Identifying the Adult Immunosuppressed Subgroups Most Vulnerable to Severe COVID-19 infection.



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By

Meredith Frances Leston

Linacre College, University of Oxford

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For the patients who have been so patient.

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Abstract

Introduction: Immunosuppressed individuals face higher risks for infections but are often excluded from clinical trials and poorly represented in disease surveillance. Meanwhile, inconsistent definitions of immunosuppression undermine research comparability, affecting therapy development and pharmacovigilance. These issues became critical during the COVID-19 pandemic; data extrapolated from the general population underserved the immunosuppressed and obscured subgroups at highest risk for adverse infection and vaccine outcomes.

Method: This thesis combines literature review, meta-analysis, international consensus building, and analysis of medical datasets to identify immunosuppressed subgroups at greatest risk for severe COVID-19. Reviews and meta-analysis quantified the diversity of immunosuppressed COVID-19 prognoses – evidence then utilised by international clinical experts to construct a novel COVID-19 risk stratified phenotype for extracting adult immunosuppressed cohorts from databases. Phenotype predictions for subgroup risk were tested against real-world evidence before a patient panel voted on its adoption into UK disease surveillance.

Results: Heterogeneity in COVID-19 severity was significant between and within immunosuppressed subgroups. While risk assessments evolved – increasingly emphasising PIDs, CKD and dialysis - the extreme vulnerability of transplantation and haematological or metastasising malignancy patients was consistent across outputs. Conversely, solid tumour, IMID, asplenia and drug-manged HIV patients and more transient forms of immunosuppression (anorexia, pregnancy, anaemia

etc.) showed relative resilience. The novel phenotype was ratified for UK disease surveillance.

Discussion: Within-subgroup differences in COVID-19 outcomes demonstrate the importance of disaggregating immunosuppressed data and looking beyond common clinical denominators when doing so. The novel phenotype accomplishes this but does not yet incorporate prescription data. Likewise, it is incapable of risk allocating comorbid immunosuppression and has not been tested internationally or outside of COVID-19.

Conclusion: This thesis identified the immunosuppressed subgroups most vulnerable to COVID-19. Its COVID-19 risk stratified phenotype produces higher resolution insights on immunosuppressed outcomes than was previously achievable. As such, this body of work represents a significant contribution to primary care research.

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Abbreviations:

A&E	Accident & Emergency
ACIP	Advisory Committee on Immunization Practices
ACP	Association of Clinical Psychologists
AHRQ	Agency for Healthcare Research and Quality
AI	Artificial Intelligence
AIDS	Acquired immunodeficiency syndrome
AIFELL	Altered sense of smell/taste, Inflammation, radiological Infiltrates, Fever, Elevated Lactate dehydrogenase, and Lymphocytopenia
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
ANCA	Antineutrophil cytoplasmic antibodies
aVE	Average vaccine effectiveness
BMA	British Medical Association
BMI	Body mass index
CAR-T	Chimeric antigen receptor T-cells
CCP-UK	Clinical Characterisation Protocol UK
CDC	Centers for Disease Control and Prevention
CEPI SAC	Coalition for Epidemic Preparedness Innovations Scientific Advisory Committee
CIHORG	Clinical Informatics and Health Outcomes Research Group
CKD	Chronic kidney disease
CMR	Computerised medical record
COVAD	COVID-19 Vaccination in Autoimmune Disease
COVID-19	Coronavirus disease of 2019
CPRD	Clinical Practice Research Datalink
CUREC	Central University Research Ethics Committee
CVD	Cardiovascular event diagnosis
DARS	Data Access Request Service
DESTINIES	eDELphi STudy to fully defINe and COVID-risk stratify ImmunosupprESsion
dm+d	Dictionary of Medicines and Devices
ECL	Expression Constraint Language
eDelphi	electronic Delphi
EMA	European Medicines Agency
EMBASE	Excerpta medica database
EPOCH	Emerging Populations and Outcomes associated with COVID-19-Health Conditions in the United States
ES	Effect Size
EULAR	European Alliance of Associations for Rheumatology
EULAR PARE	EULAR People with Arthritis/Rheumatism in Europe
GACVS	Global Advisory Committee on Vaccine Safety
GIHC	Global Immunocompromised Health Coalition

HES	Hospital Episode Statistics
HIV	Human immunodeficiency virus
IC	Immunocompetent
ICD-10	International Classification of Diseases, 10th Revision
ICU	Intensive care unit
ID	Identifiers
IMID	Immune-mediated inflammatory disorders
INFORM	INvestigation oF cOvid-19 Risk amongst iMmunoompromised
IR	Incidence rate
IRG	Internal Reference Group
IRR	Incidence rate ratio
IS	Immunosuppressed
ISARIC	International Severe Acute Respiratory and emerging Infections Consortium
JCVI	Joint Committee on Vaccination and Immunisation
LMIC	Low- or middle-income country
LRTI	Lower respiratory tract infection
LSHTM	London School of Hygiene and Tropical Medicine
MCAS	Mast Cell Activation Syndrome
ME/CFS	Myalgic encephalomyelitis/ chronic fatigue syndrome
MELODY	Mass Evaluation of Lateral Flow Immunoassays for the Detection of SARS-CoV-2 Antibody in Immunosuppressed People
MMR	Mumps, measles and rubella
mRNA	Messenger ribonucleic acid
MRP	Multilevel regression and poststratification
N antibodies	Nucleocapsid protein antibodies
NDM	Nuffield Department of Medicine
NDPCHS	Nuffield Department of Primary Care Health Sciences
NHS	National Health System
NIHR	National Institute of Health Research
NIMS	National Immunisation Management System
nMABs	Neutralising Monoclonal Antibodies
NPI	Non-pharmaceutical interventions
OCTAVE	Observational Cohort trial T cells, Antibodies and Vaccine Efficacy in SARS-CoV-2
ONS	Office of National Statistics
ORCHID	Oxford Clinical Information Digital Hub
ORCHID-E	ORCHID-Epidemiology
ORS	Objective Risk Stratification
Oxford-RCGP RSC	Oxford-Royal College General Practitioners Research and Surveillance Centre
PECO	Population, Exposure, Comparator, Outcome
PID	Primary immunodeficiency

POCT	Point of care testing
PPE	Personal Protective Equipment
PRIMDISC	Primary Care Hosted Research Datasets Independent Scientific Committee
PRIMIS	Primary Care Information Services
PRISMA	Preferred Reporting Items for Systematic Review and Meta Analysis
PROSPERO	International prospective register of systematic reviews
RAND	Research and development
RECAP	Remote COVID-19 Assessment in Primary Care
RECOVERY	Randomised Evaluation of COVID-19 ThERapY
RSV	Respiratory syncytial virus
SAGE	Scientific Advisory Group for Emergencies
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDoH	Social determinants of health
SGSS	Second Generation Surveillance System
SMD	Standard mean differences
SNOMED CT	Systematised Nomenclature of Medicine Clinical Terms
SOT	Solid organ transplantation
SQL	Structured Query Language
STRAVINSKY	Stratification of Clinically Vulnerable People for COVID-19 Risk Using Antibody Testing
SUS	Secondary Uses Service
T2D	Type 2 Diabetes
TADDS	Themes Access Dynamic Data Services
TNCC	Test-negative case control
TRE	Trusted Research Environment
UK	United Kingdom
UKHSA	United Kingdom Health Security Agency
USA	United States of America
VAERS	Vaccine Adverse Events Reporting System
WHO	World Health Organisation

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Structure of Thesis:

Chapter 1, *Introduction*: This introductory chapter establishes why this thesis is needed. It provides prerequisite information about the immunosuppressed as a population and what was known about their variable COVID-19 prognoses at the outset of this doctoral programme before outlining key evidence gaps, discrepancies and their collective consequences for effective clinical management, vaccination and non-pharmaceutical intervention internationally. It explains how the thesis will synthesise findings from literature review, meta-analysis, international consensus building, real-world evidence and patient engagement exercises to confirm highest-risk subgroups, stratify immunosuppressed COVID-19 surveillance accordingly and, in so doing, evidence the needs-based approach to immunosuppressed COVID-19 prevention and care that is urgently needed.

Chapter 2, *Is COVID-19 mortality compared to the immunocompetent capable of risk stratifying the adult immunosuppressed population? Output from rapid scoping and systematic literature reviews and meta-analysis:* This chapter examines whether the immunosuppressed COVID-19 medical literature is sufficiently detailed to capture and compare prognoses for all major subgroups; attempts using data from other infections for this purpose have failed. A case is made for using the disparity between immunosuppressed and immunocompetent COVID-19 mortality outcomes obtained in medical literature to risk stratify subgroups in disease surveillance dataflows.

H1: COVID-19 prognoses, namely excess mortality compared to the immunocompetent, can serve as a standardised metric to risk stratify the entire immunosuppressed population.

Chapter 3, *Can the Electronic Delphi (eDelphi) paradigm surface and ratify an internationally harmonised, COVID-19 risk stratified and computerised medical record (CMR) compatible phenotype for adult immunosuppression?* Addressing limitations of the previous chapter, this work sees a panel of international experts at the intersection of immunology, vaccinology and infectious disease build clinical consensus on the definition of immunosuppression and the COVID-19 risks of definition constituents. The DESTINIES phenotype that surfaces – internationally harmonised, COVID-19 risk stratified and CMR compatible - is approved for use in real-world disease surveillance dataflows.

H1: The eDelphi paradigm can build international clinical consensus on the diagnoses and procedures that confer immunosuppression in adults and their respective risks for severe COVID-19 outcomes to inform a new digital phenotype.

Chapter 4, *How do prototype digital phenotypes for adult immunosuppression perform in real-world infection and vaccination datasets? Output from the segmentation of linked and non-linked UK primary care data, secondary analysis of global surveys and a patient engagement exercise*: This chapter summarises all implementation studies performed over the course of the doctoral programme. Here we applied our pilot phenotype (based on rapid scoping review

findings) and final DESTINIES phenotype (based on eDelphi findings) to segment real-world COVID-19 vaccination and infection data. Their performance was assessed in turn with phenotype predictions for COVID-19 risk compared to real-world outcomes. DESTINIES phenotype outputs were then presented to a panel of immunosuppressed patients for approval. This tool is now ratified for ongoing use in disease surveillance by expert clinicians and patients alike - a unique accomplishment.

H1: Literature review and eDelphi consensus for COVID-19 risk in the immunosuppressed are consistent with real-world outcomes.

Chapter 5, *Discussion*: This concluding chapter summarises key thesis findings, how they compare to similar research initiatives and their implications, limitations and future potential. The immunosuppressed subgroups at greatest risk for severe COVID-19 outcomes are clarified and resultant recommendations for clinical management, vaccination and non-pharmaceutical intervention are outlined in full.

1

Introduction

This doctoral thesis sets out to identify the immunosuppressed subgroups most susceptible to severe COVID-19 infection through the following three methods: literature review, international consensus building and analysis of real-world data. In keeping with Centers for Disease Control and Prevention (CDC) guidelines, severe COVID-19 infection is classified here as that requiring hospitalisation, intensive care unit (ICU) admission, intubation, mechanical ventilation, or resulting in death [1]. This thesis only considers adult outcomes, defined as 18 years and over, and its commentary is UK-centric unless stated otherwise. Although retrospective in outlook, focusing on events that occurred within the acute phase of the COVID-19 pandemic (2020-2023, as per World Health Organisation [WHO] determination [2]), this work offers important and potentially transferable insights for immunosuppressed infection management moving forwards.

At this moment in time there is a dearth of comparative evidence available on differential COVID-19 severity in the immunosuppressed, and patient care – either in the form of COVID-19 prophylaxis or triage and treatment once infected – is impaired as a result [3]. What literature is available is muddied by ongoing disagreement on the very definition of immunosuppression and its constituent conditions and procedures [4]. Findings from discordant populations cannot be easily compiled or compared.

Working in parallel, the three workstreams specified will introduce an internationally aligned and computerised medical record (CMR) compatible means of defining and subdividing the immunosuppressed population to harmonise the contemporary research and surveillance landscape and pinpoint where severe COVID-19 outcomes are concentrated. This intelligence is sorely needed [5]. Irrespective of vaccine status, COVID-19 hospitalisation and mortality rates remain disproportionately high amongst immunosuppressed patients [6]. Only the targeted surveillance [5] and vaccination [7] that such work affords will be capable of addressing this ongoing burden.

This introductory chapter provides pre-requisite detail on immunosuppression, how the immunosuppressed were managed during the acute phase of the COVID-19 pandemic and the knowledge base and knowledge gaps that continue to surround their COVID-19 vaccination and infection outcomes. By addressing aspects of the latter, this thesis aims to supply new strategies for COVID-19 prevention and management in this clinical risk group – ensuring their ongoing proportionality to patient need.

1. Contested definitions and subdivisions of immunosuppression:

The term immunosuppression is generally accepted as referring to those patients who, either due to their current condition or treatment regimen, are less able to mount appropriate immune responses to infection and disease [8]. There has been substantial growth in this clinical risk group [9]. This is largely attributed to improved survival outcomes (the safety and effectiveness of pharmacological and procedural interventions have increased dramatically in recent decades) [10], though changes in

lifestyle [11], sanitation [12], environmental conditions and antimicrobial prescribing have also been implicated [13].

The exact criteria for immunosuppression are still debated, however [14]. As described by Cohen (2010),

'The term [immunosuppression] has no formal definition but embraces a group of overlapping conditions… it is helpful to think of such patients as falling into one of several distinct groups' [15].

In this, more expansive interpretations can host opposing aetiologies with immunodeficiencies (acquired or congenital) referenced alongside autoimmune, hyperinflammatory or immunoproliferative disorders [16]. More restrictive interpretations can instead demarcate medication-specific immunosuppressants from immunocompromising diagnoses [17; 18]. Definitions are also inconsistent in their inclusion of important modifiers, including disease progression or severity [19], drug management [20], time since last treatment [21], medication dosage (with or without factoring in patient age or weight)[16] and the demographic or lifestyle factors that exacerbate vulnerability (e.g. old age, comorbidity, polypharmacy, malnutrition, obesity, underweight and stress)[17].

These disagreements are visible between and within clinical guidelines. The United Kingdom's (UK) *Immunisation against infectious disease: The Green Book* [22] epitomises this inconsistency: the definition it offers for immunosuppression, its expansiveness, and its recognition of modifying variables, are markedly different to that of comparable national handbooks [23; 24; 25] and change between chapters [16; 26].

Attempts at population sizing reflect these internal debates. Depending on the criteria used, current estimates can range from 2% [9] to over 7% [27] of the general population. As a result, the composition of immunosuppressed cohorts differs substantially between studies [28]; this undermines the ability of policymakers, or the public at large, to account for or fully appreciate the scale of clinical risk in their communities [29].

Without a standardised definition, there is also no consistency in how the immunosuppressed patient spectrum and their infection outcomes are subdivided for higher resolution disease surveillance [27; 30]. Current options are usually categorical or binary in nature, anchoring on the deficiencies of specific immune organs or cells [31] or the intensity of immunosuppression (moderate vs severe) [32], its point of origination [33], its temporality (primary or secondary and transient or permanent [34]) and its medication- or condition-specific nature [35]. At present, no option is easily implementable within digital systems, however. These prospective points of segmentation are not amenable to codification or consistently identifiable in CMRs and can produce sample sizes that are underpowered for subgroup comparisons in epidemiological research [36].

Efforts to distinguish immunosuppressed subgroups through continuous measures have proven just as challenging due to the internal heterogeneity of these conditions. Even amongst patients with the same diagnosis, there is often very little consistency between genotypic profile, biological sampling results and the extent of immune dysfunction, symptomology, or prognosis [37]. This makes any net score of immunosuppression [38] incredibly difficult to calculate with confidence, to use

comparatively between or within patient types, and by extension, to implement in CMRs. Biometric means of subdivision are undermined by the same logic. Despite the many candidates presented in Table 1.1 [39], there remains no standardised test to confirm, codify and compare immune health between timepoints and patients [40].

