Risk factors for severe COVID-19 in immunocompromised populations

v2, 23 August 2023

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; and **wave 4 (omicron B.1.1.529)** from Dec 15 2021 to April 28 2022.

Secondary objective
Determine risk factors for severe COVID-19 outcomes among immunocompromised individuals infected with the Omicron variant between 26 December 2021 and 31 March 2022.

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. Four 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).

Table 1: Eligibility for inclusion

Condition	Timescale	Codelists
(1) Solid organ or bone marrow transplant	Any history at baseline	opensafely/other-organ-transplant/79caeeee opensafely/kidney-transplant/2020-07-15 opensafely/bone-marrow-transplant/2020-04-15
(2) Haematologic malignancy	Any history at baseline	opensafely/haematological-cancer/2020-04-15
(3) Primary or acquired immunosuppressive condition, or recent history of immunosuppressive medication*	Any history at baseline for conditions **Wave 1/2** Any medication exposure in 6 months before baseline **Wave 3/4** Any medication exposure since 01/07/2020**	primis-covid19-vacc-uptake/immdx_cov/v1 primis-covid19-vacc-uptake/immrx/v1
(4) Recent chemotherapy or radiotherapy	**Wave 1/2** Any medication exposure in 6 months before baseline **Wave 3/4** Any medication exposure since 01/07/2020**	primis-covid19-vacc-uptake/dxt_chemo_cod/v.1.5.3

* 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.

** Follows UK HSA Vaccination Uptake Reporting Specifications, which state that a look back period to 01/07/2020 is recommended to ensure that patients "whose latest immunosuppressant medication issue was originally within the [recommended] 6 month timescale but then subsequently exceeds it are still included in the at-risk group".

(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. Hazard ratios (HRs) and 95% CIs will be calculated for the following risk factors:

- Vaccination status (0, 1, 2, 3+ doses);
- Time since most recent vaccination (1–2 weeks, 3–12 weeks, 13–24 weeks, 24 weeks+);
- Era-specific SARS-CoV-2 exposure (WT only, Alpha only, Delta only, Alpha+prior, Delta+prior);
- Hybrid immunity dose response (0, 1, 2, 3, 4, 5+ where each vaccine dose and era-specific exposure counts as 1 unit);
- Age (18–39; 40–49; 50–59; 60–69; 70–79; 80+);
- Sex (male, female);
- Ethnicity (White, Black, Asian, Mixed, Other, Unknown);
- Index of multiple deprivation quintile;
- Care home residence;
- Immunosuppressive comorbidities:
    - Solid organ or bone marrow transplant (0, 1);
    - Haematologic malignancy (0, 1);
    - Immunosuppression (combining diagnostic conditions and recent medication) (0, 1);
    - Recent chemotherapy or radiotherapy (0, 1);
- 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]);
    - Smoking status (Never or unknown, previous, current);
    - 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).

For each covariate, we will explore minimally adjusted models (including age as restricted cubic splines with four knots and sex), stratified by region to account for geographic differences in infection rates. We will also fit models that additionally adjust for vaccination status and era-specific exposure to account for baseline immune status.

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	–
v3, 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.