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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	We used clinical data (existing health records) from patients of the US Veterans Affairs (VA) Healthcare System.
Data analysis	All analyses were conducted using SAS (Version 9.2, SAS Institute Inc., Cary, NC, USA).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The data supporting the findings of this study are not publicly available due to the inclusion of identifiable protected health information from the Veterans Health Administration. Privacy regulations prevent the open sharing of the individual-level data used in this study and any data covered under these regulations cannot be shared. The Veterans Health Administration may approve the sharing of some study data after verifying de-identification, though this may not include all final study

data. Each request is subject to approval by the ethics board, privacy office, and information systems and security office. For such requests, please contact the corresponding author.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	We reported on sex (Male or Female).
Reporting on race, ethnicity, or other socially relevant groupings	We reported on race (Black, White, or other race) and ethnicity (Hispanic or non-Hispanic).
Population characteristics	We reported on age (18–64, 65–74, >75 years), sex (male or female), race (Black, White, or other race), ethnicity (Hispanic or non-Hispanic), body mass index (BMI) categories (underweight, healthy weight, overweight, obese, missing), Charlson Comorbidity Index (0, 1, 2, 3, ≥ 4), receipt of influenza vaccine during the 2023–2024 season (yes or no), receipt of pneumococcal vaccine in the past 5 years (yes or no), encounters with the VA healthcare system in the year prior (intensive care unit admission, hospital admission, nursing home admission, ED visit, primary care visit; 0 or ≥1 for each), smoking status (current or former smoker or never smoker), immunocompromised (yes or no), Census region (Northeast, Midwest, South, or West), and prior documented SARS-CoV-2 infection.
Recruitment	As this was a retrospective study of existing health records, participant recruitment did not occur.
Ethics oversight	This study was determined to be exempt by the VA Providence Healthcare System (VAPHS) Institutional Review Board (IRB) and approved by the VAPHS Research and Development Committee.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	As this was a retrospective study of existing health records, the sample size was determined by the data source.
Data exclusions	Patients were excluded if they (1) did not have at least one visit to the VA Healthcare System in the previous 12 months, (2) had another prior positive SARS-CoV-2 test in the 90 days prior to their ARI episode, (3) received an XBB vaccine other than BNT162b2, (4) received BNT162b2 XBB vaccine within 8 weeks of a prior COVID-19 vaccine dose, (5) received BNT162b2 XBB vaccine within 14 days of prior to their ARI episode, (6) received BNT162b2 XBB vaccine but the date of administration was unknown, or (7) received a COVID-19 antiviral (nirmatrelvir/ritonavir, remdesivir, or molnupiravir) within 30 days prior to of their ARI episode. Patients could contribute more than one ARI episode to the study if the episodes were more than 30 days apart.
Replication	Replication was not used.
Randomization	This was a retrospective, observational study. Randomization was not used.
Blinding	This was a retrospective, observational study. Blinding was not used.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	Not applicable.
Study protocol	Not applicable.
Data collection	We assessed the effectiveness of the BNT162b2 XBB vaccine among adult patients ≥18 years of age diagnosed with an acute respiratory infection (ARI; see Supplemental Table 1) in the hospital, emergency department (ED), urgent care (UC), or outpatient setting (in-person or virtual) between September 25, 2023 and January 31, 2024. To be included, patients had to be tested for SARS-CoV-2 via nucleic acid amplification test (NAAT) or rapid antigen test (RAT) within 14 days prior through 3 days after the ARI encounter. All ARI encounters within a 30-day window were considered a single ARI episode and the encounter at the highest level of care (i.e., hospitalization > ED/UC visit > outpatient visit) was selected for inclusion (Supplemental Figure 1). Exclusions are noted above.
Outcomes	Three mutually exclusive ARI episode outcome categories were assessed: (1) hospital admission, (2) ED or UC visit (without subsequent hospital admission), and (3) outpatient visits (without a subsequent ED/UC visit or hospital admission). Within each ARI outcome category, cases were those with a positive SARS-CoV-2 NAAT or RAT result, and controls were those who tested negative.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*