Table 1.1: Tabulated summary of biometric approaches to diagnosing and differentiating levels of immunosuppression as presented by Bright et al (2014)

Laboratory grouping	Test type	Diagnostic capability
Biochemistry	Immunoglobulins	Autoimmunity Immunodeficiency (primary/secondary) Allergies Severity of coeliac disease Antibody deficiency
	Serum-free light chains	B-Cell malignancy
	Serum globulin gap	Antibody deficiency
	Serum protein electrophoresis	Antibody deficiency
Haematology	Lymphocyte count	Immunodeficiency (primary) Severe Combined Immune Deficiency (SCID) HIV/ HIV progression
	Monocyte count	HPV Myobacterial infection Myeloid leukaemia
	Platelet count	Immunodeficiency HIV Primary Immunodeficiency (PID) Common variable immune deficiency (CVID)
	Platelet volume	Wiskott-Aldrich syndrome
Blood transfusion testing	Reverse crossmatch	Cancer
Genetics	Cytogenetics	T-cell deficiency SCID
Microbiology/virology	Specific vaccine responses	Poor seroconversion/ seronegativity Antibody deficiencies T-Cell deficiencies Complement deficiencies
	Histopathology	PIDs/CVID Crohn's disease Coeliac disease

Attempts to subdivide the immunosuppressed are also thwarted by ongoing uncertainties around immunopathology itself. Historically, immunology has

represented a ‘black box’ in medicine and loose metaphors for immune function and dysfunction – ordinarily militaristic [41], mnemonic [42], locomotive [43] or linguistic [44; 45] – proliferated where scientific evidence was sparse. Lab-based discoveries of recent decades have only added to these uncertainties, however. For example, new evidence for an integrated human immune system - cross talking with endocrine and nervous systems [46] - may represent a step forward from crude demarcations between innate and adaptive systems and the former dominance of mice models [47] but have only complicated attempts at immune mapping. The absence of the immunosuppressed from largescale clinical trials [30; 48; 49] entrenches these knowledge gaps.

All the above obstructs our ability to measure and monitor the true burden of a given disease in the immunosuppressed, their vulnerability to adverse infection or pharmaceutical outcomes and heterogeneity within all these domains across the patient spectrum [28]. Without a standardised and digitally compatible approach to defining an immunosuppressed cohort and segmenting their health outcomes meaningfully, researchers have conventionally restricted comparative analysis to dominant subgroups [50], returning under-powered results with wide confidence intervals [51], or have defaulted to aggregated analysis [5], risking the erasure of sub-trends of clinical importance in the process [5]. Ambitions for targeted care and health equity will not be achieved until this challenge is resolved: at present, insufficient evidence is available for the needs-based prioritisation of economic support and medical supplies within the immunosuppressed population [52] and insufficient resources are available [53] to guarantee ongoing provision for all patients concerned, especially in times of international emergency [54].

2. Relevance to the COVID-19 pandemic:

The COVID-19 pandemic is a germane example of how a poorly defined and undifferentiated immunosuppressed clinical risk group can obfuscate those most or least vulnerable to infection and lead to inefficiencies of care and adverse patient outcomes as a result. This chapter will now outline the COVID-19 pandemic experience of the immunosuppressed, highlighting instances of underservice before summarising how this thesis has been structured to provide resolution.

In many respects, the emergence of the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus and resultant COVID-19 pandemic has served as a catalyst for more targeted research of the immunosuppressed [55]. The pandemic elicited an unparalleled level of international collaboration [56] and protecting the vulnerable has remained a unifying, if imperfectly executed [57], priority even beyond its acute phase [16]. Global investments into community testing delivered an unprecedented scientific evidence base for the infection and vaccine outcomes of the immunosuppressed [58] – the accuracy, resolution, and timeliness of which enabled more rigorous disease surveillance than that achieved for comparable illnesses [59; 60].

Aggregated assessments consistently point to excess vulnerability in immunosuppressed COVID-19 cases. As per Singson and colleagues' (2022) COVID-NET initiative in the United States, these patients accounted for over 12% of all COVID-related hospitalisations recorded across multiple US sites [61] between 2020 and 2022; this inflated to 22% of COVID-19 hospitalisations, 28% of COVID-19 ICU admissions and 24% of COVID-19 deaths in similar analysis in the UK [62].

Incidences of complications from COVID-19 (e.g. pneumonia, secondary infection, thromboembolic disease, myocarditis, sepsis, acute respiratory distress syndrome and multi-organ failure) have also appeared disproportionately high when analysed at the immunosuppressed population level [50]. The characteristics of COVID-19 infection in hospitalised immunosuppressed patients are often atypical, however; work by Brehm and colleagues (2021) [63] confirmed these patients were younger than counterparts diagnosed with seasonal influenza and reported fewer comorbidities and higher adverse outcomes including extended hospital stay and in-hospital mortality.

Viral persistence is also pronounced in immunosuppressed patients - most notably amongst those experiencing B-cell dysfunction or depletion due to myeloma, lymphoma, or anti-CD19/20 chimeric antigen receptor T-cells (CAR-T) therapies [64]. Specific adaptations of the SARS-CoV-2 virus facilitate reservoirs of survival within the human body; reports of viral detection in the immunosuppressed over 200 days after their initial diagnosis are not unheard of as a result [65; 66]. This represents an ongoing capacity of certain immunosuppressed patients to infect others and to incubate disease variants with drug resistant potential [67; 68]. In recognition of these risks, CDC-recommended isolation times for immunosuppressed cases were extended from 10 to 20 days [69]. Drug redundancies have already occurred, however: Evusheld, a combination monoclonal antibody therapy previously ring-fenced for the clinically vulnerable, was discontinued in light of poor performance against the then dominant Omicron variant [70]. Resistance against Paxlovid, a combined antiviral, is also especially common in immunosuppressed populations [71].

This homogenised picture is at odds with subgroup analyses of immunosuppressed COVID-19 outcomes, however: once segmented, infections convert into significantly different hospitalisation, ICU admission and death outcomes [72; 73]. For example, minimal excess risk has often been reported in those with clinically supervised HIV and autoimmunity, whereas heightened vulnerability has been reported amongst patients with primary immunodeficiencies, active malignancies (most notably of a haematological nature) and transplant recipients of any kind [6; 73] – though dissenting data have been published even on this [74]. Likewise, the uniquely therapeutic effect of certain immunosuppressive medications for COVID-19 is hypothesised to put long-term recipients of these agents at a relative advantage [75]. Dexamethasone, tocilizumab and baricitinib are all newly established treatments for the hyperinflammatory stages of critical COVID-19 cases amongst all patient types; this compares to the increased vulnerability seen amongst those receiving anticancer therapies or immunomodulators [76]. Such a conflicting evidence base has led some researchers to question whether immunosuppression even promotes or protects against severe COVID-19 [75].

These are nuances that have yet to be evaluated systematically or, if corroborated, translated into targeted strategies for immunosuppressed COVID-19 prevention or care [73; 77; 78]. Instead, as we shall now see, universalised policies have become the default out of an abundance of caution and all those identified as immunosuppressed have been prioritised for shielding notices, accelerated medical triage and additional COVID-19 vaccine doses [78; 79]. Maintaining such a commitment has proven economically and socially fraught [80].

i. Clinical management of immunosuppressed patients:

Continuity of care for the immunosuppressed was not sufficiently protected in the acute phase of the COVID-19 pandemic [81]. Lockdown mandates curtailed patient access to both inpatient and outpatient facilities [82; 83] and specialist medical personnel were often redeployed to COVID-19 case management [84]. The resources that were ringfenced for immunosuppressed patients were also unequally distributed between populations [85; 86]. This was most observable in cancer care where, according to research by Cancer Research UK, cancer screening and surgical procedures were more disrupted than radiotherapy or chemotherapy [87]. At-home alternatives for immunosuppressive treatments were also scarce, with privileged access amongst the socioeconomically advantaged [88; 89].

Consequently, immunosuppressed patient engagement with healthcare systems declined significantly over the course of the pandemic. Just looking within the UK National Health System (NHS) between 2020-2021, planned admissions amongst the immunosuppressed decreased by 51%, outpatient appointments by 48%, Accident & Emergency (A&E) attendance by 42% and emergency admissions by 32% [90]. Participation in most clinical trials also halted [91]. Though hard to quantify in full, resulting increases in later-stage diagnosis, delayed interventions and preventable acute events have undoubtedly been harmful to overall patient prognoses [92].

Fearfulness around nosocomial infection has contributed to this poor engagement. Not without reason: work by Ponsford and colleagues [93] reported 1.3 times greater risk of mortality in the immunosuppressed from hospital-acquired COVID-19 infection

versus community-acquired disease. Furthermore, the transition to endemic COVID-19 has seen the discontinuation of many of the measures that did exist to mitigate nosocomial infection in the immunosuppressed [94]. Examples still in place include strategic scheduling or delaying of highly immunosuppressive protocols, scaling up at-home or telemedicine consultations and a needs-based approach to allocating in-person appointments – though these remain inconsistent and geographically selective [95]. Meanwhile, masking mandates, test and triage hubs and rigorous patient screening, quarantining, decontamination and general practice or hospital ward separation protocols are now only rarely implemented [96; 97; 98]. The prioritisation of Personal Protective Equipment (PPE) for healthcare workers and the extremely vulnerable has also been difficult to assure with periods of marked global shortage [99]. These inconsistencies have placed immunosuppressed patients at continued risk and insufficient effort has gone into identifying the subgroups that could benefit from ongoing access [52].

Looking beyond treatment provision and preventative measures, it is important to acknowledge areas where clinical practice has successfully adapted to support confirmed immunosuppressed COVID-19 patients. Indeed, it can sometimes be difficult to assess whether the elevated COVID-19 hospitalisations seen in these patients – reportedly 4.3-23 times higher than those without immunosuppression [100] - should be attributed to true excess vulnerability or lowered clinical thresholds for admission [101].

The introduction of COVID-19 risk score calculators and other algorithmic triage tools were key to this prioritisation. Those considered eligible for enhanced medical

supervision expanded drastically from their implementation [102]. Noteworthy examples include QCOVID [103], the British Medical Association's Objective Risk Stratification (ORS) tool [104], the AIFELL score (Altered sense of smell/taste, Inflammation, radiological Infiltrates, Fever, Elevated Lactate dehydrogenase, and Lymphocytopenia) [105], and the RECAP tool (Remote COVID-19 Assessment in Primary Care) [106]. However, these tools depend upon the digital maturity of the health system in question – thereby remaining unsuitable for nations without the infrastructure or data quality and quantity necessary to support them [102; 107; 108] – and often underperform when audited or implemented in real-world settings [109]. Mirroring stated criticisms of immunosuppressed definitions, crude inclusion and exclusion criteria have also seen certain immunosuppressed groups overtreated (e.g. prioritising an individual with a history of uncomplicated gestational diabetes over a current Type 2 Diabetic [110]) and others underserved, especially those with the atypical or muted COVID-19 presentations that are commonplace amongst certain patients [111]. The absence of the immunosuppressed from clinical trials has only exacerbated the limitations of these automated triage tools; current treatment algorithms generalise guidance from an almost exclusively immunocompetent evidence base [49].

Attempts to ringfence access to antiviral, monoclonal antibody, convalescent plasma and experimental therapeutics have proven just as problematic. Clinical guidelines have consistently recommended that these resources, sometimes scarce and expensive, be allocated on a needs-basis and thereby select for the immunosuppressed [112]. High dose, extended and repeat courses are also recommended for these patients in recognition of their propensity for prolonged

infection [113; 114; 115]. This has been difficult to achieve in practice, however, as resources are inequitably distributed and inconsistently available [116; 117]. Even the most well-resourced healthcare settings have struggled to release these medications to those who need them most: the ill-defined nature of immunosuppression has not translated well to the clinical support tools or decision-trees that dictate these prescriptions [118] and access is often determined by the medical literacy and agency of the patient [119]. As a result, immunosuppressed patients can still find themselves ineligible for these products – or unaware of their eligibility - and at risk of adverse infection outcomes that might have been avoided [120]. Targeted communications are needed to clarify medication eligibility for clinicians and patient alike [121; 122]; current efforts in this regard remain minimal, however [122]. Until this is addressed, only those with confidence navigating complex health systems will be able to benefit from them, perpetuating the inverse care law [119].

Despite sincere motivation to enhance clinical support and response, the above demonstrates that these efforts have been, and remain, piecemeal for protecting the immunosuppressed from COVID-19. Shifting definitions, low resolution data and the discontinuation of health protections continue to have significant negative consequences for immunosuppressed patient care and confidence.

ii. Vaccinating immunosuppressed patients against COVID-19:

The COVID-19 pandemic has proven a unique moment in vaccinology: the evolving nature of the virus and the scientific understanding underpinning it has resulted in a highly iterative approach to vaccination [123]. With vulnerable patients eligible for as

many as ten doses by the winter of 2024 [124], no other disease in human history has been inoculated against with such intensity [125; 126]. It remains to be seen whether this approach has curbed or exacerbated mutation risk, however [127].

Once available, the immunosuppressed were unanimously prioritised for vaccination against COVID-19 [128]. Best practice from immunosuppressed-specific vaccine campaigns has included bespoke timing (mitigating non-response if administered too close to highly immunosuppressive regimens), pacing (mitigating accelerated waning and risks for breakthrough infection), messaging (including targeted outreach, where possible) and wraparound immunisation for those that typically come into contact with immunosuppressed patients (family members, healthcare workers and full-time carers)[123; 129; 130].

Although initial uptake amongst the immunosuppressed in developed contexts was impressive [123; 131], maintaining adherence to booster vaccine scheduling has proven difficult over time [123]. A 2022 analysis of four-dose or five-dose uptake (the contemporary maximum) in a US immunosuppressed cohort revealed that only 41% had received four doses and 1% had received five doses [132]. Similar attrition was seen in the UK context, where poor communication and a haphazard approach to targeting the immunosuppressed delayed boosting [133]. Moreover, the absence of an established registry for immunosuppressed patients and the ever-changing definitions of the clinically vulnerable derailed attempts to automate outreach [133].

Socioeconomic inequalities have also contributed to these declines, with enormous racial disparities seen in vaccine uptake data [134]. Despite targeted outreach efforts

amongst black, Asian, and ethnic minority groups, coverage is comparatively far poorer than that achieved amongst white counterparts [134]. These ethnicity-specific health inequalities were also borne out in immunosuppressed data. Analysis of NHS England data by Blood Cancer UK revealed over 84% of white immunosuppressed people had taken up their booster dose when advertised; this compared to just 43% of eligible Pakistani patients [135]. Economic status has also proven a key determinant of uptake: vaccination demands an amount of disposable time and income that many cannot afford to give – especially the unemployed, uninsured or those without reliable means of transportation [136]. Only the most economically advantaged nations were able to support their citizens to overcome these financial and geographical obstacles to inoculation [137; 138] – though with political support wavering and per unit vaccine prices increasing, subsidised access is at risk or highly constrained even in these contexts [139].

COVID-19 vaccine hesitancy is also not insignificant in the immunosuppressed. Recent work surveying those with immune-mediated inflammatory disease [140; 141] measured vaccine hesitancy or refusal at almost 50%. This runs in worrying contrast to their excess vulnerability to severe COVID-19 infection outcomes [142]. The most frequently cited reasons for COVID-19 vaccine refusal or hesitancy in the immunosuppressed are concerns around the exclusion of patients like themselves from vaccine development trials and resultant uncertainties around vaccine effectiveness, side effects or contraindications with existing medications [143]. These concerns are exacerbated by negative and often sensationalised media coverage of vaccine outcomes [144]. The increasing politicisation of vaccination has also

dissuaded many from taking up their invitation to vaccinate or boost their immunity [145].

We have seen some of these concerns to be justifiable. Immunosuppressed patients are indeed mostly absent from the vaccine development trials that determine if a candidate is fit for public use [48; 49]. This means that the safety of these products for the immunosuppressed are extrapolated from immunocompetent data in the first instance [48]. Once these products are released, post-marketing surveillance - including pharmacovigilance - still generally only handles immunosuppressed data at the aggregate level [5] or limits outcome comparisons to those between dominant subgroups [50]. This affects experts' ability to pinpoint the conditions at greatest risk for adverse events, poor immunogenicity, accelerated vaccine waning or breakthrough infection and, by extension, undermines decision-making on vaccine scheduling, dosing, boosting or replacement with passive alternatives [52].

