | 121 (2.3)  | 0.55 (0.43 - 0.70) | 9.01E-07 |
| 4-5 | 309 (0.6)  | 218 (0.4)  | 91 (1.7)  | 0.72 (0.49 - 1.07) | 0.11 |
| 5-6 | 233 (0.4)  | 167 (0.3)  | 66 (1.2)  | 0.76 (0.49 - 1.17) | 0.21 |
| 6 or more | 627 (1.2)  | 560 (1.1)  | 67 (1.3)  | 0.65 (0.43 - 1.00) | 0.05 |
| Immune-suppressive medications before breakthrough (%) | 1353 (2.5)  | 1045 (2.1)  | 308 (5.8)  | 1.18 (0.99 - 1.40) | 0.07 |
| Before breakthrough Chemotherapy | 3518 (6.5)  | 2613 (5.4)  | 905 (17.0)  | 2.54 (2.29 - 2.82) | <1.0E-08 |
| Before breakthrough Cytokine-blocking | 958 (1.8)  | 718 (1.5)  | 240 (4.5)  | 2.42 (1.91 - 3.07) | <1.0E-08 |
| Before breakthrough Glucocorticoids | 309 (0.6)  | 218 (0.4)  | 91 (1.7)  | 1.85 (1.24 - 2.76) | 0.002 |
| Before breakthrough Lymphocyte-depleting | 233 (0.4)  | 167 (0.3)  | 66 (1.2)  | 0.76 (0.49 - 1.17) | 0.21 |
| Before vaccine Chemotherapy | 627 (1.2)  | 560 (1.1)  | 67 (1.3)  | 0.65 (0.43 - 1.00) | 0.05 |
| Before vaccine Cytokine-blocking | 1353 (2.5)  | 1045 (2.1)  | 308 (5.8)  | 1.18 (0.99 - 1.40) | 0.07 |
| Before vaccine Glucocorticoids | 679 (1.3)  | 545 (1.1)  | 134 (2.5)  | 0.80 (0.58 - 1.09) | 0.15 |
| Before vaccine Lymphocyte-depleting | 107 (0.2)  | 78 (0.2)  | 29 (0.5)  | 0.90 (0.45 - 1.78) | 0.75 |
| Persistent positive test (%) | 229 (0.4)  | 181 (0.4)  | 48 (0.9)  | 1.31 (0.92 - 1.86) | 0.14 |

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| Comorbidities (%) | Number (Percentage) | Number (Percentage) | Number (Percentage) | Number (Percentage) | p-value |
|-------------------|--------------------|--------------------|--------------------|--------------------|---------|
| Underweight       | 353 (0.7)          | 255 (0.5)          | 98 (1.8)           | 1.65 (1.23 - 2.22) | 9.4E-04 |
| Normal            | 7108 (13.1)        | 6065 (12.4)        | 1043 (19.6)        | 1.0 (referent)     |         |
| Overweight        | 16077 (29.7)       | 14622 (29.9)       | 1455 (27.3)        | 0.74 (0.67 - 0.82) | 1.8E-08 |
| Obesity I         | 15048 (27.8)       | 13728 (28.1)       | 1320 (24.8)        | 0.84 (0.76 - 0.94) | 0.002   |
| Obesity II        | 8248 (15.2)        | 7485 (15.3)        | 763 (14.3)         | 0.98 (0.86 - 1.10) | 0.69    |
| Severe Obesity    | 5073 (9.4)         | 4504 (9.2)         | 569 (10.7)         | 1.37 (1.20 - 1.57) | 6.0E-06 |
| Unknown           | 2257 (4.2)         | 2172 (4.4)         | 85 (1.6)           | 0.88 (0.67 - 1.15) | 0.34    |
| Acquired hypothyroidism | 2201 ( 4.1) | 1842 ( 3.8) | 359 ( 6.7) | 0.95 (0.82 - 1.10) | 0.47    |
| Anemic            | 12628 (23.3)       | 11673 (23.9)       | 955 (17.9)         | 0.97 (0.88 - 1.06) | 0.48    |
| Asthma            | 1713 ( 3.2)        | 1549 ( 3.2)        | 164 ( 3.1)         | 1.04 (0.85 - 1.26) | 0.72    |
| Atrial fibrillation | 2770 ( 5.1) | 2001 ( 4.1) | 769 (14.4) | 1.29 (1.15 - 1.44) | 1.9E-05 |
| Bipolar disorder  | 2972 ( 5.5)        | 2676 ( 5.5)        | 296 ( 5.6)         | 1.16 (0.99 - 1.36) | 0.07    |
| Chronic kidney disease | 5692 (10.5) | 4275 ( 8.8) | 1417 (26.6) | 1.64 (1.48 - 1.80) | <1.0E-08 |
| Chronic obstructive pulmonary disease and bronchiectasis | 3693 ( 6.8) | 2676 ( 5.5) | 1017 (19.1) | 1.63 (1.47 - 1.80) | <1.0E-08 |
| Colorectal cancer | 319 ( 0.6)         | 255 ( 0.5)         | 64 ( 1.2)          | 1.02 (0.73 - 1.43) | 0.90    |
| Depression        | 10761 (19.9)       | 9803 (20.1)        | 958 (18.0)         | 1.00 (0.90 - 1.10) | 0.95    |
| Diabetes          | 12310 (22.7)       | 10243 (21.0)       | 2067 (38.8)        | 1.25 (1.15 - 1.35) | 9.3E-08 |
| Epilepsy          | 529 ( 1.0)         | 414 ( 0.8)         | 115 ( 2.2)         | 1.55 (1.20 - 2.01) | 8.1E-04 |
| Heart failure     | 2684 ( 5.0)        | 1807 ( 3.7)        | 877 (16.4)         | 1.69 (1.50 - 1.90) | <1.0E-08 |
| HIV/AIDS          | 492 ( 0.9)         | 439 ( 0.9)         | 53 ( 1.0)          | 1.32 (0.93 - 1.86) | 0.12    |
| Hyperlipidemia    | 14228 (26.3)       | 12324 (25.2)       | 1904 (35.7)        | 0.85 (0.79 - 0.93) | 2.9E-04 |
| Hypertension      | 18346 (33.9)       | 15488 (31.7)       | 2858 (53.6)        | 1.08 (1.00 - 1.18) | 0.06    |
| Ischemic heart disease | 5126 (9.5) | 4012 (8.2) | 1114 (20.9) | 0.96 (0.86 - 1.06) | 0.43    |
| Leukemias and lymphomas | 631 (1.2) | 455 (0.9) | 176 (3.3) | 1.71 (1.35 - 2.17) | 7.8E-06 |
| Liver disease: cirrhosis and other liver conditions except viral hepatitis | 2094 ( 3.9) | 1768 (3.6) | 326 (6.1) | 1.24 (1.07 - 1.45) | 0.005   |
| Lung cancer       | 410 ( 0.8)         | 281 ( 0.6)         | 129 ( 2.4)         | 1.60 (1.23 - 2.06) | 3.8E-04 |
| Mobility impairments | 565 (1.0) | 375 (0.8) | 190 (3.6) | 2.29 (1.83 - 2.86) | <1.0E-08 |
| Multiple sclerosis and transverse myelitis | 234 (0.4) | 192 (0.4) | 42 (0.8) | 2.44 (1.60 - 3.72) | 3.5E-05 |
| Peripheral vascular disease | 1521 (2.8) | 1100 (2.3) | 421 (7.9) | 1.13 (0.97 - 1.31) | 0.11   |
| Pressure and chronic ulcers | 676 (1.2) | 436 (0.9) | 240 (4.5) | 1.46 (1.19 - 1.80) | 3.3E-04 |
| Prostate cancer   | 2027 (3.7)         | 1689 (3.5)         | 338 (6.3)          | 0.88 (0.76 - 1.02) | 0.08    |
| Schizophrenia and other psychotic disorders | 1343 (2.5) | 1130 (2.3) | 213 (4.0) | 1.60 (1.33 - 1.92) | 4.7E-07 |
| Condition                        | Observed 1 | Expected 1 | Observed 2 | Expected 2 | OR (95% CI) | p-value |
|---------------------------------|------------|------------|------------|------------|-------------|---------|
| Tobacco use                     | 4256 (7.9) | 3709 (7.6) | 547 (10.3) | 1.34 (1.19 - 1.52) | 1.6E-06*   |
| Viral hepatitis                  | 754 (1.4)  | 623 (1.3)  | 131 (2.5)  | 0.96 (0.75 - 1.22) | 0.72       |
| Death from breakthrough infection| 772 (1.4)  | 0 (0.0)    | 772 (14.5) |             |             |

*Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.03 in this analysis. OR = odds ratio. CI = 95% confidence interval.
