Risk factors for COVID-19 disease progression in immunocompromised populations during the Omicron era

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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, *medRxiv* 2022). 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, *medRxiv* 2022; 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 disease progression remains a key knowledge gap.

Primary 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. Key factors of interest include dose-response effects of vaccination and era-specific natural infection.

Methods (Primary objective)

(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. This includes six key subgroups of immunocompromised individuals (**Table 1**). Notably, all individuals in this population would have been eligible to receive three COVID-19 vaccine doses prior to the study period of interest. **Baseline characteristics will be defined on the date of the first positive SARS-CoV-2 test between 26 December 2021 and 31 March 2022.**

Table 1: Eligibility for inclusion

Condition	Timescale	Codelists
(1) Solid organ transplant	Any history at baseline	opensafely/other-organ-transplant/79caeeee OR opensafely/kidney-transplant/2020-07-15
(2) Bone marrow transplant	Any history at baseline	opensafely/bone-marrow-transplant/2020-04-15
(3) Haematologic malignancy	Any history at baseline	opensafely/haematological-cancer/2020-04-15
(4) Primary or acquired immunosuppressive condition	Any history at baseline	primis-covid19-vacc-uptake/immdx_cov/v1
(5) Recent history of immunosuppressive medication*	Any exposure since 01/07/2020**	primis-covid19-vacc-uptake/immrx/v1
(6) Recent chemotherapy or radiotherapy	Any 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

- At least one positive SARS-CoV-2 test between 26 December 2021 and 31 March 2022;
- ≥18 years of age at baseline;
- ≥1 indicator of moderate-to-severe immunosuppression (**Table 1**) at baseline.

(iv) Outcomes

- All-cause hospitalisation or mortality;
- All-cause mortality.

Given that follow-up starts at the point of a positive SARS-CoV-2 test and the population is (by definition) moderately or severely immunosuppressed, all hospitalisation and mortality events will be assumed potentially COVID-19-related. For descriptive purposes, we will quantify the proportion of outcome events that include relevant ICD-10 codes for

(v) Statistical analysis

Risk factors will be assessed using Cox proportional hazards models with time since positive test 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);
- Era-specific SARS-CoV-2 exposure (WT only, Alpha only, Delta only, Alpha+prior, Delta+prior);
- Hybrid immunity dose response (0–2, 3, 4, 5, 6+ 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);
- Index of multiple deprivation quintile;
- Care home residence;
- Immunosuppressive comorbidities:
    - Solid organ transplant (0, 1);
    - 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:
    - Severe obesity (0, 1);
    - Diabetes (0, 1);
    - Chronic respiratory disease, including asthma (0, 1);
    - Chronic heart disease (0, 1);
    - Chronic kidney disease (none, 3a, 3b, 4, 5, RRT [dialysis/kidney transplant]);
    - Chronic liver disease (0, 1);
    - Asplenia (0, 1);
    - Chronic neurological disease (0, 1);
    - Learning disability (0, 1);
    - Severe mental illness (0, 1).

For each covariate, we will explore minimally adjusted models (including only age and sex) and adjusted models (additionally including vaccination status, era-specific exposure, ethnicity, IMD, care home residence, and immunosuppressive comorbidities).

(vi) Planned subgroup analyses

For the primary outcome (hospitalisation or death), we will perform the analyses above in the following subgroups:

- Solid organ or bone marrow transplant (combined due to low anticipated numbers);
- Haematologic malignancy;
- Immunosuppression (combining diagnostic conditions and recent medication);
- Recent chemotherapy or radiotherapy