The Observational Cohort trial T cells, Antibodies and Vaccine Efficacy in SARS-CoV-2 (OCTAVE) study [146] represents some of the most rigorous comparative efforts on seroconversion, however. Here, 89% of immunosuppressed participants were seen to generate anti-Spike antibodies in response to two doses of COVID-19 vaccine – 49% of which only achieved low levels of seroconversion. This compares to the 100% response rate recorded amongst immunocompetent controls. Broken down by disease type, poorest response was seen amongst 87% of Rituximab treated ANCA-Associated Vasculitis patients, 51% of inflammatory arthritis patients, 29% of Haemodialysis patients (though 42% of those on also receiving immunosuppressive therapy), 36% of patients with Hepatic disease, 10% of solid

cancer patients, 33% of Haematological malignancy patients, and 17% of haemopoietic stem cell transplant recipients. Although follow-up study (OCTAVE-DUO) indicated some resolution of these impaired results by the third dose, this too proved unstable across the patient spectrum with poor seroconversion still detectable amongst those with chronic kidney disease, lymphoid malignancy and B-cell targeted therapy recipients [147]. Comparable work in the vaccine effectiveness remit by Embi and colleagues (2021) [148] identified similar between-subgroup heterogeneity: effectiveness ranged from 81% in rheumatological disorders versus only 59% in organ or stem cell transplant recipients. These and many other indications of suboptimal immunogenicity in the immunosuppressed have created the impetus behind international booster campaigns for this group [149]. Such decisions remain poorly targeted, however [150], and potentially carry unchartered risks for immune exhaustion in this already vulnerable group [149].

What pharmacovigilance efforts do exist indicate that COVID-19 vaccines are extremely well-tolerated amongst the immunosuppressed [151]. Indeed, combined analysis of the Centers for Disease Control's V-Safe and Vaccine Adverse Events Reporting System (VAERS) suggests the immunosuppressed may in fact encounter less debilitation after receiving their COVID-19 vaccination than immunocompetent counterparts [152]. No unexpected or unusual reporting patterns were detected and fatigue, myalgia, and pain local to injection site were the most frequently experienced symptoms. Reports of debilitation to the point of being unable to perform daily activities or needing to seek out medical attention were also vanishingly rare in the immunosuppressed. Although still undifferentiated, work such as this is

demonstrative of the value of robust adverse event reporting systems and should be reassuring for patients themselves.

However, side effect reporting remains restricted to the few countries that have these systems instated. Data entry is currently dependent upon clinician or patient digital literacy and access [153] and is vulnerable to false reporting (intentional or otherwise) [154]. Non-uniformity in clinical coding undermines the interoperability of these systems [155] and reporting forms are often criticised for their length and lack of plain language [156]; this can discourage both doctors and patients alike from providing evidence [153]. Relatedly, serious adverse events are typically over-represented as there is little public or clinical motivation to report milder side effects [156]. Furthermore, despite being observed in as many as 15% of patients in a previous autoimmune cohort study [157], post-inoculation flares of pre-existing conditions are only ever detected in the most enhanced of pharmacovigilance systems [158]. Newer side effects can also go ignored until a critical threshold of evidence is reached [154]. Finally, these systems do not currently have the resolution to establish whether side effect symptomology, duration or severity differs within clinical risk groups [155]. Given that the immunosuppressed patient spectrum contains both immunoproliferative and immunodeficient patient profiles, this seems intuitively likely – though, at present, only evidenced by disparate safety profiling efforts [159; 160].

Collectively, these factors can result in an incomplete, inaccurate, or distorted view of the post-vaccine experience in the immunosuppressed. The widespread failings associated with the Indian COVID-19 vaccine safety system (misreported or non-reported side effects, improper oversight, poor follow-up by investigators, and low

self-reporting in the community) best exemplify these criticisms and demonstrate how improper, inaccessible, and undifferentiated vaccine surveillance can exacerbate, and not ameliorate, vaccine hesitancy in the vulnerable [161; 162].

The information summarised casts serious aspersions on COVID-19 vaccine benefit-risk in the immunosuppressed. Without precise information on vaccine effectiveness and adverse events, this cornerstone of medical ethics has not been achieved in the remit of COVID-19 for this population [163]. It is essential that those underserved by conventional courses of vaccination are identified and prioritised for boosting, passive immunisation, and enhanced medical support when a case is confirmed. Pharmacovigilance is insufficiently sophisticated to accommodate this at present.

iii. *Non-Pharmaceutical Interventions (NPIs) for the immunosuppressed:*

The diversity, stringency and global co-ordination of socioeconomic restrictions associated with the COVID-19 pandemic have been unprecedented [164]. As already stated, protecting the clinically vulnerable was a key justification for these mandates [56] - one that was generally accepted by the public and strengthened their cooperation with emergency legislation [165]. Maintaining these levels of goodwill and compliance has proven difficult, however, as contradictory policies, the prioritisation of economic recovery and general ‘COVID fatigue’ has eroded public support over time [166; 167;168]. Like the short-lived reforms seen in the clinical management of immunosuppressed patients, most of the non-pharmaceutical measures implemented for their benefit have either been discontinued or significantly rolled back [169; 170].

The non-pharmaceutical interventions (NPIs) most aligned to the interests of the immunosuppressed included shielding directives, working from home, community testing and the distribution of personal protective equipment (PPE) and pulse oximeters. Regardless of how short-lived their implementation, the success of these policies for minimising severe COVID-19 infection in the immunosuppressed will be evaluated in turn.

Where and when possible, shielding notices were instated to protect those presumed to be at highest risk for COVID-19 and to prevent health services from being overwhelmed (colloquially ‘flattening the curve’) [171]. Even Sweden, notable in its initial decision not to lockdown during peak periods of transmission, always mandated shielding for those in residential care settings [172]. In this, those deemed clinically vulnerable, including the immunosuppressed, were advised to self-isolate until community transmission stabilised [173]. They were required to remain in their homes and reduce all non-essential social contact – including that with household members [174]. To offset the pressures of isolation, several nations offered government subsidised delivery services for essential goods [175; 176] and stimulus payments for those unable to work remotely [174]. This proved impossible for resource-constrained nations to replicate, however [177].

In the UK, shielding was recommended for all immunosuppressed patients in the earliest phases of the pandemic, without exception, to maximise the safety of vulnerable patients in a time of uncertain risks [173]. The value of shielding has been contested by some, however. For example, in Scotland, declines seen to the incidence of COVID-19 were not statistically different between shielded and non-

shielded groups after the introduction of this policy [178]. Of even greater concern, work by Jani and colleagues (2021) [179] determined that UK shielded populations were in fact still eight times likelier to have confirmed infection than the low-risk population – though this may be attributable to disproportionate numbers of symptomatic cases and access to home testing amongst the shielded as opposed to isolation itself. The typically blanket nature of shielding invitations also came under criticism [180] and were not always implementable in practice. Invitations were highly dependent on overstretched local health systems and identifying algorithms that failed to accommodate regional variations in coding quality; how many high-risk patients went unnotified as a result remains uncertain [180].

Patients' ability to shield was also contingent on their socioeconomic conditions and the accessibility, and resourcing, of their local support services [180]. Instructions on when and how to leave shielding were also poorly communicated to patients. What instructions were given were homogenised, with no information provided on whether certain groups would benefit from continuing to stay isolated [181]; these decisions were instead left to the judgment of patients themselves [181; 182]. Given the significant economic and psychological consequences of long-term shielding and the barriers that staying housebound created for accessing routine care [183; 184; 185], more personalised COVID-19 risk information would support immunosuppressed patients to make the best decisions for their own safety during periods of high transmission. This has yet to be offered [185].

The parallel criticisms of poor international scope, continued disease exposure and socioeconomic burden have also been levelled at the work from home mandate.

Only high-income countries with digitally enabled economies were able to successfully implement this policy [186]; such a directive was untenable amongst economies built on high levels of manual labour or subsistence agriculture by comparison. Furthermore, its execution has extended far beyond brief interludes of lockdown for the immunosuppressed [187]. Those of shielding status have had no choice but to remain out of office and, according to the UK Office of National Statistics (ONS), almost 50% experienced unemployment during the first year of the pandemic as a result [188]. Multiple journalistic outlets attempted to raise awareness of the mental and financial health impacts consequences of this on already vulnerable persons [189; 98].

While certain workplaces have attempted to provide reasonable accommodations for their immunosuppressed staff (offering remote work, part-time work, regular risk assessments, isolated workstations, protective plexiglass screens, additional sanitation measures etc.) [190] this can also have the unintended consequence of singling said employees out, opening them up to discrimination, stigmatisation and even harassment in the process [189]. Moreover, the lack of clinical consensus on criteria for immunosuppression and their constituent risks for COVID-19 have made it difficult for employers to confirm when these measures are proportionate to at-work risk [189]. Without agreed definitions and risk assessments, vulnerable workers, or those living with the vulnerable [191], can slip past the provisions and protections that might otherwise have been made available [189]. This example underscores how the poor standardisation of immunosuppression is as detrimental to impactful policymaking and social support as it is insightful clinical research.

The introduction of community testing was extremely valuable for the immunosuppressed, however. Beyond its value for curbing rates of transmission and subsequent hospitalisation [192], community testing data flows also informed policy, drug discovery and optimal routes of patient triage [193] – all of which was to the benefit of the immunosuppressed. While available, government subsidised rapid tests were of considerable reassurance to these patients, providing an additional level of visibility and control over their exposure risk [194]. They were vital tools for ensuring the ongoing safe passage of these patients through healthcare settings - minimising risk of nosocomial infection [195]. Furthermore, when sequenced, samples from community testing efforts provided line of sight into COVID-19 mutation and early warnings for viral escape from first line therapeutics and vaccinations [196]. These data informed pharmaceutical research and development, including timely vaccine recomposition [197], and resulted in the adaptable products that optimised vulnerable patients' protection from COVID-19 and their prognosis if infected [198; 199]. The scale of data available also facilitated immunosuppressed-specific research efforts: the decentralisation of research trials, enabled by increases to digital maturity reported over the course of the pandemic [200], improved the inclusivity of recruitment and the study of rarefied or marginalised conditions [201]. Centralised studies of immunosuppressed patients have traditionally been hampered by low sample sizes [202].

The availability of antibody testing was of mixed benefit for the clinically vulnerable by comparison. Although laboratory-based serological testing provided public health agencies with real-time intelligence on vaccine response, waning and escape [5], commercial forms of these tests sowed confusion amongst the clinically vulnerable

when used unsupervised [203; 204; 205]. Antibody generation is by no means a perfect proxy for an individual's immune profile; concordance between this humoral response and T-Cell reactivity is not guaranteed, for example, meaning patients without measurable antibodies for COVID-19 via self-testing might still mount a sufficient immune response upon disease exposure [206]. Layman users of these tests were not necessarily aware of these nuances, however, and may have been unnecessarily alarmed upon returning negative results after vaccination or a confirmed COVID-19 case [207]. Furthermore, despite recommendations from public health officials and dedicated researchers to do so, the subsidisation and distribution of antibody tests were too meagre to provide an additional arm of vaccine effectiveness surveillance or an evidence base to prioritise passive forms of immunisation [207; 208]. Recent evidence supplied by the MELODY Study (Mass Evaluation of Lateral Flow Immunoassays for the Detection of SARS-CoV-2 Antibody in Immunosuppressed People) confirmed the missed opportunity this represented: at-scale, these tools were seen to provide valuable line of sight into differential seroconversion amongst the immunosuppressed population and elevated instances of post-shielding infection amongst those with depleted or non-detectable antibodies - data which would have proven invaluable for personalising disease prevention and vaccine scheduling policies [209].

Furthermore, government emphasis on self-testing was criticised as creating a tacit expectation that the public should take a more autonomous or community-oriented approach to their health and safety – especially when combined with parallel constraints of medical supervision or closures of medical faculties [208; 210; 211]. In the UK, this shift in duty of care was – and, for some, remains - inequitably

resourced and has been negatively received by many as a result [212; 213; 214]. For example, wraparound offerings including the *Your COVID Recovery* portal and the distribution of remote monitoring devices, are highly dependent on the digital maturity, disposable income and English fluency of the patient and struggle to adapt to complex cases such as the immunosuppressed [215; 216; 217]. However, it is the near-total discontinuation of nationalised COVID-19 NPIs that has received most criticism [218]. In the UK, this includes the termination of community and wastewater testing [219; 220], self-isolation support for COVID-19 cases [221] and regular public health messaging [222] as well as cuts to central funding for the volunteer and community sector [223] and PPE in health settings [224]. There has been minimal effort to retain these resources for the benefit of the most vulnerable and isolated [223; 225; 226]. This, combined with the ongoing reticence of the immunosuppressed to re-engage with health services, puts these individuals at an extreme disadvantage [221; 225].

In sum, the immunosuppressed are not provided with the targeted information, protections and support needed to see them reengage in public life in a way that is commensurate with their risk for severe COVID-19 infection. At present, what is available is homogenised and restricted to periods of high disease transmission – something increasingly difficult to identify with ongoing divestments from community testing [220; 222].

3. Outstanding research questions:

This chapter has outlined ongoing uncertainties around the very definition of immunosuppression, the COVID-19 prognoses of these patients and the resulting

impacts on policies that aim to protect their interests. Poor differentiation of COVID-19 infection and vaccination data has affected researchers' ability to pinpoint excess risk or comparative resilience within this patient spectrum and, thereby, the ability of policymakers and clinicians to target, tailor or titrate resources accordingly. Unless addressed, preventative measures and patient care will remain insufficiently specialised.

Issues of resourcing, either in the form of supportive public policies, vaccine equity or drug availability, are also recurrent in this introduction. Economically advantaged and disadvantaged contexts alike have struggled to prioritise scarce medical supplies or supervision for the vulnerable. Demarcating higher from lower COVID-19 risk immunosuppressed patients has significant prospective benefit for addressing these resource constraints at a global level, ensuring that those set to benefit most from them are prioritised. Enhancing support for the entire immunosuppressed population is not financially tenable, but equity can be achieved.

Finally, poor visibility for within-immunosuppressed differences in vaccine benefit and risk raises urgent ethical questions. There is insufficient data to identify which exact immunosuppressed patients respond poorly to COVID-19 vaccination, either in terms of impaired seroconversion or elevated adverse events. It is unclear whether this is subgroup-specific or if these phenomena are distributed across the immunosuppressed population, contingent instead on comorbidities, medications or socioeconomic variables. Addressing this evidence gap has substantial prospective value for resource prioritisation and for making timely adjustments to vaccine composition and scheduling, such as changes to dosing, adjuvant use and enacting

or delaying parallel immunosuppressive regimens. Continuing to base COVID-19 vaccine scheduling - or, indeed, mandating take-up – for the immunosuppressed and their carers on data extrapolated from the general population or trial-and-error implementation is arguably a violation of medical ethics and potential amplifier of vaccine hesitancy in our most vulnerable.

All the above justifies the stated aims of this thesis: to identify the immunosuppressed subgroups most vulnerable to severe COVID-19 via a systematic appraisal of the literature, the building of international consensus and analysis of real-world evidence. These lines of inquiry will come together to surface and refine a clinically meaningful means of segmenting immunosuppressed COVID-19 infection and vaccination data and, with this differentiated evidence base, suggest new directions for preventative and responsive care. Though the acute phase of the pandemic has ended, the ongoing vulnerability of certain immunosuppressed patients to this disease warrants this retrospective analysis. Lessons learned here may also have transferrable potential for wider disease domains and provide valuable direction for future pandemic response.

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2

Is COVID-19 mortality compared to the immunocompetent capable of risk stratifying the adult immunosuppressed population? Output from rapid scoping and systematic literature reviews and meta-analysis:

Introduction: The proliferation of immunosuppressed medical literature that occurred throughout the COVID-19 pandemic presents a unique opportunity to capture and compare infection outcomes across all subgroups.