eTable 20. Subcohort of Patients Who Received the Moderna Vaccine, Data and Analysis

|                          | Overall | Non-severe | Severe | Multivariable OR (CI) | P (multi) |
|--------------------------|---------|------------|--------|-----------------------|-----------|
| **N**                    | 45530   | 41289      | 4241   |                       |           |
| **Sex (%)**              |         |            |        |                       |           |
| Male                     | 40717 (89.4) | 36586 (88.6) | 4131 (97.4) | 1.0 (referent) |           |
| Female                   | 4813 (10.6)  | 4703 (11.4)  | 110 (2.6)  | 0.59 (0.47 - 0.72) | 6.5E-07 a |
| **Age ranges (%)**       |         |            |        |                       |           |
| Less than 40             | 4626 (10.2)  | 4591 (11.4)  | 35 (0.8)   | 0.74 (0.44 - 1.23) | 0.25      |
| 40-45                    | 2257 (5.0)   | 2227 (5.4)   | 30 (0.7)   | 1.22 (0.71 - 2.07) | 0.47      |
| 45-50                    | 2268 (5.0)   | 2241 (5.4)   | 27 (0.6)   | 1.0 (referent)      |           |
| 50-55                    | 3602 (7.9)   | 3521 (8.5)   | 81 (1.9)   | 1.72 (1.09 - 2.70) | 0.02 a    |
| 55-60                    | 4218 (9.3)   | 4064 (9.8)   | 154 (3.6)  | 2.58 (1.68 - 3.94) | 1.4E-05 a |
| 60-65                    | 5238 (11.5)  | 4919 (11.9)  | 319 (7.5)  | 3.59 (2.38 - 5.41) | <1.0E-08 a|
| 65-70                    | 5209 (11.4)  | 4734 (11.5)  | 475 (11.2) | 4.80 (3.20 - 7.22) | <1.0E-08 a|
| 70-75                    | 8139 (17.9)  | 7111 (17.2)  | 1028 (24.2)| 6.68 (4.47 - 9.99) | <1.0E-08 a|
| 75-80                    | 5336 (11.7)  | 4505 (10.9)  | 831 (19.6)| 8.50 (5.66 - 12.8) | <1.0E-08 a|
| 80 or greater            | 4637 (10.2)  | 3376 (8.2)   | 1261 (29.7)| 15.0 (10.0 - 22.6) | <1.0E-08 a|
| **Race (%)**             |         |            |        |                       |           |
| American Indian or Alaska Native | 363 (0.8)   | 328 (0.8)   | 35 (0.8)   | 1.44 (0.96 - 2.16) | 0.08      |
| Asian                    | 577 (1.3)   | 561 (1.4)   | 16 (0.4)   | 0.69 (0.39 - 1.22) | 0.20      |
| Black or African American| 9178 (20.2) | 8559 (20.7) | 619 (14.6)| 0.91 (0.81 - 1.01) | 0.08      |
| Native Hawaiian or other Pacific Islander | 460 (1.0)   | 437 (1.1)   | 23 (0.5)   | 0.58 (0.34 - 0.99) | 0.05      |
| White                    | 31634 (69.5) | 28296 (68.5) | 3338 (78.7) | 1.0 (referent) |           |
| Unknown                  | 3318 (7.3)  | 3108 (7.5)  | 210 (5.0)  | 0.88 (0.73 - 1.05) | 0.15      |
| **Ethnicity Hispanic/Latino (%)** |         |            |        |                       |           |
| Hispanic or Latino       | 4742 (10.4) | 4466 (10.8) | 276 (6.5) | 0.91 (0.78 - 1.06) | 0.24      |
| Not Hispanic or Latino   | 38505 (84.6) | 34687 (84.0) | 3818 (90.0) | 1.0 (referent) |           |
| Unknown                  | 2283 (5.0)  | 2136 (5.2)  | 147 (3.5)  | 1.11 (0.89 - 1.38) | 0.35      |
| **US Region (%)**        |         |            |        |                       |           |
| Continental              | 7586 (16.7) | 6862 (16.6) | 724 (17.1) | 1.06 (0.94 - 1.20) | 0.32      |
| Midwest                  | 9220 (20.3) | 8204 (19.9) | 1016 (24.0)| 0.96 (0.86 - 1.08) | 0.50      |
| North Atlantic           | 9887 (21.7) | 8974 (21.7) | 913 (21.5)| 0.85 (0.76 - 0.96) | 0.007 a   |
| Pacific                  | 8057 (17.7) | 7393 (17.9) | 664 (15.7)| 0.93 (0.82 - 1.06) | 0.27      |
| Southeast                | 10068 (22.1) | 9149 (22.2) | 919 (21.7) | 1.0 (referent) |           |
| Unknown                  | 712 (1.6)   | 707 (1.7)   | 5 (0.1)    | 0.31 (0.13 - 0.77) | 0.01 a    |
| **Period of dominant variant (%)** |         |            |        |                       |           |
| Pre-delta period         | 1117 (2.5)  | 872 (2.1)   | 245 (5.8)  | 1.0 (referent) |           |

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| Delta period                      | 11809 (25.9) | 9968 (24.1) | 1841 (43.4) | 0.70 (0.56 - 0.89) | 0.003<sup>a</sup> |
|---|---|---|---|---|---|
| Omicron period                   | 32604 (71.6) | 30449 (73.7) | 2155 (50.8) | 0.40 (0.31 - 0.51) | <1.0E-08<sup>a</sup> |
| History of infection before vaccinated (%) | 1747 ( 3.8) | 1576 ( 3.8) | 171 ( 4.0) | 0.88 (0.72 - 1.07) | 0.20 |
| Months since full vax at breakthrough (%) | | | | | |
| 4 or less                        | 4006 ( 8.8) | 3537 ( 8.6) | 469 (11.1) | 1.0 (referent) |
| 4-5                               | 2487 ( 5.5) | 2203 ( 5.3) | 284 ( 6.7) | 1.07 (0.87 - 1.33) | 0.52 |
| 5-6                               | 3047 ( 6.7) | 2633 ( 6.4) | 414 ( 9.8) | 1.12 (0.92 - 1.38) | 0.27 |
| 6-7                               | 3492 ( 7.7) | 3054 ( 7.4) | 438 (10.3) | 1.24 (1.01 - 1.52) | 0.04 |
| 7-8                               | 4932 (10.8) | 4484 (10.9) | 448 (10.6) | 1.35 (1.10 - 1.64) | 0.003<sup>a</sup> |
| 8-9                               | 8236 (18.1) | 7672 (18.6) | 564 (13.3) | 1.27 (1.04 - 1.54) | 0.02<sup>a</sup> |
| 9-10                              | 9136 (20.1) | 8498 (20.6) | 638 (15.0) | 1.22 (0.99 - 1.49) | 0.06 |
| 10-11                             | 7132 (15.7) | 6459 (15.6) | 673 (15.9) | 1.56 (1.26 - 1.93) | 4.1E-05<sup>a</sup> |
| 11-12                             | 2772 ( 6.1) | 2492 ( 6.0) | 280 ( 6.6) | 1.72 (1.34 - 2.19) | 1.5E-05<sup>a</sup> |
| 12 or more                        | 290 ( 0.6) | 257 ( 0.6) | 33 ( 0.8) | 2.16 (1.38 - 3.40) | 7.9E-04<sup>a</sup> |
| Months since boosted at breakthrough (%) | | | | | |
| Not boosted                       | 33195 (72.9) | 29763 (72.1) | 3432 (80.9) | 1.0 (referent) |
| 1 or less                         | 2657 ( 5.8) | 2506 ( 6.1) | 151 ( 3.6) | 0.60 (0.49 - 0.72) | 1.7E-07<sup>a</sup> |
| 1-2                               | 4145 ( 9.1) | 3956 ( 9.6) | 189 ( 4.5) | 0.41 (0.35 - 0.49) | <1.0E-08<sup>a</sup> |
| 2-3                               | 3084 ( 6.8) | 2871 ( 7.0) | 213 ( 5.0) | 0.47 (0.40 - 0.57) | <1.0E-08<sup>a</sup> |
| 3-4                               | 1186 ( 2.6) | 1067 ( 2.6) | 119 ( 2.8) | 0.57 (0.45 - 0.72) | 3.7E-06 |
