Risk factors for severe COVID-19 in immunocompromised populations

v3, 14 July 2025

Github page

https://github.com/opensafely/covid-risk-immunocompromised

Background

Individuals with compromised immune systems are particularly vulnerable to the effects of SARS-CoV-2, and have endured a disproportionate burden of COVID-19-related morbidity and mortality throughout the course of the pandemic (Nab et al, *Lancet Public Health* 2023). Strategies to mitigate the risk of disease in these individuals have evolved over time. In the UK, key measures have included: (i) 'shielding' to reduce contact with potentially infected individuals; (ii) early eligibility for additional vaccine doses (including third primary and booster doses); and (iii) post-infection treatment with neutralising monoclonal antibodies and antiviral medicines to reduce the risk of disease progression. Given high rates of community transmission across multiple waves of the pandemic, exposure to one or more SARS-CoV-2 variants may also have induced natural immunity that interacts with the measures above to alter the risk of infection and severe disease in an immunocompromised individual.

Although several studies have assessed risk factors for COVID-19-related hospitalisation and mortality in the general population (Williamson et al, *Nature* 2020; Hippisley-Cox et al, *BMJ* 2023; Agrawal et al, *Lancet* 2022), studies focusing specifically on immunocompromised populations are lacking. In particular, the potential contribution of vaccination and natural immunity to the likelihood of severe disease remains a key knowledge gap.

Primary objective

Determine wave-specific risk factors for severe COVID-19 outcomes among immunocompromised individuals. Key factors of interest include vaccination status, era-specific natural infection, and clinical risk factors. Waves of interest include **wave 1 (WT)** from March 23 to May 30 2020; **wave 2 (alpha)** from Sep 7 2020 to April 24 2021; **wave 3 (delta)** from May 28 to Dec 14 2021; **wave 4 (omicron B.1.1.529)** from Dec 15 2021 to April 28 2022; and the **JN.1 wave** from Dec 04 2023 to March 31 2024.

Methods

(i) Data

The OpenSAFELY-TPP database covers 24 million people across GP surgeries using the TPP SystmOne software. Primary care data is linked directly with vaccination status via the National Immunisation Management System (NIMS), and can be linked (via NHS number) with: (i) A&E attendance and hospital records using NHS Digital's Hospital Episode Statistics (HES); (ii) COVID-19 testing records using Second Generation Surveillance System (SGSS); and (iii) national death registry records from the Office for National Statistics (ONS).

(ii) Population

Our study population will align with the definition of 'Immunosuppression' used in Table 3 of the Green Book. Five hierarchical subgroups of immunocompromised individuals will be established, as defined in **Table 1**. Populations will defined at the start of each wave: March 23 2020 for wave 1 (wt); Sep 7 2020 for wave 2 (alpha); May 28 2021 for wave 3 (delta); Dec 15 2021 for wave 4 (omicron); and Dec 04 2023 for the JN.1 wave[1].

Table 1: Eligibility for inclusion

Subgroup	Timescale	Codelists
(1) Solid organ transplant	Any prior code in primary care record	opensafely/other-organ-transplant/79caeeee opensafely/kidney-transplant/2020-07-15
(2) Bone marrow compromise, including haematologic malignancy or bone marrow transplant	Any prior code in primary care record	opensafely/haematological-cancer/2020-04-15 opensafely/bone-marrow-transplant/2020-04-15
(3) Active radiotherapy or chemotherapy	Any code in primary care record in the 6 months preceding index date	primis-covid19-vacc-uptake/dxt_chemo_cod/v2.5
(4) Active immunosuppressive medication*	Any code in primary care record in the 6 months preceding index date	primis-covid19-vacc-uptake/immrx/v2.5
(5) Primary or acquired immunodeficiency	Any prior code in primary care record	primis-covid19-vacc-uptake/immdx_cov/v2.5

* Prednisolone was included in vaccine prioritisation criteria in a dose-dependent manner. However, since it is not possible to calculate daily dose of prednisolone, individuals receiving this medication are not included, as per UK HSA Vaccination Uptake Reporting Specifications.

To avoid replication across subgroups, we will assign individuals hierarchically according to anticipated decreasing risk from (1) solid organ transplant to (5) primary or acquired immunodeficiency. This risk hierarchy is informed by a prior meta-analysis (Leston et al, *J Infect* 2024) and scoping review (Leston et al, Front Immunol 2025), alongside our previous cohort studies of COVID-19-related mortality in the general population (Williamson et al, *Nature* 2020; Nab et al, *Lancet Public Health* 2023).

[1] The start date of the JN.1 wave reflects the first date in which this variant became nationally dominant in UK Health Security Agency (UKHSA) genomic surveillance records while the end date follows the sustained reduction in COVID-19-related hospitalisations in March 2024 (based on UKHSA data dashboard).