Method: Two literature reviews aimed to quantify the COVID-19 risks associated with all subgroups referenced in the UK definition for immunosuppression. A rapid scoping review (pp. 47 to 57) tested the feasibility of this exercise, populating mortality data for each subgroup; a systematic literature review and meta-analysis (pp. 57 to 80) refined and elaborated on this initial approach.

Results: Both exercises revealed significant heterogeneity in COVID-19 mortality risks between and within immunosuppressed categories. Despite differences in reviews' scope, there was also strong coherence in the immunosuppressed subgroups identified as at greatest and, by comparison, least risk for COVID-19 mortality. The mortality risks of extremely rare or complex immunosuppressed subgroups and international differences in outcomes could not be established in this chapter, however.

Discussion: These exercises demonstrated that, overall, there is sufficient medical literature dedicated to COVID-19 mortality in the immunosuppressed to risk stratify the entire patient population. Furthermore, within-category heterogeneity indicates that segmenting disease surveillance by common clinical denominator alone risks erasing sub-trends of key clinical concern. The absence of reliable data on the COVID-19 outcomes of rare and complex immunosuppressed subgroups and the poor international representation in these exercises could only be resolved by the international consensus building study that follows. This work also foreshadowed difficulties incorporating immunosuppressive medications in analysis.

Elements of this chapter have been published [1, 2, 3].

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1. Introduction:

The previous chapter summarised what was known about the diverse and disproportionate impacts of the COVID-19 pandemic on the adult immunosuppressed patient spectrum at the outset of this doctoral programme. Aggregated data reveal consistently higher incidences of severe COVID-19 infection [4; 5; 6] and poorer vaccine responses [7] amongst these patients compared to immunocompetent counterparts. However, there has been insufficient research to confirm how these risks might differ between key subgroups [8; 9; 10] – here pertaining to the specific diagnoses, medications or procedures that confer immunosuppressed status in adults and used interchangeably with categories and subcategories, as below. Indeed, reports from large cohort studies or surveillance datasets have conventionally handled this risk group as a singular entity [11] or have restricted differentiated analysis to dominant conditions [12]. This erases COVID-19 infection trends that may be of clinical importance both between and within immunosuppressive subgroups and, as we have seen, undermines targeted policymaking and care [13]. Worse still, despite the stated urgency of better differentiating these data, there remains no universally accepted, clinically meaningful or CMR compatible classification of adult immunosuppressed patients to support this process [14; 15].

The objective of this chapter was therefore to conduct both rapid scoping and systematic literature reviews of COVID-associated mortality in the adult immunosuppressed population to:

1. Capture and compare COVID-19 risk across the entire adult immunosuppressed patient spectrum

2. Establish whether adult immunosuppressed COVID-19 mortality compared to the immunocompetent baseline offers a viable means of risk stratifying this population going forwards.

While also addressing the central objective of this thesis, the doctoral candidate hypothesised that converting such a literature-informed COVID-19 risk hierarchy into a digital phenotype (a set of machine-readable rules that can be applied to CMRs to identify, extract and differentiate specific cohorts and/or events of interests) would meet the specified need for a clinically meaningful, universally acceptable and digitally practical classification of immunosuppression. Compared to cruder segmentation by clinical class (malignancy, transplantation, autoimmunity etc.), this COVID-19 risk stratified approach would be less likely to erase important within-subgroup differences in outcomes and, by extension, better equipped to evidence resource distribution [13] and audit the effectiveness and proportionality of COVID-19 protections and social restrictions [16].

In the reviews presented below, adult immunosuppression was defined in accordance with UK '*Immunisation against infectious disease (Green Book) Chapter 14a*' [17] criteria, provided in Panel 1 below. This choice was justified by its ongoing influence over UK COVID-19 vaccine prioritisation and its expansive interpretation of immunosuppression as a condition- and medication-inclusive definition.

Panel 1: Immunosuppression in adult populations, as defined by Chapter 14a (COVID-19) of UK immunisation against infectious disease (Green Book)

Immunosuppression	Immunosuppression due to disease or treatment, including patients undergoing chemotherapy leading to immunosuppression, patients undergoing radical radiotherapy, solid organ transplant recipients, bone marrow or stem cell transplant recipients, HIV infection at all stages, multiple myeloma or genetic disorders affecting the immune system (e.g. IRAK-4, NEMO, complement disorder, SCID). Individuals who are receiving immunosuppressive or immunomodulating biological therapy including, but not limited to, anti-TNF, alemtuzumab, ofatumumab, rituximab, patients receiving protein kinase inhibitors or PARP inhibitors, and individuals treated with steroid sparing agents such as cyclophosphamide and mycophenolate mofetil. Individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day for adults. Anyone with a history of haematological malignancy, including leukaemia, lymphoma, and myeloma. Those who require long term immunosuppressive treatment for conditions including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, scleroderma and psoriasis. Some immunosuppressed patients may have a suboptimal immunological response to the vaccine (see Immunosuppression and HIV).

Both exercises benefited from the proliferation of immunosuppressed infection data that has occurred throughout the pandemic [18] – an evidence base that, for the first time, also centres the complex and rarified forms of immunosuppression cited in Green Book Chapter 14a. Unprecedented levels of international collaboration [19], data sharing [20] and community testing [21] have enabled this granularity and inspired the doctoral candidate's hypothesis that COVID-19 infection outcomes specifically would act as the much-needed common denominator for differentiating vulnerability across the entire immunosuppressed patient spectrum. Seasonal influenza literature does not offer the same level of resolution by comparison [22].

2. Rapid scoping review:

i. Methods:

The rapid scoping review was performed at the outset of the doctoral programme to inform the design of the systematic literature review that followed and to offer colleagues at the United Kingdom Health Security Agency (UKHSA) an initial means

of risk stratifying their immunosuppressed vaccine effectiveness data (Chapter 4). This work aimed to establish if, as of 2022, COVID-19 mortality outcomes were accessible in the medical literature for all immunosuppressed categories cited in the Green Book Chapter 14a adult definition [17] and whether visible clusters of mortality risk existed even at this crude level of analysis. It adhered to the following PECO structure: Population – COVID-19 infection; Exposure – Adult Immunosuppression; Comparator – Immunocompetent; Outcome – COVID-19 mortality. As summarised in Panel 2, all conditions, medications and procedures explicitly mentioned within the Green Book Chapter 14a definition of adult immunosuppression were entered into Google Scholar (Alphabet, Inc.) as search terms alongside COVID-19 and mortality syntax. Searches were iterative and utilised the 'relevant articles' function of Google Scholar (Alphabet, Inc.) to redundancy. Search dates were January 2020 to August 2022 inclusive.

Panel 2: Example Search Terms and Inclusion & Exclusion Criteria for Rapid Scoping Review

Search terms included in Google Scholar search:
COVID-19 AND "excess mortality" AND chemotherapy OR radiotherapy OR "solid organ transplant*" OR transplant OR "bone marrow" OR "stem cell" OR myeloma OR complement OR biologics OR "biological therap*" OR immunotherapy OR PID OR HIV OR AIDS OR steroid OR prednisolone OR malignancy OR lymphoma OR "rheumatoid arthri*" OR IBS OR scleroderma OR lupus OR psoriasis OR "steroid sparing" OR "anti-TNF" OR leukaemia OR "genetic disorder*" OR rituximab OR "protein kinase inhib*" OR "PARP*" OR cyclophosphamide OR "mycophenolate mofetil" OR "long term immuno*" OR "long-term immuno*" OR IRAK-4 OR NEMO OR SCID OR alemtuzumab OR ofatumumab

Inclusion criteria:

- Study investigated the impact of COVID-19 on a specific immunosuppressed category (as defined by *Immunisation against infectious disease* [Green Book] Chapter 14a)[17]
- Mortality data were provided in some form (proportion deceased and/or comparative mortality to immunocompetent via effect measure)
- Study reported adult data (over 18 years)

Exclusion criteria:

- Study did not investigate the impact of COVID-19 on a specific immunosuppressed category (as defined by *Immunisation against infectious disease* [Green Book] Chapter 14a)[17]
- Mortality data were not provided in any form
- Multiple/overlapping risk groups were assessed (e.g. pregnant/diabetic immunosuppressed patients)
- Immunosuppressives were investigated as a prospective treatment for COVID-19, not as a risk factor
- Study included paediatric data (under 18 years)

Eligible literature was then organised into summary categories of Green Book Chapter 14a Immunosuppressed terms; these categories streamlined the source's listed approach. Out of this literature, exemplar studies for each category were identified. Screening for said exemplar studies occurred first by title and abstract before full text was reviewed; selections were based on study design, sample size, data completeness and efforts taken by authors to minimise bias.

Once identified, a data extraction form was populated to compare COVID-19 mortality outcomes between exemplar studies. Exchanges would be made to exemplar studies if invalid, ineligible or superior data were identified during second and third review. The following data points were tabulated: Green Book category, Title, Author(s), Year, Country, Excess COVID-19 Mortality (Effect Measure), 95% Confidence Interval, Proportion Mortality amongst All COVID-19 Case Types and Proportion Mortality in Hospitalised COVID-19 Cases.

COVID-19 mortality data was contextualised by setting (hospitalised; outpatient) to reflect the elevated vulnerability of patients triaged into hospital; cases unwell enough to require this level of medical supervision and intervention were significantly more likely to succumb to the virus than those treated as outpatients [23]. Meanwhile, the umbrella term, effect size (ES), quantified any disparities between immunosuppressed COVID-19 mortality versus that of the immunocompetent baseline; as argued by Symons & Moore [24], the mathematical equivalence of hazard, odds and risk ratios when reporting time-restricted outcomes in rare patient groups allowed for these data to be handled synonymously without adjustment or formal standardisation. It is acknowledged that this approach can risk inflating effect

sizes, however. A forest plot of effect size data was constructed on R version 4.3.1 [25]. Statistical significance was predefined at $p<0.05$.

ii. Results:

Once Green Book Chapter 14a terms were summarised, twelve categories were left to be populated with data from their respective exemplar studies [26-34]. The completed data extraction form is provided in Table 2.1 below.

Table 2.1: Completed data extraction form of exemplar rapid scoping review cohort studies comparing COVID-19 associated mortality between adult immunosuppressed (IS) categories and immunocompetent (IC) comparators.

Green Book Category	Reference	Year	Country	IS cases (n)	IS mortality (n)	IC cases (n)	IC mortality (n)	All case IS mortality* (%)	Hospitalised IS mortality** (%)	Effect Size	LCI	UCI	*p-value*
Chemotherapy	Lee et al	2020	UK	281	75	272	92	*Not reported*	27.00%	1.18	(0.81	1.72)	0.38
Radical radiotherapy	Lee et al	2020	UK	76	18	272	92	*Not reported*	24.00%	0.65	(0.36	1.18)	0.159
Solid Organ Transplantation	Sun et al	2021	USA	11392	875	1426984	23830	7.68%	*Not reported*	3.38	(3.35	3.41)	<0.01
Bone Marrow / Stem Cell Transplantation	Ljungman et al	2021	Global	382	95	*Not reported*	*Not reported*	25.20%	*Not reported*	*Not reported*	*Not reported*	*Not reported*	*Not reported*
Human Immunodeficiency Virus (HIV)	Hadi et al	2021	USA	404	20	404	15	4.95%	*Not reported*	1.33	(0.69	2.57)	*Not reported*
Multiple Myeloma	Chari et al	2020	Global	617	203	*Not reported*	*Not reported*	*Not reported*	33.00%	*Not reported*	*Not reported*	*Not reported*	*Not reported*
Primary Immunodeficiencies	Shields et al	2021	UK	310	55	*Not reported*	*Not reported*	17.70%	*Not reported*	*Not reported*	*Not reported*	*Not reported*	*Not reported*
Biologics	Suárez-García et al	2021	Spain	183	49	11095	2143	*Not reported*	26.70%	1.97	(1.33	2.91)	0.001
Steroid sparing agents	Yousaf et al	2020	Global	213	13	213	15	6.10%	*Not reported*	0.87	(0.42	1.78)	0.696
Systemic steroids	Suárez-García et al	2021	Spain	570	202	11095	2143	*Not reported*	35.40%	2.16	(1.8	2.61)	<0.001
Haematological malignancies	Passamonti et al	2020	Italy	536	198	239627	33498	37.00%	*Not reported*	2.04	(1.77	2.34)	<0.001
Long Term Immunosuppressives	Suárez-García et al	2021	Spain	394	109	11095	2143	*Not reported*	27.70%	2.06	(1.64	2.6)	<0.001

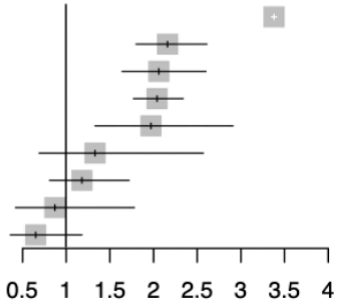
* Percentage of deaths recorded amongst all COVID-19 cases

** Percentage of deaths recorded exclusively amongst cases hospitalised with COVID

Due to the heterogeneity of exemplar studies' designs and sample sizes, effect size estimates of excess COVID-19 mortality were prioritised over raw percentage data. A forest plot of effect size data is provided in Figure 2.1. Here, a demarcation can be tentatively drawn between the higher excess mortality reported amongst solid organ transplant (ES: 3.38, 95% CI: 3.35 to 3.41, p <0.01), systemic steroids (ES: 2.16, 95% CI: 1.80 to 2.61, p <0.001), long-term immunosuppressives (ES: 2.06, 1.64 to 2.60, p <0.001), haematological malignancy (ES: 2.04, 95% CI: 1.77 to 2.34, p <0.001) and biologics (ES: 1.97, 95% CI: 1.33 to 2.91, p = 0.001) categories versus those reported for HIV (ES: 1.33, 95% CI: 0.69 to 2.57), chemotherapy (ES: 1.18, 95% CI: 0.81 to 1.72, p = 0.38), steroid sparing agents (ES: 0.87, 95% CI: 0.42 to 1.78, p = 0.696) and radical radiotherapy (ES: 0.65, 95% CI: 0.36 to 1.18, p = 0.159) categories.

Figure 2.1: Forest plot of excess COVID-19 mortality between adult Green Book Immunosuppressed (IS) Categories and Immunocompetent (IC) Comparators

Green Book Category	Reference	IS Cases	IC Cases	IS Mortality	IC Mortality	Effect Size	Lower CI	Upper CI
Solid Organ Transplantation	Sun et al (2021)	11,392	1,426,984	875	23,830	3.38	3.35	3.41
Systemic steroids	Suárez–García et al (2021)	570	11,095	202	2,143	2.16	1.80	2.61
Long Term Immunosuppressives	Suárez–García et al (2021)	394	11,095	109	2,143	2.06	1.64	2.60
Haematological malignancies	Passamonti et al (2020)	536	239,627	198	33,498	2.04	1.77	2.34
Biologics	Suárez–García et al (2021)	183	11,095	49	2,143	1.97	1.33	2.91
Human Immunodeficiency Virus (HIV)	Hadi et al (2021)	404	404	20	15	1.33	0.69	2.57
Chemotherapy	Lee et al (2020)	281	272	75	92	1.18	0.81	1.72
Steroid sparing agents	Yousaf et al (2020)	213	213	13	15	0.87	0.42	1.78
Radical radiotherapy	Lee et al (2020)	76	272	18	92	0.65	0.36	1.18



When cross-referencing these data with mortality percentages, evidence was also provided for disparities within immunosuppressed diagnosis and medication types: haemapoietic transplantation patients experienced worse COVID-19 mortality outcomes (37% mortality, all cases) than their solid organ counterparts (7% mortality, all cases) and biologic recipients fared worse (ES: 1.97; 95% CI: 1.33 to 2.91, p= 0.001) than those being treated for their cancer (ES: 1.18, 95% CI: 0.81 to 1.72, *p* = 0.38 for chemotherapy and ES: 0.65, 95% CI: 0.36 to 1.18, *p* = 0.159 for radical radiotherapy), respectively.

iii. Discussion:

Principal findings and their implications:

This rapid scoping review was conducted by the doctoral candidate to determine whether sufficient literature was available to extract COVID-19 mortality outcomes for all adult immunosuppressed categories referenced within a prevailing UK definition. Initial checks were also made to gauge whether these data were varied enough to segment this spectrum going forwards.