| 4-5                               | 664 ( 1.5) | 579 ( 1.4) | 85 ( 2.0) | 0.70 (0.52 - 0.93) | 0.01<sup>a</sup> |
| 5-6                               | 180 ( 0.4) | 157 ( 0.4) | 23 ( 0.5) | 0.76 (0.46 - 1.26) | 0.29 |
| 6 or more                         | 419 ( 0.9) | 390 ( 0.9) | 29 ( 0.7) | 0.77 (0.49 - 1.21) | 0.26 |
| Immune-suppressive medications before breakthrough (%) | | | | | |
| Before breakthrough Chemotherapy   | 398 ( 0.9) | 282 ( 0.7) | 116 ( 2.7) | 2.39 (1.77 - 3.23) | 1.3E-08<sup>a</sup> |
| Before breakthrough Cytokine-blocking | 682 ( 1.5) | 608 ( 1.5) | 74 ( 1.7) | 1.30 (0.88 - 1.93) | 0.19 |
| Before breakthrough Glucocorticoids | 3338 ( 7.3) | 2573 ( 6.2) | 765 (18.0) | 2.13 (1.90 - 2.37) | <1.0E-08<sup>a</sup> |
| Before breakthrough Leukocyte-inhibitory | 836 ( 1.8) | 619 ( 1.5) | 217 ( 5.1) | 2.57 (1.97 - 3.37) | <1.0E-08<sup>a</sup> |
| Before breakthrough Lymphocyte-depleting | 246 ( 0.5) | 164 ( 0.4) | 82 ( 1.9) | 1.60 (0.99 - 2.59) | 0.05 |
| Immune-suppressive medications before initial vaccination (%) | | | | | |
| Before vaccine Chemotherapy        | 173 ( 0.4) | 134 ( 0.3) | 39 ( 0.9) | 0.74 (0.45 - 1.23) | 0.25 |
| Before vaccine Cytokine-blocking   | 485 ( 1.1) | 443 ( 1.1) | 42 ( 1.0) | 0.77 (0.47 - 1.25) | 0.29 |
| Before vaccine Glucocorticoids     | 1154 ( 2.5) | 877 ( 2.1) | 277 ( 6.5) | 1.51 (1.26 - 1.82) | 8.5E-06<sup>a</sup> |
| Before vaccine Leukocyte-inhibitory | 589 ( 1.3) | 472 ( 1.1) | 117 ( 2.8) | 0.81 (0.58 - 1.13) | 0.22 |
| Before vaccine Lymphocyte-depleting | 97 ( 0.2) | 58 ( 0.1) | 39 ( 0.9) | 2.31 (1.14 - 4.68) | 0.02<sup>a</sup> |
| Persistent positive test (%)       | 181 ( 0.4) | 133 ( 0.3) | 48 ( 1.1) | 1.95 (1.34 - 2.85) | 5.1E-04<sup>a</sup> |

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| Condition                                      | Underweight | Normal       | Overweight    | Obesity I     | Obesity II    | Severe Obesity | Unknown      | Comorbidities (%)                                                                 |
|------------------------------------------------|-------------|--------------|--------------|--------------|--------------|----------------|--------------|-----------------------------------------------------------------------------------|
| Underweight                                    | 261 (0.6)   | 192 (0.5)    | 69 (1.6)     | 1.41 (0.99 - 2.02) | 0.06         |                |              | Acquired hypothyroidism                                                            |
| Normal                                         | 5872 (12.9) | 4989 (12.1)  | 883 (20.8)   | 1.0 (referent) |              |                |              | Acute myocardial infarction                                                        |
| Overweight                                     | 13659 (30.0)| 12443 (30.1) | 1216 (28.7)  | 0.72 (0.64 - 0.80) | <1.0E-08     |                |              | Alzheimers disease and related disorders or senile dementia                       |
| Obesity I                                      | 13032 (28.6)| 12021 (29.1) | 1011 (23.8)  | 0.74 (0.65 - 0.83) | 3.7E-07      |                |              | Anemia                                                                            |
| Obesity II                                     | 6842 (15.0) | 6246 (15.1)  | 596 (14.1)   | 0.93 (0.81 - 1.07) | 0.32         |                |              | Anxiety disorders                                                                 |
| Severe Obesity                                 | 13032 (28.6)| 12021 (29.1) | 1011 (23.8)  | 0.74 (0.65 - 0.83) | 3.7E-07      |                |              | Asthma                                                                            |
| Unknown                                        | 1515 (3.3)  | 1464 (3.5)   | 51 (1.2)     | 0.79 (0.57 - 1.09) | 0.15         |                |              | Atrial fibrillation                                                              |
| Acquired hypothyroidism                        | 2301 (5.1)  | 1943 (4.7)   | 358 (8.4)    | 1.10 (0.95 - 1.27) | 0.22         |                |              | Bipolar disorder                                                                 |
| Acute myocardial infarction                    | 304 (0.7)   | 231 (0.6)    | 73 (1.7)     | 1.14 (0.81 - 1.60) | 0.44         |                |              | Chronic kidney disease                                                            |
| Alzheimers disease and related disorders or    | 1309 (2.9)  | 848 (2.1)    | 461 (10.9)   | 1.99 (1.72 - 2.31) | <1.0E-08     |                |              | Chronic obstructive pulmonary disease and bronchiectasis                          |
| senile dementia                                |             |              |              |              |              |                |              | Colorectal cancer                                                                |
| Anemia                                         | 3402 (7.5)  | 2650 (6.4)   | 752 (17.7)   | 1.25 (1.11 - 1.40) | 2.7E-04      |                |              | Depression                                                                       |
| Anxiety disorders                              | 10546 (23.2)| 9821 (23.8)  | 725 (17.1)   | 0.83 (0.74 - 0.93) | 0.001*       |                |              | Diabetes                                                                         |
| Asthma                                         | 1414 (3.1)  | 1299 (3.1)   | 115 (2.7)    | 0.87 (0.69 - 1.10) | 0.24         |                |              | Epilepsy                                                                         |
| Atrial fibrillation                            | 2587 (5.7)  | 1975 (4.8)   | 612 (14.4)   | 1.13 (1.00 - 1.28) | 0.06         |                |              | Heart failure                                                                    |
| Bipolar disorder                               | 2508 (5.5)  | 2255 (5.5)   | 253 (6.0)    | 1.35 (1.14 - 1.60) | 5.6E-04*     |                |              | HIV/AIDS                                                                         |