(iii) Inclusion criteria

- ≥18 years of age at baseline;
- ≥1 indicator of moderate-to-severe immunosuppression (**Table 1**) at baseline.

(iv) Outcomes

- COVID-19-related hospitalisation or mortality;
- COVID-19-related mortality.

(v) Statistical analysis

This study will follow the statistical framework adopted in the wave-specific mortality paper conducted by Nab et al, 2023, with minor modifications. Risk will be assessed using Cox proportional hazards models with time since baseline as the time scale. All analyses will be stratified by immunocompromised subgroup, as defined in **Table 1**. Hazard ratios (HRs) and 95% CIs will be calculated for the following risk factors:

Demography

- Age (18–39; 40–49; 50–59; 60–69; 70–79; 80+);
- Sex (male, female);
- Ethnicity (White, Black, South Asian, Other);
- Index of multiple deprivation quintile;
- Care home residence;
- Smoking status (Never or unknown, previous, current)

Vaccination and infection history

- Vaccination status (0, 1, 2, 3+ doses; or 0–4, 5–6, or 7+ for JN.1 wave);
- Time since most recent vaccination (1–12 weeks, 13–26 weeks, 27 weeks+);
- Prior infection status (most recent record of infection across the following waves: wave 1, alpha, delta, omicron BA.1/BA.2, omicron BA.5/BA.6);
- Hybrid immunity (a composite of time since vaccination and era-specific infection)

Clinical comorbidities

- Other clinical comorbidities:
- Obesity (No obesity, class I [(30.0–34.9 kg/m^2], class II [35.0–39.9 kg/m^2], class III [≥40.0 kg/m^2]);
- Asthma (No asthma, with no oral steroid use, with oral steroid use)
- Diabetes (No diabetes, Controlled diabetes, Diabetes not controlled, No recent $HbA1_c$ measure);
- Chronic kidney disease (none, 3a, 3b, 4, 5, RRT [dialysis], RRT [transplant]);
- Hypertension (0, 1);
- Chronic respiratory disease (0, 1);
- Chronic cardiac disease (0, 1);
- Cancer (non-haematologic) (0, 1);
- Chronic liver disease (0, 1);
- Stroke (0, 1);
- Dementia (0, 1);
- Other neurological disease (0, 1);
- Asplenia (0, 1);
- Learning disability (0, 1);
- Severe mental illness (0, 1)
- Comorbidity count based on: chronic respiratory disease (including asthma); chronic cardiac disease; chronic kidney disease; chronic liver disease; chronic neurological disease (including learning disability); diabetes; asplenia; severe obesity; and severe mental illness.

For each covariate, we will assess: (i) baseline models adjusting for age (using a restricted cubic spline with four knots) and sex; (ii) extended models further adjusting for time since last vaccine dose and prior infection; and (iii) fully adjusted models further adjusting for ethnicity, deprivation quintile, and comorbidity count. All models will include region as a stratification variable to account for geographic variation in infection rates.

A sensitivity analysis will be conducted censoring on receipt of a subsequent vaccine dose to account for changes in immune status during the study period. Note that SARS-CoV-2 infection could also lead to a change in immune status, but is not appropriate as a censoring criterion given that the primary outcome is COVID-19-related hospitalisation or mortality.

Notes on protocol history

Version	Description of changes
v1, 28 November 2022	–
v2, 23 August 2023	Shift to wave-specific cohort approach given potential risk of collider bias by starting follow-up on date of positive test. The original approach is retained here as a secondary objective.
v3, 14 July 2025*	- JN.1 wave (Dec 04 2023 to March 31 2024) added to assess whether associations remain relevant to contemporary contexts. - Secondary objective on risk of progression dropped due to time constraints. - Broader categories adopted for ethnicity and time since vaccination to account for smaller size of several immunocompromised subgroups following hierarchical assignment. - Comorbidity count added as a composite variable combining clinical risk groups. - Fully adjusted models (further adjusting for ethnicity, deprivation quintile, and comorbidity count) added to support interpretation of hazard ratios (e.g., given potential confounding with vaccination status). - Definitions of prior infection status and hybrid immunity simplified to support harmonised implementation across waves.

* This is submitted as a *post-hoc* amendment to reflect code run between February and June 2024. The hierarchical assignment approach for immunocompromised subgroups was not included in protocol versions v1 or v2 but was specified prior to the implementation of statistical models from February 2024. Code is fully accessible on Github (https://github.com/opensafely/covid-risk-immunocompromised). Full logs of job requests for this project are available at: https://jobs.opensafely.org/risk-factors-for-covid-19-disease-progression-in-immunocompromised-populations/.