In both these respects, this exercise was a success. The scale and specificity of the COVID-19 immunosuppressed literature base meant that appropriate exemplar studies could be identified for every adult immunosuppressed category. As indicated, this was not the case when this exercise was attempted for influenza mortality (seasonal or otherwise; Appendix 1); at the time of search, no eligible data was available on critical influenza amongst primary immunodeficiency, biologics, chemotherapy, radiotherapy, steroid sparing agent or long-term immunosuppressive patients. This justified the doctoral candidate's singular focus on COVID-19 even as

the acute phase of the pandemic passed: at the time this work was conducted, fully comparative literature reviews could only be produced for this disease domain.

Furthermore, the speed of this exercise provided an additional check on UKHSA booster COVID-19 dose allocations in the winter of 2022. Elaborated upon in Chapter 4, pilot scoping review findings were sufficiently timely and valuable to inform the segmentation of UKHSA immunosuppressed COVID-19 vaccine effectiveness data between 2022-2023.

Comparison to existing literature:

Even while based on single study estimates, this first attempt at a comparative analysis of immunosuppressed COVID-19 mortality revealed a demarcation between the excess vulnerability of transplant, haematological malignancy, systemic steroid and long-term immunosuppressive categories and the comparable resilience of HIV and cancer therapy patients; mortality in latter groups were more aligned with the immunocompetent baseline. These observations echoed risk categorisations made by Li and colleagues [35]: here, transplantation and haematological malignancy patients were labelled as *Severely Immunocompromised* whereas HIV and treated cancer patients were designated *Non-Severe Immunocompromised.* When tested within real-world data, said categorisations revealed significantly longer pathogenic clearance, reduced humoral responses and higher risks of developing resistance to therapeutic monoclonal antibodies amongst the *Severely Immunocompromised* group than their *Non-Severe Immunocompromised* counterparts – validating their composition and, by extension, our own preliminary higher versus lower risk demarcation.

The tentative evidence this rapid scoping review supplied for within-category differences in COVID-19 mortality – most visibly between immunosuppressive and transplantation types – was also meaningful. Replicated in earlier work [36; 37], this nuance must be adopted when digital phenotyping; approaching segmentation through clinical common denominator alone would conceal excess vulnerability or relative immunocompetence into group averages and, in so doing, misdirect benefit-risk assessments. This adds weight to a risk stratified approach to segmented immunosuppressed disease surveillance.

Limitations:

The following limitations of this exercise must be noted, however.

Firstly, the categories that segmented the source definition for immunosuppression successfully still collapsed diverse patient and medication types into single COVID-19 mortality estimates. Although this amounts to a step forward from risk assessments at the population level, the approach is extremely crude. By way of example, primary immunodeficiencies constitute over 450 separate errors of inborn immunity [38]; the single study estimate for excess mortality that this work reports does nothing to communicate the individual experiences of these patient subtypes. Such estimates are also highly susceptible to inaccuracy or bias and, as a result, are unlikely to reflect true population outcomes [39]. Failing to pre-publish a research protocol, standardise a control group (immunocompetence was not defined beforehand, with difficulty obtaining completely immunocompetent counterpoints to medication-specific forms of immunosuppression), secure an additional, independent reviewer and document numbers of screened and rejected articles exacerbated

these risks and reduced the overall rigour and replicability of this hypothesis-generating exercise [40].

The heterogeneity of exemplar studies also calls the generalisability of findings into question: study year, geolocations, sample sizes, patient demographics, COVID-19 case types (exclusively vs non-exclusively hospitalised), and mortality metrics varied substantially between categories. Neither effect size, mortality percentage or control group outcomes for either metric was available for every immunosuppressed category, weakening comparisons as a result. This work also made no attempt to control for broader explanatory variables of excess COVID-19 mortality, such as age, ethnicity, gender or study year.

As a result of the above, when sharing this rapid scoping review with UKHSA stakeholders, the doctoral candidate contextualised findings as preliminary and highly speculative. The systematic review and meta-analysis that follows were conducted to address the limitations cited and to produce more standardised, detailed and - thereby – reliable comparisons of COVID-19 risk in the adult immunosuppressed population.

3. Systematic literature review and meta-analysis:

i. Methods:

Aspects of this systematic literature review and meta-analysis replicated the rapid scoping review that preceded them. As before, this work adhered to the following PECO structure: Population – COVID-19 infection; Exposure – Adult Immunosuppression; Comparator: Immunocompetence; Outcome – excess COVID-

19 mortality. Search dates were also set to January 2020 to August 2022 inclusive in the first instance and all forms of immunosuppression cited within Green Book Chapter 14a [17] were converted into search terms compatible with literature databases. However, to address previous criticisms of over-simplification, where possible, Green Book adult immunosuppressed categories were further subdivided into subcategories for systematic review. Subsequent data screening, extraction, bias assessment and analysis were also underpinned by guidance from the Cochrane Handbook for Systematic Reviews and Interventions (Version 6.3) [41], Preferred Reporting Items for Systematic Review and Meta Analysis (PRISMA) [42] and a pre-published protocol, hosted on PROSPERO (registration number CRD42022360755) [1] – a departure from the rapid scoping review.

This systematic review and meta-analysis extracted contemporary literature from OVID (EMBASE, MEDLINE, Transplant Library and Global Health inclusive), PubMed and Google Scholar databases. A flow chart depicting the conversion from Green Book immunosuppressed syntax to search terms compatible with these databases is provided in Appendix 2. Search terms compatible with all databases are provided in full in Appendix 3. Three, independent reviewers supported screening. The two primary reviewers comprised of the doctoral candidate and a colleague within the Oxford-Royal College General Practitioners Research and Surveillance Centre (RCGP RSC) this research was based within; the third, another colleague, was available to resolve eligibility disputes.

As specified by the research protocol [1], it was initially unclear when planning this research whether sufficient subcategory-level data would be available to support

detailed meta-analysis or if a narrative review would be all that was tenable. As such, screening occurred at two levels of stringency.

As depicted in Panel 3, Phase 1 criteria facilitated broad data extraction. Inclusion and exclusion criteria were less restrictive at this stage. Once Phase 1 confirmed the feasibility of subcategory meta-analysis, Phase 2 eligibility criteria were applied to select exclusively for studies that could support this process – namely cohort designs that reported mortality data on both immunosuppressed subcategory and immunocompetent comparators via effect size or that provided raw case and mortality figures (enabling the imputation of the former). To maximise study catchment, the Phase 1 literature base was first forwards and backwards citation tracked with Google Scholar before Phase 2 constraints were enacted. As per the rapid scoping review, Google Scholar's 'Relevant articles' function was applied until redundancy. To retain consistency and to mitigate the influence of vaccines and novel therapeutics on our analysis, forward citation tracking was capped at 2022 inclusive.

Panel 3: Phase 1 and Phase 2 inclusion and exclusion criteria for Systematic Literature Review and Meta-Analysis

Phase 1
Inclusion Criteria were as follows:

- Study investigated the impact of COVID-19 on at least one immunosuppressed subcategory (as defined by UK guidance); pre-prints were permissible.
- COVID-19 associated mortality data was provided in some form on an immunosuppressed subcategory basis.

Exclusion Criteria were as follows:

- Study did not investigate the impact of COVID-19 on at least one immunosuppressed subcategory (as defined by UK guidance); studies that only assessed this at the aggregate level of 'the immunosuppressed' were also ineligible.
- Mortality data was not provided in any form.
- Study only presented indirect COVID-19 mortality data – that created by disruptions to diagnosis or treatment seen over the course of the pandemic.
- N <50 for either immunosuppressed or immunocompetent groups.
- Multiple or overlapping risk groups were assessed (e.g. pregnant/ diabetic immunosuppressed patients).
- Immunosuppressants were studied as a prospective treatment for COVID-19, not as a risk factor for adverse infection outcomes.
- Study included paediatric patients (under 18 years).
- Study only presented case series (n <50) or single-centre data.

Phase 2
As per Phase 1, and
Additional Inclusion Criteria:

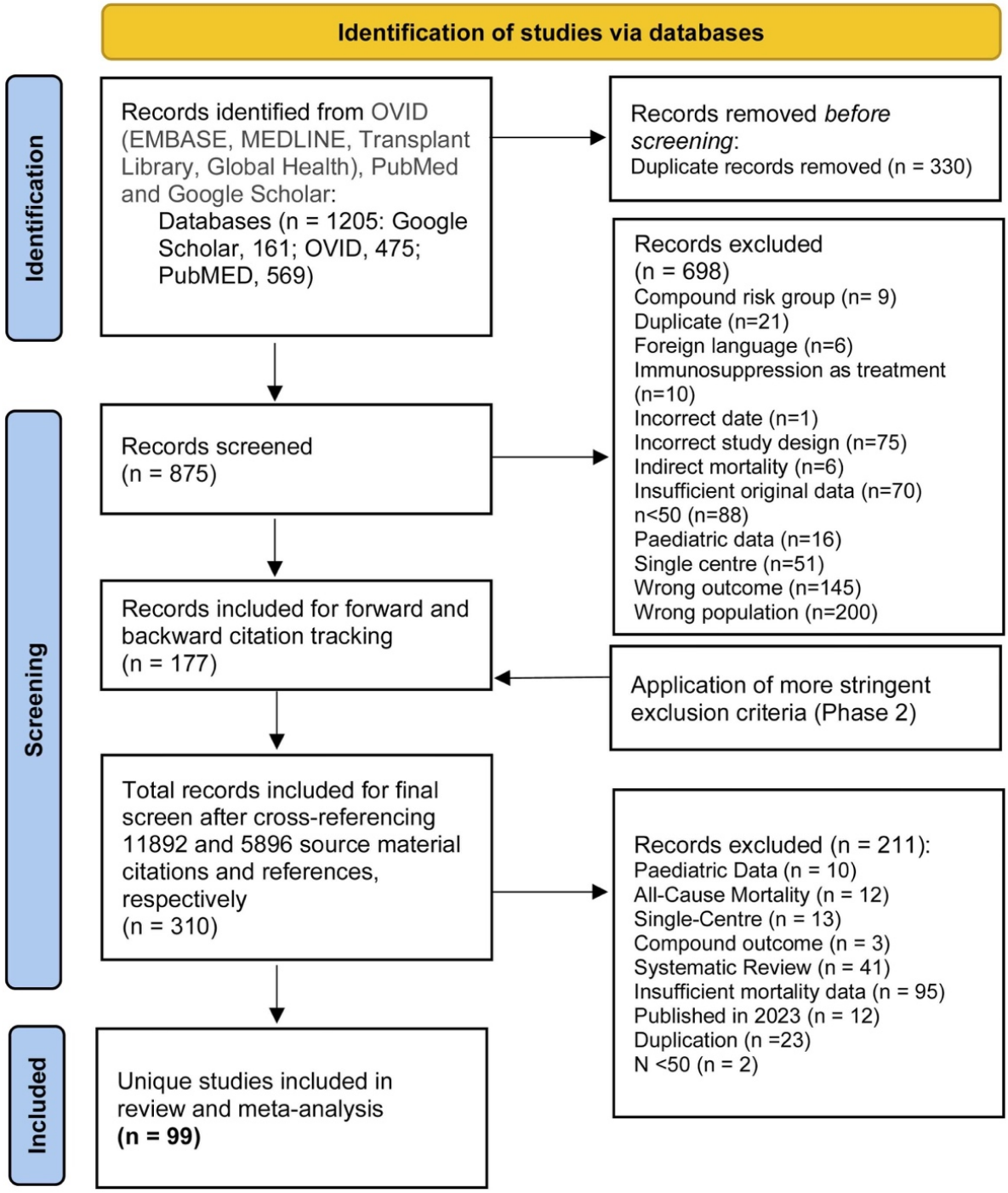
- Mortality data was sufficiently detailed for meta-analysis: studies reported mortality for both the relevant immunosuppressed subcategory and their immunocompetent control either through a combination of sample size and proportion mortality or via comparative effect measures and their respective 95% confidence intervals.

Additional Exclusion Criteria:

- Study was published in 2023.
- Study used established population-level mortality statistics in lieu of a formal control group.
- Study only reported compound critical outcomes (e.g. ICU and mortality).
- Study only reported all-cause mortality.
- Study presented a combined estimate of excess mortality via meta-analysis.
- Study did not present its own mortality data but summarised other investigations' findings.

The overall screening process is illustrated in the PRISMA flow diagram provided (Figure 2.2)[42]. Screening was blinded and supported by a data extraction form – an abridged version of which is available in Appendix 4. The web application, Rayyan [43], provided a central portal for reviewers to review each other's determinations and automate deduplication.

Figure 2.2: PRISMA flow diagram for study selection



The final study set was then evaluated using a configured version of the Newcastle Ottawa Scale [44] to measure and compare the presence of bias in each entry. To better suit the aims of this investigation, 28 days was considered sufficient follow-up time for outcomes. Another departure from conventional versions of this scale, this

study discounted marital status as a necessary variable for adjustment. These data were rarely reported in COVID-19 literature and were felt to have minimal, if any, bearing on mortality outcomes. Primary reviewers completed bias assessments independently; the third reviewer was available for resolving conflict. The results of this exercise are provided in Appendix 5.

Studies finalised for inclusion were allocated into the Green Book Chapter 14a aligned subcategories listed in Table 2.2. Data analyses were run at the disaggregated subcategory and aggregated category level.

Table 2.2: Immunosuppressed categories and their constituent subcategories

Immunosuppressed categories	**Immunosuppressed subcategories**
Transplantation	Mixed transplant cohort (*study cohort included outcomes amongst solid and haemopoietic transplant recipients)* Kidney transplant cohort Liver transplant cohort Other (*Lung/heart)* transplant cohort
Malignancy	Mixed cancer cohort (*study cohort included outcomes amongst both solid tumour and haematological cancer patients)* Haematological cancers Solid tumours
Immunosuppressive agents	Mixed immunosuppressive cohort (*study cohort included outcomes amongst multiple immunosuppressive types)* Biologics Systemic steroids Cancer treatments *(Chemotherapy and radiotherapy)*
Rheumatological Conditions	Generalised conditions (*general autoimmune disease, general inflammatory conditions, SLE etc.)* Conditions affecting the gut (*Irritable Bowel, Ulcerative Colitis, Crohn's disease etc.)* Conditions affecting the joints *(Rheumatoid arthritis etc.)* Conditions affecting the skin (*Psoriasis etc.)*
HIV	HIV/Acquired Immunodeficiency Syndrome (*any stage)*

The form provided in Appendix 6 standardised and blinded the data extraction process. Where available, the following information was recorded: title, author(s), publication year, study country, income level of study country (in accordance with World Bank classifications [45], whereby 'higher' was used to denote high-income countries and 'lower' denoted low, lower-middle and upper-middle income countries; multi-country studies had their highest income country extracted), immunosuppression type, case type (All cases or exclusively Hospitalised), time to mortality as well as sample size, average age, number of deaths and/or comparative effect measure type, value, confidence interval (95% CI) and *p-value* for both immunosuppressed and immunocompetent comparator groups. Effect sizes were imputed as odds ratios (specified in Appendix 7) for studies where only sample size and corresponding mortality figures were available. Detail on data adjustment was also recorded – most notably whether our minimum criteria had been met (pre-determined as age, sex and comorbidity adjusted) – and whether obtained values were based on matched or unmatched cohorts.

The two primary reviewers completed this form independently for all studies; the third reviewer was available for dispute resolution. Studies that reported viable data on multiple immunosuppressed subcategories were alphabetised; when calculating total study population sizes, these entries were carefully demarcated (also Appendix 7) to prevent double counting. To minimise the heterogeneity that was introduced to our analysis, we did not explore gradations of excess risk within a given subcategory (e.g. that conferred by multiple malignancy, multiple transplantations, polypharmacy etc.). To obtain the most accurate estimates of baseline excess COVID-19 mortality in the adult immunosuppressed compared to the immunocompetent, we

preferentially extracted the earliest timepoints and most protracted time-to-mortality data that were available. The former was especially important for minimising the influence of novel therapeutics and vaccination in later publications. Similarly, matched and maximally adjusted mortality data were prioritised over unmatched and unadjusted alternates.