| Chronic kidney disease                         | 5041 (11.1) | 3993 (9.7)   | 1048 (24.7)  | 1.36 (1.22 - 1.52) | 2.0E-08*     |                |              | Hyperlipidemia                                                                   |
| Chronic obstructive pulmonary disease and      | 3827 (8.4)  | 2840 (6.9)   | 987 (23.3)   | 1.82 (1.64 - 2.02) | <1.0E-08*    |                |              | Ischemic heart disease                                                            |
| bronchiectasis                                 |             |              |              |              |              |                |              | Colorectal cancer                                                                |
| Colorectal cancer                              | 240 (0.5)   | 194 (0.5)    | 46 (1.1)     | 1.06 (0.72 - 1.55) | 0.77         |                |              | Depression                                                                       |
| Depression                                     | 9087 (20.0) | 8266 (20.1)  | 801 (18.9)   | 1.17 (1.05 - 1.31) | 0.005*       |                |              | Diabetes                                                                         |
| Diabetes                                       | 11381 (25.0)| 9708 (23.5)  | 1673 (39.4)  | 1.26 (1.16 - 1.38) | 2.4E-07*     |                |              | Epilepsy                                                                         |
| Epilepsy                                       | 435 (1.0)   | 355 (0.9)    | 80 (1.9)     | 1.57 (1.16 - 2.12) | 0.003*       |                |              | Heart failure                                                                    |
| Heart failure                                  | 2313 (5.1)  | 1594 (3.9)   | 719 (17.0)   | 1.78 (1.57 - 2.03) | <1.0E-08*    |                |              | Hypertension                                                                     |
| HIV/AIDS                                       | 305 (0.7)   | 282 (0.7)    | 23 (0.5)     | 1.29 (0.79 - 2.11) | 0.30         |                |              | Hyperlipidemia                                                                   |
| Hyperlipidemia                                 | 13758 (30.2)| 12241 (29.6) | 1517 (35.8)  | 0.76 (0.69 - 0.83) | <1.0E-08*    |                |              | Ischemic heart disease                                                            |
| Hypertension                                   | 16693 (36.7)| 14451 (35.0) | 2242 (52.9)  | 1.05 (0.96 - 1.15) | 0.32         |                |              | Leukemias and lymphomas                                                          |
| Ischemic heart disease                         | 4930 (10.8) | 3992 (9.7)   | 938 (22.1)   | 0.98 (0.88 - 1.09) | 0.70         |                |              | Liver disease: cirrhosis and other liver conditions except viral hepatitis       |
| Leukemias and lymphomas                        | 620 (1.4)   | 472 (1.1)    | 148 (3.5)    | 1.58 (1.23 - 2.02) | 3.1E-04*     |                |              | Lung cancer                                                                       |
| Liver disease: cirrhosis and other liver       | 1589 (3.5)  | 1357 (3.3)   | 232 (5.5)    | 1.46 (1.22 - 1.75) | 3.7E-05*     |                |              | Mobility impairments                                                             |
| conditions except viral hepatitis               |             |              |              |              |              |                |              | Multiple sclerosis and transverse myelitis                                       |
| Lung cancer                                    | 373 (0.8)   | 266 (0.6)    | 107 (2.5)    | 1.40 (1.06 - 1.86) | 0.02*        |                |              | Peripheral vascular disease                                                      |
| Mobility impairments                           | 380 (0.8)   | 288 (0.7)    | 92 (2.2)     | 1.73 (1.30 - 2.31) | 1.9E-04*     |                |              | Pressure and chronic ulcers                                                     |
| Multiple sclerosis and transverse myelitis      | 187 (0.4)   | 144 (0.3)    | 43 (1.0)     | 3.99 (2.62 - 6.06) | <1.0E-08*    |                |              | Prostate cancer                                                                  |
| Peripheral vascular disease                    | 1327 (2.9)  | 975 (2.4)    | 352 (8.3)    | 1.29 (1.10 - 1.52) | 0.002*       |                |              | Schizophrenia and other psychotic disorders                                       |
| Pressure and chronic ulcers                    | 542 (1.2)   | 358 (0.9)    | 184 (4.3)    | 1.57 (1.24 - 1.98) | 1.7E-04*     |                |              |                                                                           |
| Prostate cancer                                | 1551 (3.4)  | 1304 (3.2)   | 247 (5.8)    | 0.98 (0.83 - 1.16) | 0.81         |                |              |                                                                           |
| Schizophrenia and other psychotic disorders    | 1107 (2.4)  | 933 (2.3)    | 174 (4.1)    | 1.87 (1.53 - 2.28) | <1.0E-08*    |                |              |                                                                           |

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| Condition                        | Count (1.1) | Count (1.0) | Count (1.8) | OR (95% CI)       | *p*       |
|---------------------------------|-------------|-------------|-------------|-------------------|-----------|
| Tobacco use                     | 3657 (8.0)  | 3180 (7.7)  | 477 (11.2)  | 1.48 (1.30 - 1.68)| <1.0E-08  |
| Viral hepatitis                  | 504 (1.1)   | 427 (1.0)   | 77 (1.8)    | 1.04 (0.77 - 1.41)| 0.80      |
| Death from breakthrough infection| 646 (1.4)   | 0 (0.0)     | 646 (15.2)  |                   |           |

*a Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.03 in this analysis. OR = odds ratio. CI = 95% confidence interval.