As before, analysis and data visualisation were conducted on R version 4.3.1 [25]; meta and metafor packages were utilised for meta-analysis [46; 47]. Statistical significance was predefined at $p \leq 0.05$. Random effects modelling was conducted to reflect observed heterogeneity between studies' sample sizes, settings, case types and effect measures. Individual effect measures – either reported or imputed as odds ratios – were referred to as effect size. This decision was justified by Symons and Moore's aforementioned [24] case for the mathematical approximation between odds, hazard and risk ratios when evaluating either rare diseases or outcomes within short follow-up periods; however, it is again acknowledged that synonymising effect measure data in this way can produce slight overestimates of true effects. The weighted average of these odds ratios produced the pooled intervention effect of the adult immunosuppressed category or subcategory over the likelihood of COVID-19 mortality compared to the immunocompetent.

I^2 values were reported as a measure of category and subcategory heterogeneity; as per Cochrane guidance, values of 0-40%, 40-75% and 75-100% denoted low, moderate and substantial heterogeneity respectively [41]. I^2 were not produced for single study estimates. Select subgroup analyses were also conducted to appraise the influence of national income, COVID-19 case type, effect measure, data

matching, data adjustment and publication year over pooled excess mortality estimates. Instances of confounding, attenuation or gradient flattening were documented, though insufficient data was available to perform this analysis for immunosuppressed subcategories. Meta-regressions for the impact of average participant age over excess COVID-19 mortality were also run for each immunosuppressed category to understand whether elevated vulnerability was static across the lifespan or if critical windows existed. In this, bubble plots were constructed, and slope values and 95% confidence intervals were reported.

ii. Results:

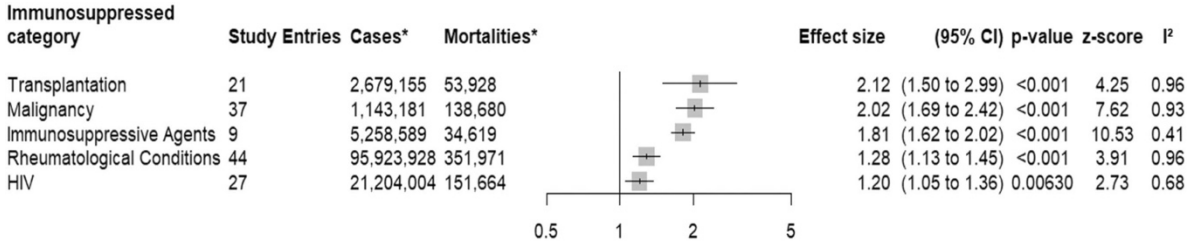
99 unique studies were carried forward for analysis [48-146]. 18 of these studies reported viable mortality data for multiple immunosuppressed groups. As per Appendix 7, in all, COVID-19 infection data from 1,542,097 unique adult immunosuppressed patients and 56,248,181 unique immunocompetent comparators were incorporated in our analysis. Exclusions are presented in Appendix 8. Table 2.3 provides a summary of final literature characteristics, including the results of Newcastle Ottawa Scale-based bias (converted into Agency for Healthcare Research and Quality [AHRQ] standards [44]).

Table 2.3: Summary table of unique studies included in comparative meta-analysis

Study variable		Number of studies	Percentage
Immunosuppressed category	Transplantation	13	13.13
	Malignancy	26	26.26
	Immunosuppressive agents	4	4.04
	Rheumatological conditions	27	27.27
	HIV	26	26.26
	Multiple	3	3.03
AHRQ Standard Fairness Assessment	Good	86	86.86
	Fair	0	0.00
	Poor	13	13.13
Year	2020	21	21.21
	2021	29	29.29
	2022	49	49.49
Cohort type	Prospective	10	10.1
	Retrospective	89	89.89
Income level	Higher	90	90.91
	Lower	9	90.09
Case type	All cases	48	48.48
	Hospitalised	51	51.52
Matching	Matched	61	61.62
	Unmatched	38	38.38
Adjustment	Adjusted	39	39.39
	Unadjusted	60	60.61

Figure 2.3 presents the results of meta-analysis run at the immunosuppressed category level. To inform subsequent stratification, they are intentionally listed in descending order of pooled effect size. In keeping with rapid scoping review findings, transplantation and malignancy patients, as well as recipients of immunosuppressive agents, were seen to have elevated excess COVID-19 mortality compared to the immunocompetent than their HIV and rheumatological counterparts. With I^2 values often exceeding 90%, within-category heterogeneity was, once again, substantial. This further justified the subcategory analysis that follows.

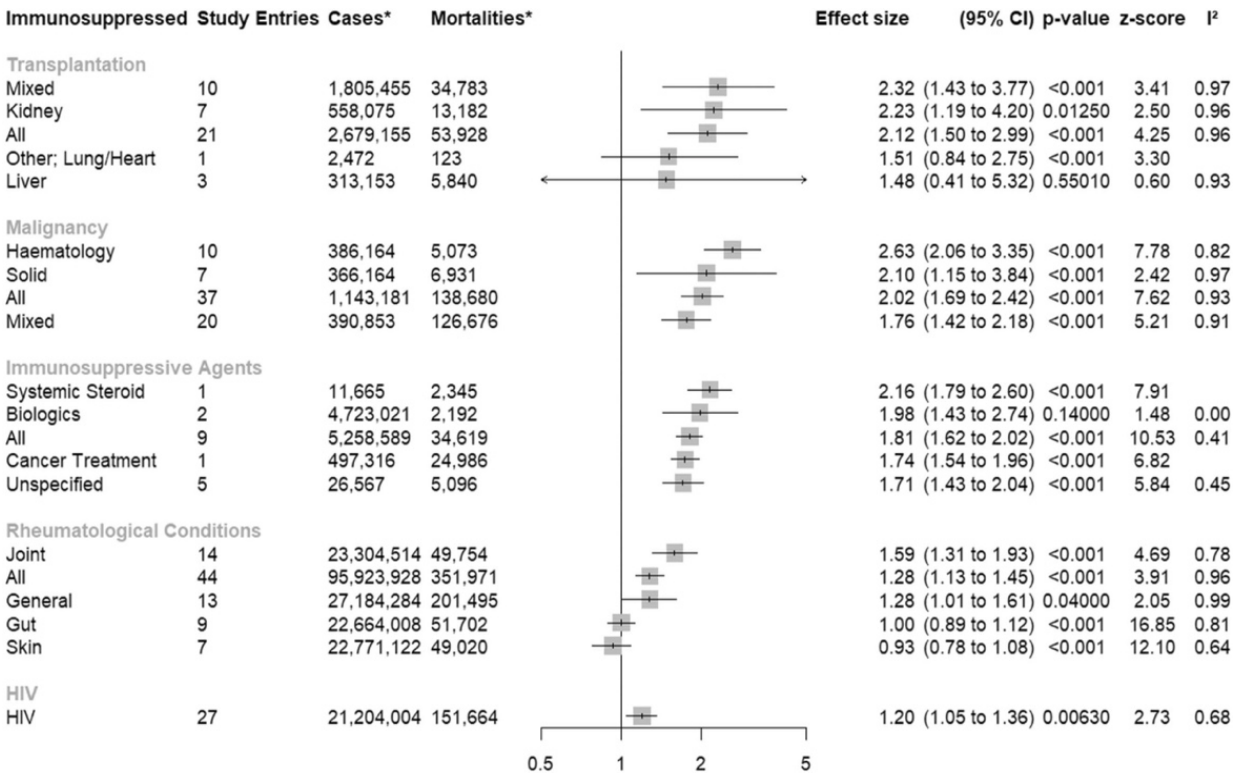
Figure 2.3: A forest plot of excess COVID-19 mortality compared to the immunocompetent presented by immunosuppressed category



*The column labelled as Cases indicates the total number of participants, immunosuppressed and immunocompetent combined. The column labelled as Mortalities indicates the total number of deaths registered in participants, immunosuppressed and immunocompetent combined. Instances of multiple counts were not removed.

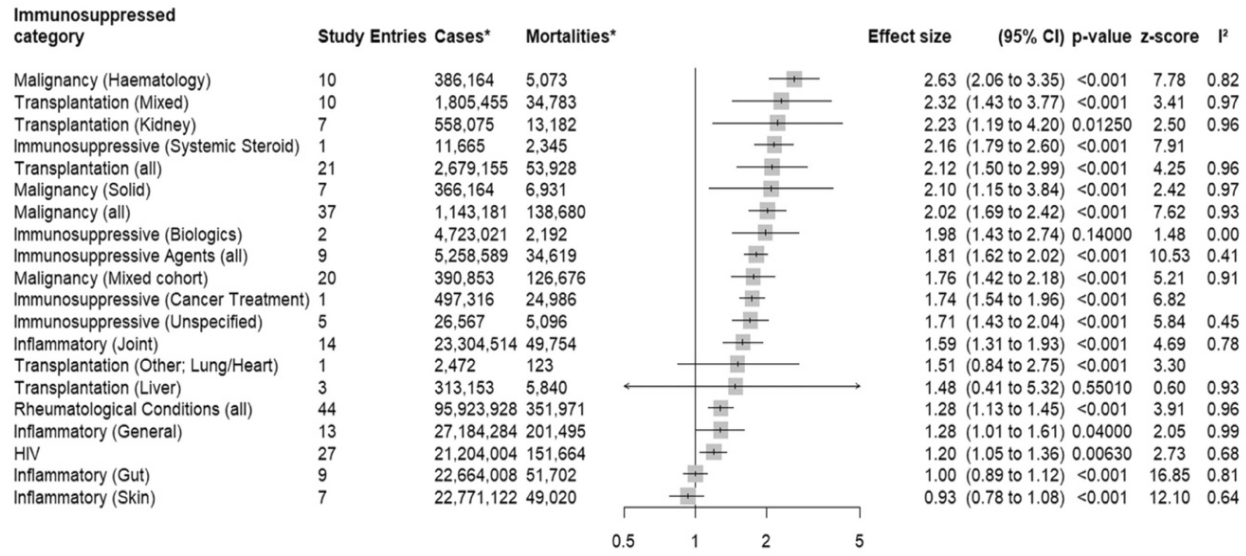
Figure 2.4 presents the results of meta-analysis run at the immunosuppressed subcategory level. Figure 2.5 presents this information in combination with category-specific pooled estimates to indicate when specific subcategories returned excess mortalities above or below category averages. Both list this information in descending order of pooled effect size. HIV was not subcategorised, however, as data on disease stage, CD4 count data and other forms of differentiation were not available consistently enough between studies to facilitate this.

Figure 2.4: A segmented forest plot of excess COVID-19 mortality compared to the immunocompetent presented by immunosuppressed category and subcategory.



*The column labelled as Cases indicates the total number of participants, immunosuppressed and immunocompetent combined. The column labelled as Mortalities indicates the total number of deaths registered in participants, immunosuppressed and immunocompetent combined. Instances of multiple counts were not removed.

Figure 2.5: A non-segmented forest plot of excess COVID-19 mortality compared to the immunocompetent presented by immunosuppressed category and subcategory.



*The column labelled as Cases indicates the total number of participants, immunosuppressed and immunocompetent combined. The column labelled as Mortalities indicates the total number of deaths registered in participants, immunosuppressed and immunocompetent combined. Instances of multiple counts were not removed.

At the category level, all pooled effect sizes were statistically significant; this was not the case for all subcategory estimates or rapid scoping review results. Within-category heterogeneity was also substantial. For example, pooled estimates for excess mortality in haematological malignancy (ES: 2.63, 95% CI: 2.06 to 3.35, p <0.001) versus immunocompetent comparators were far higher than those experienced within solid tumour (ES: 2.10, 95% CI: 1.15 to 3.84, *p* <0.001) or mixed cohorts (ES: 1.76, 95% CI: 1.42 to 2.18, *p* <0.001). Inflammatory joint conditions also returned comparatively elevated excess mortality estimates (ES: 1.59, 95% CI: 1.31 to 1.93, *p* <0.001) than the category standard (ES: 1.28, 95% CI: 1.13 to 1.45, *p* <0.001 and gut- (ES: 1.00, 95% CI: 0.89 to 1.12, *p* <0.001) or skin-specific (ES: 0.93, 95% CI: 0.78 to 1.08, *p* < 0.001) counterparts. However, it is important to note where subcategory pooled estimates were underpowered and, by extension, unlikely to reflect the true experience of their referents. The clinical accuracy of single study estimates and those that pooled data from very few exemplars (systemic steroids, biologics, cancer treatment, liver and lung/heart transplantation) should be questioned.

Collectively, Table 2.4 and Appendix 9 illustrate the flattening effect of publication year, national income, COVID-19 case type, effect measure, use of matching and use of adjustment over pooled estimates of excess COVID-19 mortality compared to the immunocompetent. Reduced effect sizes were returned amongst the studies set in higher income nations that appraised excess COVID-19 mortality amongst HIV, malignancy and rheumatological patients. The difference between pooled estimates from higher versus lower income nations reached statistical significance in these categories. While this trend's apparent reversal in transplant patients is of note (ES:

2.13, 95% CI: 1.48 to 3.04 vs 1.90, 95% CI: 0.76 to 4.73 in Higher and Lower Income studies respectively), the comparison is only supported by a single study and the difference is not statistically significant (p = 0.82).

Table 2.4: Results of subgroup analyses

Immunosuppression	Subgroup Analysis	Number of Study Entries	Effect Size	(95% CI)	I²	*p-value*
		Subgroup analysis by country income				
Transplantation	Higher	20	2.13	(1.48-3.04)	96.3%	0.82
	Lower	1	1.90	(0.76-4.73)	-	
Malignancy	Higher	30	1.82	(1.49-2.21)	87.6%	0.007
	Lower	7	2.96	(2.17-4.05_	97.2%	
Immunosuppressive agents	Higher	9	1.81	(1.62-2.02)	41.2%	NA
	Lower	0	-	-	-	
Rheumatological conditions	Higher	42	1.27	(1.11-1.44)	96.3%	<0.001
	Lower	2	1.74	(1.57-1.93)	0.0%	
HIV	Higher	24	1.13	(1.00-1.28)	57.0%	0.001
	Lower	3	1.78	(1.39-2.28)	43.6%	
		Subgroup analysis by COVID-19 case type				
Transplantation	All cases	10	3.36	(1.95-5.78)	95.6%	0.003
	Hospitalised cases	11	1.37	(1.05-1.77)	79.6%	
Malignancy	All cases	15	2.21	(1.49-2.97)	91.1%	0.76
	Hospitalised cases	22	1.98	(1.61-2.43)	93.6%	
Immunosuppressive agents	All cases	3	1.63	(1.22-2.17)	46.0%	0.38
	Hospitalised cases	6	1.88	(1.63-2.18)	47.8%	
Rheumatological conditions	All cases	35	1.31.	(1.14-1.51)	96.9%	0.50
	Hospitalised cases	9	1.18	(0.9-1.55)	87.9%	
HIV	All cases	10	1.32	(1.05-1.65)	80.1%	0.22
	Hospitalised cases	17	1.11	(0.96-1.29)	43.7%	
		Subgroup analysis by level of confounder adjustment				
Transplantation	Adjusted	15	1.68	(1.25-2.25)	95.7%	0.00758
	Unadjusted	6	3.72	(1.63-8.5)	95.2%	
Malignancy	Adjusted	19	1.95	(1.49-2.55)	94.2%	0.6992
	Unadjusted	18	2.1	(1.7-2.7)	90.1%	
Immunosuppressive agents	Adjusted	9	1.81	(1.62-2.02)	41.2%	NA
	Unadjusted	0	-	-	-	
Rheumatological conditions	Adjusted	33	1.23	(1.09-1.39)	84.7%	0.4
	Unadjusted	11	1.43	(1.03-1.99)	94.5%	
HIV	Adjusted	14	1.35	(1.12-1.62)	73.4%	0.05
	Unadjusted	13	1.06	(0.92-1.22)	53.9%	
		Subgroup analysis by matching of immunocompetent and immunocompromised				
Transplantation	Matched	12	1.36	(1.04-1.79)	72.2%	0.0017
	Unmatched	9	3.55	(2.09-6.04)	95.9%	
Malignancy	Matched	9	1.69	(1.34-2.13)	70.7%	0.1664
	Unmatched	28	2.13	(1.7-2.66)	93.8%	
Immunosuppressive agents	Matched	2	0.97	(0.52-1.84)	0.0%	0.05
	Unmatched	7	1.85	(1.65-2.06)	38.7%	
Rheumatological conditions	Matched	18	1.18	(0.99-1.41)	74.3%	0.28
	Unmatched	26	1.35	(1.14-1.6)	97.6%	
HIV	Matched	7	1.06	(0.79-1.42)	48.3%	0.32
	Unmatched	20	1.24	(1.09-1.43)	66.3%	
		Subgroup analysis by publication year				
Transplantation	2020	6	1.44	(0.84-2.50)	89.5%	
	2021	6	2.27	(1.60-3.21)	92.5%	0.31
	2022	9	2.58	(1.31-5.05)	97.4%	
Malignancy	2020	15	1.68	(1.36-2.07)	82.9%	
	2021	15	1.97	(1.45-2.67)	91.8%	0.03
	2022	7	3.05	(2.02-4.61)	91.9%	
Immunosuppressive	2020	0	-	-	-	
agents	2021	8	1.82	(1.62-2.03)	48.2%	0.74
	2022	1	1.44	(0.38-5.52)	-	
Rheumatological	2020	0	-	-	-	
conditions	2021	0	-	-	-	-
	2022	44	1.28	(1.13-1.45)	0.0%	
HIV	2020	4	1.12	(0.83-1.51)	0.0%	
	2021	13	1.24	(1.04-1.48)	76.0%	0.81
	2022	10	1.14	(0.86-1.51)	61.5%	
		Subgroup analysis by effect measure type				
Transplantation	HR	2	1.61	(1.1-2.35)	0%	
	sHR	1	1.38	(0.67-2.83)	-	<0.001
	OR	15	2.6	(1.7-3.97)	96.0%	
	RR	3	0.95	(0.78-1.16)	0%	
Malignancy	OR	34	2.1	(1.74-2.54)	93.0%	
	HR	1	0.98	(0.58-1.66)	-	0.0005
	RR	1	1.15	(0.84-1.57)	-	
	SMR	1	2.04	(1.77-2.35)	-	
Immunosuppressive	OR	7	1.84	(1.63-2.08)	38.8%	
agents	HR	1	1.87	(1.3-2.69)	-	0.13
	RR	1	0.87	(0.42-1.79)	-	
Rheumatological	RR	14	1.15	(0.84-1.57)	96.70%	
conditions	OR	23	1.42	(1.21-1.65)	73.50%	0.049
	HR	6	1.12	(1.01-1.24)	89.50%	
	SIR	1	0.42	(0.09-1.86)	-	
HIV	OR	15	1.12	(0.96-1.31)	51.30%	
	HR	5	1.62	(1.21-2.17)	67.00%	
	RR	4	1.1	(0.9-1.36)	73.70%	0.15
	IRR	2	0.7	(0.29-1.69)	0%	
	SHR	1	1.13	(0.62-2.07)	-	

Pooled estimates for excess COVID-19 mortality were also seen to be elevated in studies that did not restrict analysis to hospitalised cases. However, this pattern of results only reached statistical significance amongst transplantation patients (p = 0.003).

Disparities between adult immunosuppressed and immunocompetent COVID-19 mortality outcomes were seen to decline once data was either matched or adjusted for our minimum criteria. However, these attenuations only meet statistical significance for studies appraising transplantation (p = 0.007) and immunosuppressive recipient outcomes (p = 0.05). Furthermore, the apparent reversal of this trend in adjusted studies of HIV patients is also of note (ES: 1.35, 95% CI: 1.12 to 1.62 adjusted vs ES: 1.06, 95% CI: 0.92 to 1.29 unadjusted, p = 0.05).

Subgroup analyses by publication year returned effect sizes that, broadly, increased as time progressed. This suggests that excess mortality in immunosuppressed categories compared to the immunocompetent may have increased as the pandemic progressed. However, this observation only met statistical significance in malignancy studies (p = 0.03) and the discrepancies between years of study activity and the year of publication is confounding. Meanwhile, the statistical significance of differences between pooled excess mortality estimates from various effect sizes served to confirm earlier concerns: even when effect measures are mathematically equivalent, synonymising them can lead to inaccuracies – namely overestimates of true effects.

Finally, meta-regressions on average age of study participants (reported in Table 2.5 with bubble plots available in Appendix 10) suggest that disparities between immunosuppressed and immunocompetent COVID-19 mortality decrease with age. This relationship was not statistically significant, however.

Table 2.5: Summary of meta-regression outputs between average age of study participants and excess COVID-19 associated mortality across immunosuppressed categories

Immunosuppression	Estimate	Standard Error	*p-value*	Lower slope	Upper slope
Transplantation	-0.01	0.0029	0.72	-0.07	0.05
Malignancy	-0.03	0.02	0.09	-0.06	0.09
Immunosuppressive Agents	-0.0029	0.0067	0.66	-0.02	0.01
Rheumatological conditions	-0.005	0.01	0.71	-0.03	0.02
HIV	-0.01	0.113	0.24	-0.035	0.009

iii. Discussion:

Principal findings and their implications:

This systematic review and corresponding meta-analysis reaffirmed that excess COVID-19 mortality compared to the immunocompetent was a viable means of differentiating the adult immunosuppressed patient spectrum – though at a higher level of resolution and scientific rigour than accomplished by the rapid scoping review that preceded it. A clear gradient in excess COVID-19 mortality compared to the immunocompetent could be observed – one that can inform future risk stratification efforts. Indeed, the application of this evidence to disease surveillance and pharmaceutical research and development may significantly improve the insights and outputs of both – especially regarding the subcategories seen to be at consistently higher and comparatively lower risk for critical COVID-19 outcomes. Likewise, policy-making that reflects these specific risks would denote a significant step forward from prevailing ‘one size fits all’ offerings [10; 11].

Transplant and malignancy patients, especially those with haematological cancers, were seen to be at especially high risk for succumbing to COVID-19. Conversely, patients with HIV, rheumatological conditions or those undergoing therapy for cancer exhibited mortality risks closer to the immunocompetent baseline. These observations add weight to emerging characterisations of moderate versus severe immunosuppression as opposed to unstructured or list-based definitions. Resources such as COVID-19 triage tools and vaccine handbooks more broadly would benefit from adopting this segmented approach. Doing so will ensure that relevant therapeutics, booster vaccinations and recommendations for non-pharmaceutical interventions as intensified as shielding are allocated on a needs-basis [13]. That said, evidence for within-category heterogeneity must be considered and communicated. Steroid recipients, haematological malignancy and inflammatory joint patients returned pooled excess mortality estimates above their respective category averages; recipients of liver transplants, cancer treatments inflammatory gut and skin patients fared better than category averages by comparison – though single study estimates should be further interrogated. Echoing rapid scoping review conclusions, population segmentation that fails to incorporate such nuance would be counterproductive [10; 11].

This work has also provided substantial evidence for the influence of national income, COVID-19 case type and data matching and adjustment on mortality outcomes. This is highly relevant for disease surveillance efforts at national and international levels.

The global vantage of this work provided evidence for international disparities in critical COVID-19 outcomes – particularly amongst patients with malignancies or HIV. Findings for poorer survival outcomes in lower economic contexts are in keeping with the well-established inequities in medical access, vaccine supply and drug-management of pre-existing conditions that the COVID-19 pandemic has only exacerbated [147]. Evidence provided for elevated excess mortality in transplant patients from highly resourced settings are of interest, however. Even if only based on a single study estimate, it is possible this trend reversal may reflect inequalities in access as opposed to clinical risk: this procedure is a comparable luxury in lower income settings, selecting for affluent patients who, in turn, are predisposed to better COVID-19 infection outcomes [148].

Even without achieving statistical significance, the observation that analysis restricted to hospitalised patients flattened excess COVID-19 mortality gradients is clinically meaningful. This is suggestive of a potentially 'equalising role' of inpatient care: once unwell enough to be admitted for COVID-19, immunosuppressed status may confer little additional risk to a patient's overall likelihood of succumbing to the disease. This example of Berkson's bias [149] is exacerbated by the reduced clinical thresholds that qualified an immunosuppressed patient for hospitalisation. This accelerated triage is an established precautionary tactic [150].

Failing to adjust or match study data was seen to inflate pooled estimates for excess COVID-19 mortality. This finding corresponds to criticisms of early pandemic literature, where the urgency to establish raw mortality risks often took precedence over the rigorous or longitudinal experimental designs and analytical methods known

to delay publication. Cohort matching and adjustment for confounding were standard practice in later years [150].

Meanwhile, increases seen to pooled estimates for excess COVID-19 mortality in the immunosuppressed over the course of the pandemic may be indicative of its diminishing threat to immunocompetent patients. By the later years of the pandemic, ICU admissions and in-hospital death were vanishingly rare amongst those without pre-existing conditions or age-related fragility [151] – especially as access to vaccines were universalised [152]. By comparison, immunosuppressed patients are still disproportionately represented in COVID-19 ICU data, irrespective of vaccine uptake [153]. However, this pattern of results was inconsistent between immunosuppressed categories and only reached significance amongst malignancy patients. As stated, this may be accounted for by discrepancies between years of study activity and publication year, however.

Finally, this work produced tentative evidence for the influence of age on excess immunosuppressed COVID-19 mortality compared to the immunocompetent. The consistently negative relationship that was returned for each category is intuitive given the extreme rarity of COVID-19 associated death in younger, immunocompetent patients. It is also borne out in a recent systematic review of COVID-19 infection outcomes in younger cohorts [154]. This relationship was not substantive enough to achieve statistical significance, however.

Comparison to existing literature:

Encouragingly, the findings discussed are in broad agreement with recent outputs of the INvestigation oF cOvid-19 Risk amongst iMmunoompromised populations (INFORM) study [155]. This work was the first of its kind to compare COVID-19 hospitalisations, ICU admissions and mortality across the immunosuppressed patient spectrum. A similar gradient of results was seen in this real-world investigation as our own systematic appraisal and meta-analysis of the literature. Here too, transplant and haematological malignancy patients were seen to experience consistently elevated rates of severe COVID-19 outcomes. Our work also served to add quantification, nuance and comprehensiveness to the comparable efforts of SeyedAlinaghi [156], Baek et al [157] and Belsky [158] and the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK) [153], respectively. Indeed, the comprehensiveness of this systematic review was entirely unique; as mentioned, it has not been possible to accomplish similarly differentiated work for influenza outcomes amongst the immunosuppressed [18].

Limitations:

Despite its accomplishments, this work could still benefit from addressing the following limitations.

Firstly, the population variable of interest in this work – COVID-19 infection – changed dramatically over the course of the study period. Growing medical familiarity with the virus, its continuous mutation, and the availability of vaccines and novel therapeutics meant that infection in early 2020 posed very different risks to the

immunosuppressed than infection in subsequent years [159]. Despite attempts to select for the earliest available data, it remained difficult to control for this inconsistency when pooling studies. As mentioned, discrepancies between study and publication year undermined the value of subgroup analyses by publication date for monitoring how dynamic COVID-19 mortality was over the pandemic timeline and whether patterns of risk attenuation or amplification were consistent between immunosuppressed categories and subcategories. Upon reflection, instituting a new variable, investigation start date, and differentiating analysis on this basis may have proven more informative.

Secondly, our exposure variable – adult immunosuppression (categorised and subcategorised) – was sometimes difficult to operationalise in the literature. This was especially true of medication-specific forms of immunosuppression. Our inclusion criteria were not compatible the structure of medical literature available on COVID-19 outcomes in those receiving immunosuppressives: such studies typically compared medicated immunosuppressed patients' outcomes with those of unmedicated immunosuppressed patients. Without an immunocompetent comparison point, our search parameters were violated, and potentially informative literature was discarded. Medication-specific forms of immunosuppression are also highly internally heterogeneous. The amount of immunosuppression conferred is dictated by variables including condition treated, medication dosage, time since last dose or discontinuation and patient demographics including age, sex, ethnicity, comorbidities, weight and polypharmacy – none of which were consistently reported in our literature base, precluding sensitivity or subgroup analysis. A separate systematic review and meta-analysis should therefore be carried out to risk stratify

the COVID-19 mortality risks associated with various immunosuppressive regimens, sub-analysing data by the variables specified where possible. Pooled risk estimates by medication class, as performed by this study, are too crude to be clinically informative.

Furthermore, inclusion requirements for sample sizes of over 50 patients proved prohibitive. Studies reporting the COVID-19 infection outcomes of especially rare forms of immunosuppression such as stem cell or bone marrow transplant recipients, genetically conferred conditions or less typical malignancies were excluded for this reason, despite offering eligible data in all other respects.

The choice to restrict this work's analysis to the conditions and medications that adhered to '*Immunisation against infectious disease (Green Book) Chapter 14a*' [17] criteria for immunosuppression could also be criticised. Unlike comparable sources, this definition only infers the inclusion of broader categories, but does not state them explicitly; for example, despite their well-argued immunosuppressed status [160; 161; 162; 163; 164], the COVID-19 outcomes of conditions and procedures including multiple sclerosis, asplenia and dialysis are not cited and, thereby, not examined in this work.

Comparator data from this exercise was also affected by discordant characterisations of the immunocompetent. Defining and selecting for truly well patients was challenging and close inspection of included studies' immunocompetent often revealed instances of obesity, chronic kidney disease, diabetes and other secondarily immunosuppressive conditions. This was especially common when

experimental and control cohorts were age, sex or comorbidity matched. These persistent vulnerabilities in comparator groups detracted from the validity of our pooled estimates for excess COVID-19 mortality in the immunosuppressed. It is possible that said reports were underestimates as a result.

Excess COVID-19 mortality compared to the immunocompetent, the outcome measure of this systematic review, was also not without its limitations. As already indicated, standardising the effect measures that conveyed this information (hazard, odds, incidence rate ratios etc.) likely inflated pooled estimates. Furthermore, the uniquely therapeutic effect of certain immunosuppressive medications over COVID-19 infection likely confounds the generalisability of medication-specific reporting to other infections [165]. It will be important to investigate whether the mortality gradients reported in this COVID-19 specific analysis are replicated in immunosuppressed outcomes from other types of infections. Furthermore, the exclusion of studies that reported all-cause mortality may be called into question. However, this was necessary to control for the confounding influences of indirect COVID-19 mortality on our analysis; examples such as late-stage diagnoses, treatment disruptions and mortality attributable to pre-existing diagnoses were especially prevalent in immunosuppressed cases [166; 167].

4. Chapter commentary:

The rapid scoping review and systematic review and corresponding meta-analysis broadly met their objectives: sufficient data was available within the contemporary medical literature to differentiate COVID-19 mortality outcomes between almost all Green Book immunosuppressed subgroups and, by extension, excess COVID-19

mortality compared to the immunocompetent provided a viable means of risk stratifying this diverse clinical risk group. Concordance was seen between these exercises in the following areas: there was significant heterogeneity in the immunosuppressed research landscape; a demarcation could be created between higher and lower risk immunosuppressed conditions; elevated COVID-19 mortality was seen amongst transplantation, malignancy and long-term immunosuppressive patients, lower COVID-19 mortality was seen amongst HIV and rheumatology patients. The systematic literature review and meta-analysis provided further detail on these preliminary observations, pooling the literature base to better quantify COVID-19 mortality risk in the adult immunosuppressed and identifying subcategories that experienced COVID-19 mortality levels that were disproportionate to subgroup averages. Meanwhile, the mortality data returned by the rapid scoping review on rarer immunosuppressed subgroups helped to address omissions that resulted from n>50 inclusion requirements of the systematic review.