# eTable 21. Subcohort of Patients With Rural Residence, Data and Analysis

|                  | Overall | Non-severe | Severe | Multivariable OR (CI) | P (multi) |
|------------------|---------|------------|--------|-----------------------|-----------|
| **N**            | 24572   | 21801      | 2771   |                       |           |
| **Sex (%)**      |         |            |        |                       |           |
| Male             | 22335   | 19649      | 2686   | 1.0 (referent)        |           |
| Female           | 2237    | 2152       | 85     | 0.93 (0.73 - 1.19)    | 0.58      |
| **Age ranges (%)** |        |            |        |                       |           |
| Less than 40     | 1915    | 1896       | 19     | 0.58 (0.31 - 1.10)    | 0.10      |
| 40-45            | 1031    | 1016       | 15     | 0.84 (0.43 - 1.65)    | 0.62      |
| 45-50            | 1216    | 1195       | 21     | 1.0 (referent)        |           |
| 50-55            | 1914    | 1866       | 48     | 1.28 (0.75 - 2.17)    | 0.36      |
| 55-60            | 2285    | 2183       | 102    | 2.06 (1.27 - 3.35)    | <1.0E-08  |
| 60-65            | 2626    | 2429       | 197    | 3.20 (2.01 - 5.09)    | 9.2E-07   |
| 65-70            | 2691    | 2398       | 293    | 4.36 (2.75 - 6.90)    | <1.0E-08  |
| 70-75            | 5199    | 4432       | 767    | 6.12 (3.90 - 9.59)    | <1.0E-08  |
| 75-80            | 3246    | 2650       | 596    | 8.20 (5.20 - 12.9)    | <1.0E-08  |
| 80 or greater    | 2449    | 1736       | 713    | 14.0 (8.82 - 22.1)    | <1.0E-08  |
| **Race (%)**     |         |            |        |                       |           |
| American Indian or Alaska Native | 247 (1.0) | 205 (0.9) | 42 (1.5) | 1.85 (1.23 - 2.77) | 0.003    |
| Asian            | 95 (0.4)| 94 (0.4)   | 1 (0.0)| 0.24 (0.03 - 1.78)   | 0.16      |
| Black or African American | 2834 (11.5) | 2629 (12.1) | 205 (7.4) | 0.91 (0.76 - 1.08) | 0.27      |
| Native Hawaiian or other Pacific Islander | 147 (0.6)   | 133 (0.6)  | 14 (0.5)| 0.59 (0.28 - 1.26)   | 0.17      |
| White            | 19817   | 17433      | 2384   | 1.0 (referent)        |           |
| Unknown          | 1432    | 1307       | 125    | 0.71 (0.56 - 0.90)    | 0.006    |
| **Ethnicity Hispanic/Latino (%)** | | | | | |
| Hispanic or Latino | 1049 (4.3) | 957 (4.4)  | 92 (3.3) | 1.33 (1.02 - 1.72)  | 0.03  |
| Not Hispanic or Latino | 22413 (91.2) | 19840 (91.0) | 2573 (92.9) | 1.0 (referent) | |
| Unknown          | 1110    | 1004       | 106    | 1.56 (1.20 - 2.04)    | 9.5E-04   |
| **US Region (%)**|         |            |        |                       |           |
| Continental      | 4368    | 3771       | 597    | 1.56 (1.20 - 2.04)    | 9.5E-04   |
| Midwest          | 6679    | 5976       | 703    | 1.56 (1.20 - 2.04)    | 9.5E-04   |
| North Atlantic   | 5705    | 5118       | 587    | 1.56 (1.20 - 2.04)    | 9.5E-04   |
| Pacific          | 2768    | 2498       | 270    | 1.56 (1.20 - 2.04)    | 9.5E-04   |
| Southeast        | 5052    | 4438       | 614    | 1.56 (1.20 - 2.04)    | 9.5E-04   |
| Unknown          | 247     | 205        | 42     | 1.56 (1.20 - 2.04)    | 9.5E-04   |
| **Period of dominant variant (%)** | | | | | |
| Pre-delta period | 738 (3.0) | 565 (2.6)  | 173 (6.2) | 1.0 (referent) | |
| Period          | Vaccine type (%) | History of infection before vaccinated (%) | Months since full vax at breakthrough (%) | Months since boosted at breakthrough (%) |
|-----------------|------------------|--------------------------------------------|------------------------------------------|-------------------------------------------|
| Delta period    |                  |                                            |                                          |                                           |
| Omicron period  |                  |                                            |                                          |                                           |
| Vaccine type (%)| Janssen          | 3076 (12.5)                                | 2016 (11.0)                              | 1230 (11.4)                               |
| Moderna         | 12470 (50.7)     | 11094 (50.9)                               | 9816 (49.7)                              | 7097 (49.7)                               |
| Pfizer          | 9026 (36.7)      | 7952 (36.5)                                | 1074 (38.8)                              | 717 (38.8)                                |
| History of infection before vaccinated (%) | 832 ( 3.4) | 744 ( 3.4) | 88 ( 3.2) | 0.56 (0.42 - 0.75) | 7.2E-05^a |
| Months since full vax at breakthrough (%) | 4 or less | 2810 (11.4) | 2410 (11.1) | 400 (14.4) | 1.0 (referent) |
| 4-5             | 1712 ( 7.0) | 1507 ( 6.9) | 205 ( 7.4) | 0.91 (0.72 - 1.15) | 0.44  |
| 5-6             | 2094 ( 8.5) | 1771 ( 8.1) | 323 (11.7) | 1.06 (0.86 - 1.32) | 0.58  |
| 6-7             | 2274 ( 9.3) | 1959 ( 9.0) | 315 (11.4) | 0.98 (0.79 - 1.22) | 0.86  |
| 7-8             | 2506 (10.2) | 2216 (10.2) | 290 (10.5) | 0.99 (0.80 - 1.24) | 0.96  |
| 8-9             | 3757 (15.3) | 3438 (15.8) | 319 (11.5) | 1.05 (0.84 - 1.32) | 0.64  |
| 9-10            | 4242 (17.3) | 3891 (17.8) | 351 (12.7) | 1.07 (0.84 - 1.35) | 0.59  |
| 10-11           | 3392 (13.8) | 3023 (13.9) | 369 (13.3) | 1.25 (0.97 - 1.61) | 0.08  |
| 11-12           | 1564 ( 6.4) | 1389 ( 6.4) | 175 ( 6.3) | 1.26 (0.94 - 1.69) | 0.12  |
| 12 or more      | 221 ( 0.9) | 197 ( 0.9) | 24 ( 0.9) | 1.43 (0.84 - 2.46) | 0.19  |
| Immune-suppressive medications before breakthrough (%) | Before breakthrough Chemotherapy | 239 (1.0) | 163 (0.7) | 76 (2.7) | 2.40 (1.62 - 3.56) | 1.4E-05^a |
|                 | Before breakthrough Cytokine-blocking | 399 (1.6) | 340 (1.6) | 59 (2.1) | 2.07 (1.30 - 3.31) | 0.002^a |
|                 | Before breakthrough Glucocorticoids | 2009 (8.2) | 1510 (6.9) | 499 (18.0) | 2.05 (1.79 - 2.35) | <1.0E-08^a |
|                 | Before breakthrough Leukocyte-inhibitory | 506 (2.1) | 371 (1.7) | 135 (4.9) | 2.71 (1.94 - 3.78) | <1.0E-08^a |
|                 | Before breakthrough Lymphocyte-depleting | 155 (0.6) | 109 (0.5) | 46 (1.7) | 1.74 (0.96 - 3.13) | 0.07  |
| Immune-suppressive medications before initial vaccination (%) | Before vaccine Chemotherapy | 106 (0.4) | 79 (0.4) | 27 (1.0) | 0.70 (0.37 - 1.33) | 0.28  |
|                 | Before vaccine Cytokine-blocking | 298 (1.2) | 264 (1.2) | 34 (1.2) | 0.54 (0.30 - 0.96) | 0.04  |
|                 | Before vaccine Glucocorticoids | 719 (2.9) | 562 (2.6) | 157 (5.7) | 1.13 (0.89 - 1.43) | 0.30  |
| Before vaccine Leukocyte-inhibitory | 354 (1.4) | 278 (1.3) | 76 (2.7) | 0.69 (0.46 - 1.05) | 0.08 |
|-------------------------------------|----------|----------|--------|-------------------|------|
| Before vaccine Lymphocyte-depleting | 59 (0.2) | 43 (0.2) | 16 (0.6) | 1.11 (0.45 - 2.75) | 0.82 |
| Persistent positive test (%)        | 110 (0.4) | 84 (0.4) | 26 (0.9) | 1.65 (1.02 - 2.68) | 0.04 |
| BMI Class (%)                       |          |          |        |                   |      |
| Underweight                         | 127 (0.5) | 91 (0.4) | 36 (1.3) | 1.43 (0.88 - 2.33) | 0.15 |
| Normal                              | 2872 (11.7) | 2383 (10.9) | 489 (17.6) | 1.0 (referent) |      |
| Overweight                          | 7074 (28.8) | 6334 (29.1) | 740 (26.7) | 0.69 (0.60 - 0.80) | 1.5E-06 |
| Obesity I                           | 7173 (29.2) | 6451 (29.6) | 722 (26.1) | 0.80 (0.69 - 0.93) | 0.004 |
| Obesity II                          | 4058 (16.5) | 3623 (16.6) | 435 (15.7) | 0.98 (0.83 - 1.17) | 0.85 |
| Severe Obesity                      | 2632 (10.7) | 2312 (10.6) | 320 (11.5) | 1.25 (1.03 - 1.51) | 0.02 |
| Unknown                             | 636 (2.6) | 607 (2.8) | 29 (1.0) | 0.79 (0.50 - 1.24) | 0.30 |
| Comorbidities (%)                   |          |          |        |                   |      |
| Acquired hypothyroidism             | 1397 (5.7) | 1157 (5.3) | 240 (8.7) | 0.99 (0.82 - 1.18) | 0.89 |
| Acute myocardial infarction         | 179 (0.7) | 130 (0.6) | 49 (1.8) | 1.07 (0.70 - 1.61) | 0.76 |
| Alzheimers disease and related disorders or senile dementia | 693 (2.8) | 450 (2.1) | 243 (8.8) | 1.75 (1.43 - 2.15) | 8.2E-08 |
| Anemia                              | 1830 (7.4) | 1381 (6.3) | 449 (16.2) | 1.21 (1.04 - 1.41) | 0.01 |
| Anxiety disorders                   | 5515 (22.4) | 4998 (22.9) | 517 (18.7) | 1.02 (0.89 - 1.17) | 0.78 |
| Asthma                              | 746 (3.0) | 669 (3.1) | 77 (2.8) | 0.90 (0.68 - 1.18) | 0.44 |
| Atrial fibrillation                 | 1645 (6.7) | 1270 (5.8) | 375 (13.5) | 0.93 (0.79 - 1.09) | 0.35 |
| Bipolar disorder                    | 1245 (5.1) | 1114 (5.1) | 131 (4.7) | 1.13 (0.89 - 1.43) | 0.32 |
| Chronic kidney disease              | 2647 (10.8) | 2004 (9.2) | 643 (23.2) | 1.45 (1.26 - 1.66) | 9.7E-08 |
| Chronic obstructive pulmonary disease and bronchiectasis | 2530 (10.3) | 1882 (8.6) | 648 (23.4) | 1.75 (1.54 - 1.99) | <1.0E-08 |
| Colorectal cancer                   | 141 (0.6) | 121 (0.6) | 20 (0.7) | 0.63 (0.35 - 1.12) | 0.11 |
| Depression                          | 4669 (19.0) | 4189 (19.2) | 480 (17.3) | 0.97 (0.84 - 1.13) | 0.70 |
| Diabetes                            | 6583 (26.8) | 5442 (25.0) | 1141 (41.2) | 1.32 (1.18 - 1.47) | 7.4E-07 |
| Epilepsy                            | 220 (0.9) | 183 (0.8) | 37 (1.3) | 1.28 (0.82 - 2.00) | 0.27 |
| Heart failure                       | 1393 (5.7) | 944 (4.3) | 449 (16.2) | 1.69 (1.43 - 1.99) | <1.0E-08 |
| HIV/AIDS                            | 82 (0.3) | 73 (0.3) | 9 (0.3) | 1.71 (0.78 - 3.79) | 0.18 |
| Hyperlipidemia                      | 7882 (32.1) | 6821 (31.3) | 1061 (38.3) | 0.82 (0.73 - 0.92) | 7.0E-04 |
| Hypertension                        | 9459 (38.5) | 7955 (36.5) | 1504 (54.3) | 1.09 (0.97 - 1.23) | 0.13 |
| Ischemic heart disease              | 3165 (12.9) | 2493 (11.4) | 672 (24.3) | 1.02 (0.89 - 1.16) | 0.79 |
| Leukemias and lymphomas             | 394 (1.6) | 300 (1.4) | 94 (3.4) | 1.37 (1.00 - 1.89) | 0.05 |
| Liver disease: cirrhosis and other liver conditions except viral hepatitis | 930 (3.8) | 809 (3.7) | 121 (4.4) | 1.07 (0.84 - 1.35) | 0.60 |
| Lung cancer                         | 211 (0.9) | 144 (0.7) | 67 (2.4) | 1.37 (0.95 - 1.99) | 0.10 |
| Mobility impairments                | 233 (0.9) | 164 (0.8) | 69 (2.5) | 2.10 (1.49 - 2.98) | 2.7E-05 |
| Multiple sclerosis and transverse myelitis | 110 (0.4) | 91 (0.4) | 19 (0.7) | 2.15 (1.16 - 3.99) | 0.01 |
|                               | Count (Rate) | Case (Rate) | Control (Rate) | OR (95% CI)          | P-value |
|-------------------------------|--------------|-------------|----------------|----------------------|---------|
| Peripheral vascular disease   | 792 (3.2)    | 563 (2.6)   | 229 (8.3)      | 1.31 (1.07 - 1.60)   | 0.009   |
| Pressure and chronic ulcers   | 333 (1.4)    | 207 (0.9)   | 126 (4.5)      | 1.64 (1.23 - 2.20)   | 8.6E-04 |
| Prostate cancer               | 855 (3.5)    | 709 (3.3)   | 146 (5.3)      | 0.95 (0.77 - 1.18)   | 0.64    |
| Schizophrenia and other psychotic disorders | 452 (1.8)    | 381 (1.7)   | 71 (2.6)       | 1.45 (1.06 - 1.98)   | 0.02    |
| Tobacco use                   | 2112 (8.6)   | 1810 (8.3)  | 302 (10.9)     | 1.44 (1.22 - 1.69)   | 1.5E-05 |
| Viral hepatitis                | 193 (0.8)    | 161 (0.7)   | 32 (1.2)       | 1.24 (0.78 - 1.98)   | 0.36    |
| Death from breakthrough infection | 458 (1.9)    | 0 (0.0)     | 458 (16.5)     |                      |         |

* Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.025 for this analysis. OR = odds ratio. CI = 95% confidence interval.
**eTable 22. Subcohort of Patients With Urban Residence, Data and Analysis**

|                        | Overall | Non-severe | Severe | Multivariable OR (CI) | P (multi) |
|------------------------|---------|------------|--------|-----------------------|-----------|
| **N**                  | 82350   | 74652      | 7698   |                       |           |
| **Sex (%)**            |         |            |        |                       |           |
| Male                   | 72204 (87.7) | 64804 (86.8) | 7400 ( 96.1) | 1.0 (referent) |           |
| Female                 | 10146 (12.3) | 9848 (13.2) | 298 ( 3.9) | 0.65 (0.57 - 0.75) | <1.0E-08 a |
| **Age ranges (%)**     |         |            |        |                       |           |
| Less than 40           | 10388 (12.6) | 10301 (13.8) | 87 ( 1.1) | 0.55 (0.41 - 0.75) | 1.8E-04 a |
| 40-45                  | 4783 ( 5.8) | 4716 ( 6.3) | 67 ( 0.9) | 0.83 (0.60 - 1.16) | 0.28      |
| 45-50                  | 4670 ( 5.7) | 4587 ( 6.1) | 83 ( 1.1) | 1.0 (referent) |           |
| 50-55                  | 7289 ( 8.9) | 7063 ( 9.5) | 226 ( 2.9) | 1.66 (1.28 - 2.15) | 1.6E-04 a |
| 55-60                  | 8161 ( 9.9) | 7795 (10.4) | 366 ( 4.8) | 2.19 (1.70 - 2.81) | <1.0E-08 a |
| 60-65                  | 9969 (12.1) | 9291 (12.4) | 678 ( 8.8) | 3.03 (2.38 - 3.85) | <1.0E-08 a |
| 65-70                  | 9407 (11.4) | 8375 (11.2) | 1032 (13.4) | 4.51 (3.56 - 5.72) | <1.0E-08 a |
| 70-75                  | 12877 (15.6) | 11044 (14.8) | 1833 (23.8) | 6.07 (4.80 - 7.67) | <1.0E-08 a |
| 75-80                  | 8179 ( 9.9) | 6779 ( 9.1) | 1400 (18.2) | 7.59 (5.98 - 9.63) | <1.0E-08 a |
| 80 or greater          | 6627 ( 8.0) | 4701 ( 6.3) | 1926 (25.0) | 13.6 (10.7 - 17.3) | <1.0E-08 a |
| **Race (%)**           |         |            |        |                       |           |
| American Indian or Alaska Native | 618 ( 0.8) | 573 ( 0.8) | 45 ( 0.6) | 1.09 (0.77 - 1.54) | 0.62      |
| Asian                  | 1362 ( 1.7) | 1307 ( 1.8) | 55 ( 0.7) | 0.90 (0.66 - 1.23) | 0.52      |
| Black or African American | 23112 (28.1) | 21180 (28.4) | 1932 (25.1) | 0.97 (0.90 - 1.04) | 0.34      |
| Native Hawaiian or other Pacific Islander | 920 ( 1.1) | 859 ( 1.2) | 61 ( 0.8) | 0.85 (0.63 - 1.15) | 0.30      |
| White                  | 49633 (60.3) | 44476 (59.6) | 5157 ( 67.0) | 1.0 (referent) |           |
| Unknown                | 6705 ( 8.1) | 6257 ( 8.4) | 448 ( 5.8) | 0.97 (0.85 - 1.10) | 0.62      |
| **Ethnicity Hispanic/Latino (%)** |         |            |        |                       |           |
| Hispanic or Latino     | 9526 (11.6) | 8907 (11.9) | 619 ( 8.0) | 1.00 (0.91 - 1.11) | 0.95      |
| Not Hispanic or Latino | 68231 (82.9) | 61437 (82.3) | 6794 (88.3) | 1.0 (referent) |           |
| Unknown                | 4593 ( 5.6) | 4309 ( 5.8) | 285 ( 3.7) | 0.95 (0.82 - 1.12) | 0.57      |
| **US Region (%)**      |         |            |        |                       |           |
| Continental            | 13603 (16.5) | 12318 (16.5) | 1285 (16.7) |           |           |
| Midwest                | 15036 (18.3) | 13430 (18.0) | 1606 (20.9) |           |           |
| North Atlantic         | 17739 (21.5) | 16145 (21.6) | 1594 (20.7) |           |           |
| Pacific                | 17213 (20.9) | 15782 (21.1) | 1431 (18.6) |           |           |
| Southeast              | 18759 (22.8) | 16977 (22.7) | 1782 (23.1) |           |           |
| Unknown                | 618 ( 0.8) | 573 ( 0.8) | 45 ( 0.6) |           |           |
| **Period of dominant variant (%)** |         |            |        |                       |           |
| Pre-delta period       | 2074 ( 2.5) | 1624 ( 2.2) | 450 ( 5.8) | 1.0 (referent) |           |
|                  | Delta period | Omicron period | Vaccine type (%) | History of infection before vaccinated (%) | Months since full vax at breakthrough (%) | Months since boosted at breakthrough (%) | Immune-suppressive medications before breakthrough (%) | Immune-suppressive medications before initial vaccination (%) |
|-----------------|--------------|----------------|------------------|--------------------------------------------|------------------------------------------|------------------------------------------|--------------------------------------------------------|----------------------------------------------------------|
| **Period**      | 20494 (24.9) | 17168 (23.0)   | 3326 (43.2)      | 1.04 (0.89 - 1.22)                         | 0.61                                     |                                           |                                                        |                                                          |
| **Vaccine type**|              |                |                  |                                            |                                          |                                           |                                                        |                                                          |
| Janssen         | 7674 (9.3)   | 6969 (9.3)     | 705 (9.2)        | 1.34 (1.21 - 1.49)                        | <1.0E-08                                  |                                           |                                                        |                                                          |
| Moderna         | 31681 (38.5) | 28884 (38.7)   | 2797 (36.3)      | 0.80 (0.75 - 0.84)                        | <1.0E-08                                  |                                           |                                                        |                                                          |
| Pfizer          | 42995 (52.2) | 38799 (52.0)   | 4196 (54.5)      | 1.0 (referent)                             | <1.0E-08                                  |                                           |                                                        |                                                          |
| **History**     |              |                |                  |                                            |                                          |                                           |                                                        |                                                          |
| Infection       | 3442 (4.2)   | 3121 (4.2)     | 321 (4.2)        | 0.80 (0.69 - 0.93)                        | 0.003                                    |                                           |                                                        |                                                          |
| Months since     |              |                |                  |                                            |                                          |                                           |                                                        |                                                          |
| Full vax at     | 9193 (11.2)  | 8099 (10.8)    | 1094 (14.2)      | 1.0 (referent)                             | <1.0E-08                                  |                                           |                                                        |                                                          |
| Breakthrough     | 1094 (14.2)  | 1094 (14.2)    | 1094 (14.2)      | 1.0 (referent)                             | <1.0E-08                                  |                                           |                                                        |                                                          |
| Before vaccine  | 59278 (72.0) | 53135 (71.2)   | 6143 (79.8)      | 1.0 (referent)                             | <1.0E-08                                  |                                           |                                                        |                                                          |
| **Initial**     |              |                |                  |                                            |                                          |                                           |                                                        |                                                          |
| Vaccine         | 316 (0.4)    | 230 (0.3)      | 86 (1.1)         | 0.86 (0.59 - 1.24)                        | 0.41                                     |                                           |                                                        |                                                          |
| **Immune**      |              |                |                  |                                            |                                          |                                           |                                                        |                                                          |
| Chemotherapy    | 758 (0.9)    | 525 (0.7)      | 233 (3.0)        | 2.55 (2.04 - 3.18)                        | <1.0E-08                                  |                                           |                                                        |                                                          |
| Cytokine-block  | 1166 (1.4)   | 1026 (1.4)     | 140 (1.8)        | 1.43 (1.06 - 1.92)                        | <1.0E-08                                  |                                           |                                                        |                                                          |
| Glucocorticoids | 5379 (6.5)   | 4076 (5.5)     | 1303 (16.9)      | 2.44 (2.24 - 2.66)                        | <1.0E-08                                  |                                           |                                                        |                                                          |
| Leukocyte-inhib  | 1396 (1.7)   | 1046 (1.4)     | 350 (4.5)        | 2.41 (1.96 - 2.96)                        | <1.0E-08                                  |                                           |                                                        |                                                          |
| Lymphocyte-deple | 421 (0.5)    | 291 (0.4)      | 130 (1.7)        | 1.97 (1.40 - 2.79)                        | 1.1E-04                                   |                                           |                                                        |                                                          |
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| BMI Class (%) | Before vaccine Leukocyte-inhibitory | Before vaccine Lymphocyte-depleting | Persistent positive test (%) | Comorbidities (%) |
|---------------|--------------------------------------|--------------------------------------|------------------------------|-------------------|
| Underweight   | 1001 (1.2) 808 (1.1) 193 (2.5)       | 0.84 (0.65 - 1.10)                  | 340 (0.4) 265 (0.4) 75 (1.0) | Acquired hypothyroidism 3443 (4.2) 2904 (3.9) 539 (7.0) |
| Normal        | 11099 (13.5) 9519 (12.8) 1580 (20.5) | 1.0 (referent)                     | 11099 (13.5) 9519 (12.8) 1580 (20.5) | Anemia 6155 (7.5) 4755 (6.4) 1400 (18.2) |
| Overweight    | 24588 (29.9) 22455 (30.1) 2133 (27.7) | 0.76 (0.70 - 0.82)                  | 24588 (29.9) 22455 (30.1) 2133 (27.7) | Anxiety disorders 19879 (24.1) 18481 (24.8) 1398 (18.2) |
| Obesity I     | 22889 (27.8) 21043 (28.2) 1846 (24.0) | 0.82 (0.75 - 0.90)                  | 22889 (27.8) 21043 (28.2) 1846 (24.0) | Asthma 2651 (3.2) 2419 (3.2) 232 (3.0) |
| Obesity II    | 12288 (14.9) 11213 (15.0) 1075 (14.0) | 1.00 (0.91 - 1.11)                  | 12288 (14.9) 11213 (15.0) 1075 (14.0) | Atrial fibrillation 4082 (5.0) 2974 (4.0) 1108 (14.4) |
| Severe Obesity| 7734 (9.4) 6936 (9.3) 798 (10.4)      | 1.33 (1.18 - 1.49)                  | 7734 (9.4) 6936 (9.3) 798 (10.4) | Bipolar disorder 4884 (5.9) 4378 (5.9) 506 (6.6) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Chronic kidney disease 8990 (10.9) 6902 (9.2) 2088 (27.1) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Chronic obstructive pulmonary disease and bronchiectasis 5716 (6.9) 4148 (5.6) 1568 (20.4) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Colorectal cancer 455 (0.6) 358 (0.5) 97 (1.3) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Depression 17170 (20.9) 15649 (21.0) 1521 (19.8) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Diabetes 19031 (23.1) 16066 (21.5) 2965 (38.5) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Epilepsy 838 (1.0) 665 (0.9) 173 (2.2) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Heart failure 3996 (4.9) 2703 (3.6) 1293 (16.8) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | HIV/AIDS 778 (0.9) 705 (0.9) 73 (0.9) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Hyperlipidemia 22868 (27.8) 20084 (26.9) 2784 (36.2) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Hypertension 28651 (34.8) 24508 (32.8) 4143 (53.8) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Ischemic heart disease 7701 (9.4) 6103 (8.2) 1598 (20.8) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Leukemias and lymphomas 916 (1.1) 675 (0.9) 241 (3.1) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Liver disease: cirrhosis and other liver conditions except viral hepatitis 3152 (3.8) 2663 (3.6) 489 (6.4) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Lung cancer 603 (0.7) 422 (0.6) 181 (2.4) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Mobility impairments 784 (1.0) 552 (0.7) 232 (3.0) |
| Unknown       | 3216 (3.9) 3092 (4.1) 124 (1.6)       | 0.90 (0.72 - 1.11)                  | 3216 (3.9) 3092 (4.1) 124 (1.6) | Multiple sclerosis and transverse myelitis 338 (0.4) 265 (0.4) 73 (0.9) |

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| Condition                                | Case Subjects | Control Subjects | Odds Ratio 95% CI | P-value |
|------------------------------------------|---------------|------------------|-------------------|---------|
| Peripheral vascular disease              | 2275 (2.8)    | 1654 (2.2)       | 1.19 (1.05 - 1.34) | 0.006*  |
| Pressure and chronic ulcers              | 1001 (1.2)    | 655 (0.9)        | 1.49 (1.26 - 1.77) | 4.2E-06* |
| Prostate cancer                          | 2913 (3.5)    | 2431 (3.3)       | 0.90 (0.80 - 1.02) | 0.10    |
| Schizophrenia and other psychotic disorders | 2234 (2.7)    | 1877 (2.5)       | 1.74 (1.51 – 2.00) | <1.0E-08* |
| Tobacco use                              | 7017 (8.5)    | 6123 (8.2)       | 1.34 (1.22 - 1.47) | <1.0E-08* |
| Viral hepatitis                          | 1197 (1.5)    | 998 (1.3)        | 0.90 (0.74 - 1.10) | 0.30    |
| Death from breakthrough infection         | 1079 (1.3)    | 0 (0.0)          | 1079 (14.0)       |         |

*Meets criteria for statistical significance after adjustment for multiple comparisons, P<0.03 in this analysis. OR = odds ratio. CI = 95% confidence interval.