This evidence base holds prospective value for future digital phenotyping, informing the immunosuppressed patient subgroups that should be prioritised within COVID-19 surveillance dataflows going forwards while ensuring that the clinical outcomes of those identified as historically at greatest risk are not inadvertently erased through aggregation. Indeed, Chapter 4 will demonstrate how both rapid and systematic literature review findings have been applied within targeted implementation studies and COVID-19 risk stratified disease surveillance efforts.

However, the following limitations of these literature reviews required redress by the remainder of this thesis. Firstly, the inherently backward-facing nature of literature

review reduced its predictive power for current COVID-19 risk in the immunosuppressed; historical findings may not persist over time. This intelligence can only be provided by real-time and high-resolution disease surveillance pathways.

Meanwhile, this chapter's pooled estimates for excess COVID-19 mortality were vulnerable to discordant definitions of both immunosuppression and immunocompetence; international misalignment remained unaddressed in this work. Further, the suitability of Green Book criteria for immunosuppressed patient identification and segmentation could not be fully assessed by this chapter: neither exercise was able to provide reliable estimates of the COVID-19 experiences of all conditions cited by Green Book, and comparable literature, including US Pink Book [160], US Yellow Book [161], the Australian Immunisation Handbook [163], the New Zealand Immunisation Handbook [163] and the Canadian Immunization Guide [164], propose numerous additional candidates that went unscrutinised. All these criticisms necessitated the international clinical consensus building that is described in the next chapter.

The work presented in this chapter also foreshadowed later difficulties handling and interpreting data from medication-inclusive immunosuppressed cohorts. In either literature review, it was not possible to control for variables including dosage, time on medication, time since last treatment, polypharmacy, condition being medicated and patient demographics that affect drug metabolism (age, sex, weight etc.). The uniquely therapeutic effect of certain agents on COVID-19 infection and our difficulty identifying true control groups further confounded data collection from those receiving immunosuppressive medications. Considering this, the decision was made

to develop and ratify a phenotype that only incorporated and COVID-19 risk stratified immunosuppressed diagnoses and procedures. We hypothesised, and later observed (Chapter 4), that the time and dose dependencies of medication-based immunosuppression would create major inaccuracies when codified in a digital phenotype and implemented in imperfect medical datasets. By comparison, we anticipated that phenotyping with standalone diagnostic and procedural codes would simplify extraction, analysis and interpretation without losing accuracy. Delivering and ratifying said phenotype became the primary objective of the international clinical consensus building study that follows.

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3

Can the Electronic Delphi (eDelphi) paradigm surface and ratify an internationally harmonised, COVID-19 risk stratified and computerised medical record (CMR) compatible phenotype for adult immunosuppression?

Introduction: There is currently no internationally approved definition of adult immunosuppression. Long-standing arguments regarding the procedures and diagnoses that confer immunosuppression in adults, the variables that reverse this status and the COVID-19 management of affected patients also require expert attention.

Method: 64 experts at the intersection of immunology, vaccinology and infectious disease were recruited from international vaccine advisory groups into an Electronic Delphi (eDelphi) Study to achieve consensus on a new definition of immunosuppression, the COVID-19 risks of definition constituents and the structure of a digital phenotype to COVID-19 risk stratify their surveillance moving forwards.

Results: After two rounds of anonymous questionnaire, one group feedback session and a final ratifying vote, this eDelphi panel achieved consensus on candidate diagnoses' and procedures' appropriateness for inclusion in a digital phenotype for adult immunosuppression as well as their respective vulnerability to COVID-19 compared to the immunocompetent and the wider immunosuppressed population. Consensus was also built on the variables that could reverse immunosuppressed status and the current limitations of immunosuppressed COVID-19 care. This information informed the contents and structure of the eDelphi phenotype which was approved for use in real-world data with near consensus (94%).

Discussion: This exercise surfaced an internationally harmonised, COVID-19 risk stratified and CMR compatible clinical phenotype for adult immunosuppression. The absence of prescription variables was criticised by panellists, however. Likewise, poor representation from the African and South American continents undermines the external validity of this work.

Elements of this chapter have been published [1, 2].

Leston, M., Lee, L., Ordóñez-Mena, J., Joy, M., Simon de Lusignan and Hobbs, R. (2024). Defining and Risk-Stratifying Immunosuppression (the DESTINIES Study): Protocol for an Electronic Delphi Study. JMIR research protocols, 13. doi:https://doi.org/10.2196/56271.

Leston, M., Ordóñez-Mena, J.M., Joy, M., Hobbs, F.D.R., Lusignan, S. de, Teh, B.W., Groot, I. de, McInnes, I., El, H.M., Isaacs, J., Andersson, M., Raffi, F., Lim, W.S., Conway, R., Siebert, S., Buchan, I., Underwood, M., Lowe, D., Hoerger, M. and Griffiths, C.E.M. (2025). The DESTINIES Study: an online Delphi study to build international consensus on the medical conditions and procedures that confer immunosuppression and their respective COVID-19 risk profiles. EClinicalMedicine, 83, pp.103239–103239. doi:https://doi.org/10.1016/j.eclinm.2025.103239.

1. Introduction:

Immunosuppression is a global issue. While its prevalence varies significantly between countries [3; 4; 5], it is becoming increasingly burdensome in lower income contexts. Here, population growth, aging, pollution exposure and notable increases in modifiable behavioural risks (poor dietary intake, sedentary lifestyles, tobacco and alcohol abuse etc.) have seen rates of non-communicable illnesses, including almost all forms of immunosuppression, outpace those of the communicable, neonatal, maternal and nutritional diseases that used to predominate [6]. Resource scarcity in such contexts only amplifies the need for effective needs-based allocation of medical support amongst immunosuppressed patients [7]; this is jeopardised by the non-coherence of different countries' very definitions of immunosuppression and strategies for patient prioritisation and protection [8]. A definitive approach to identifying and managing immunosuppressed patients on a needs-basis is currently missing and urgently called for [9].

The doctoral candidate hypothesised that the events of the COVID-19 pandemic, and the unprecedented evidence base it engendered, could be leveraged to supply this direction via international consensus building. Since its earliest days, protecting the clinically vulnerable has inspired unparalleled international collaboration [10]; this has encompassed global concessions to economic and social life and multilateral investments into disease surveillance infrastructure [11]. These activities have all been informed by formal consensus building exercises [12-19] – lending important precedent for the work to follow. Moreover, the universality of community testing [20] during the acute stage of the pandemic has seen immunosuppressed COVID-19 outcomes documented with unprecedented detail [21]. While this evidence base is

ripe for international consideration, it would still benefit from expert clinical consultation on the COVID-19 experiences of extremely rare or complex immunosuppressed patients and how these differ across economic contexts. Even the systematic exercise of the preceding chapter was insufficient for providing clarity on these areas with confidence. The resolution of similar knowledge gaps has required expert input at a global scale; immunosuppressed patient management is no different [22].

The eDELphi STudy to fully defINe and COVID-risk stratify ImmunosupprESsion (DESTINIES Study) responded to these developments, utilising COVID-19 prognosis as a common denominator to risk stratify the entire immunosuppressed patient spectrum. Its objectives were:

1) to achieve consensus amongst an expert panel (the DESTINIES Consortium) on the medical diagnoses and procedures that confer immunosuppressed status in adults and their respective prognoses for COVID-19 and

2) to convert this information into a COVID-19 specific, internationally aligned, risk stratified and digitally practical taxonomy of ‘adult immunosuppression’ – otherwise known as a digital phenotype – for easy integration within CMRs.

As mentioned in the preceding chapter, if realised and validated in real-world data, the latter objective has the potential to improve the granularity of immunosuppressed COVID-19 surveillance as historically highest risk patients are identified and continually monitored. As well as addressing the central objective posed by this thesis, such intelligence is vital for informing COVID-19 preventative strategies and

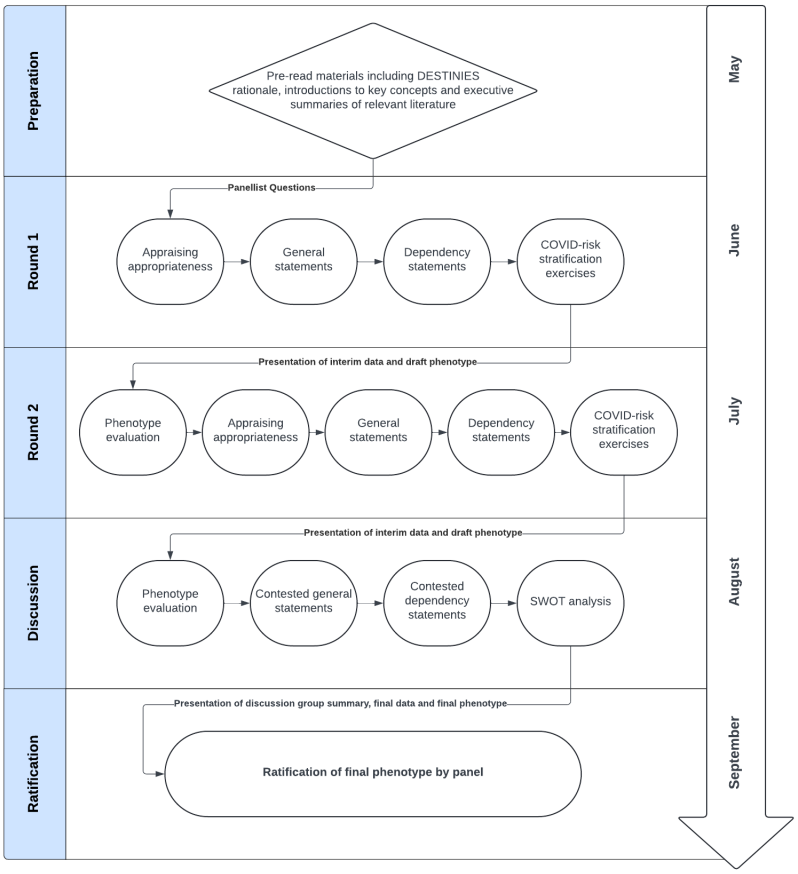
resource allocation going forwards and, subject to external validity checks, those of other disease remits.

2. Method:

Study management:

The design, implementation, analysis, write-up and dissemination of this work was directed by the DESTINIES steering group, comprised of senior researchers and statisticians at the Nuffield Department of Primary Care Health Sciences, external research collaborators, and a patient champion with lived experience of immunosuppression. This steering group met regularly over the course of the study to develop and further refine questionnaire items and data analysis plans. As per the timeline provided (Figure 3.1), this study was active between May and September 2024.

Figure 3.1: Schematic of DESTINIES Study Timeline



Ethical approval was sought for this work but, after review by both the University of Oxford Research Governance Ethics and Assurance Team and the Joint Research Office Study Classification Group, was deemed unnecessary. Both entities determined that DESTINIES study activities should be categorised as ‘pre research, priority setting or survey’ and, therefore, not subject to either the Department of Health UK Policy Framework for Health and Social Care Research [23] or sponsorship and research ethics review. This decision also aligned with directions from the Health Research Authority review algorithm [24], their attendant leaflet (*Defining Research* [25]) and the Health Care Quality Improvement Partnership *Guide for Clinical Audit, Research and Service Review* [26].

Experimental design:

Like the systematic review and meta-analysis already reported, clinical consensus exercises seek to synthesise broad, complex or contested literature to resolve prevailing conflicts in understanding or practice [27]. Unique to consensus building, however, is the diversity of sources considered: here, a greater emphasis is placed on expert opinion and qualitative methods than is standard protocol for statistical reviews [27]. Furthermore, rather than summarising a literature base or returning a cross-cutting estimate of clinical effect, consensus building exercises aim to quantify the extent to which experts or lay persons agree about a certain topic [28]. This has been integral for confirming research agendas and clinical practice guidelines or, when dissent persists, directing further investigation.

Multiple experimental designs lend empiricism to this consensus building; these include the Delphi technique, the nominal group technique and the consensus development conference [29]. Each approach operates under the working assumption that decisions or predictions made by a structured group of expert individuals are more accurate than those from said individuals alone or unstructured groups [30]. The present study opted for the Delphi method due to the compatibility of its core tenets – anonymity, iteration (data collection occurring in multiple rounds) and controlled feedback (between-round dissemination of interim results) – with the sensitivity and complexity of clinical research [27; 30]. For example, risks of group conformity (colloquially, ‘groupthink’) or deference to domineering personalities influence are especially well-controlled for in this paradigm [31].

Initially developed for military forecasting by the RAND corporation in the mid-20th century [32], the Delphi method solicits the views or testimonies of recruited experts (panellists) on prespecified topics. These panellists are presented with multiple rounds of anonymised questionnaires to systematically and quantifiably drive towards group consensus [33]; they leverage their own professional experience to do so [34], sometimes incorporating outside data or a summary of relevant literature that the research team either signposts panellists towards or provides them with directly. Depending on Delphi type (Classic, Modified, Decision, Internet/Electronic or Real-time [35]), consensus items put to panellists can range from standalone sentences to lengthy guidelines or position statements [36].

The present study utilised the Electronic, or eDelphi, method due to its advantages for international recruitment; by hosting these investigations online, geographical restrictions were removed, and the pool of prospective panellists was widened [37]. In the absence of unambiguous methodological guidelines, convention still dictates when consensus is said to have been reached in eDelphi studies [38]. In this, a quorum (or consensus threshold) is specified and agreed to by panellists before the study begins - agreement that can be measured qualitatively (via open-ended feedback) or quantitatively (via rating scales) [39]. Likewise, it is best practice to declare the number of Delphi rounds and the minimum response rate prior to study start date. A DESTINIES Study protocol was published for this purpose [1], detailing recruitment criteria, the entities approached for panellist recruitment, consensus rounds and the consensus level (≥75% panellist agreement) based on Diamond and colleagues' recommendation [40].

Recruitment:

The eDelphi methodology is not subject to a minimum or maximum sample size; as such, no sample size calculation was necessary for this investigation. Members of the following decision-making bodies were approached for recruitment to the DESTINIES Consortium:

- World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS)
- Coalition for Epidemic Preparedness Innovations (CEPI) Scientific Advisory Committee (SAC)
- The Global Immunocompromised Health Coalition (GHIC)
- The European Alliance of Associations for Rheumatology (EULAR)
- European Medicines Agency (EMA) Vaccine Working Party
- UK Joint Committee on Vaccination and Immunisation (JCVI)
- UK COVID-19 Neutralising Monoclonal Antibodies (nMABs) and Antivirals Access Independent Advisory Group (Van Tam Advisory Group)
- UK Scientific Advisory Group for Emergencies (SAGE)
- USA Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP)
- USA Food and Drug Administration (FDA) Vaccine Advisory Panel
- University of Oxford Nuffield Department of Primary Care Health Sciences (NDPCHS)
- University of Oxford Nuffield Department of Medicine (NDM)

As mentioned in the preceding chapter, only individuals with expertise in adult immunology, vaccinology or infectious disease were eligible; those with exclusively

paediatric expertise were excluded. DESTINIES Consortium recruitment was purposive, aiming to secure a globally representative and gender-balanced panel of at least 50 panellists from all clinical specialisms relevant to immunosuppression. To maximise recruitment, eligible individuals who were unable to commit to the entire study duration were invited to nominate alternates.

Those that did express an interest in participating were provided with a consent form and pre-read pack to establish baseline prior knowledge amongst panellists from diverse clinical backgrounds (Appendix 11). The latter included study rationale, executive summaries of comparative literature on COVID-19 vulnerability [21] and vaccine benefit-risk amongst the immunosuppressed [41; 42] as well as introductions to digital phenotyping [43] and clinical consensus building exercises [44]. In keeping with the Delphi principle of anonymity, panellists who returned their signed consent forms were then allocated their unique panellist identification numbers (IDs) and links to the first round of eDelphi consensus building.

In keeping with the Delphi principles of controlled feedback and iteration, panellists were given two weeks to complete each phase of the DESTINIES study and two weeks between phases to ask questions or provide feedback to Steering Group contacts (also via Google Forms) and appraise interim analyses when provided. To prevent attrition between phases, non-responding panellists were sent reminder emails on days 7, 10, 12 after the start of each new phase. Those who failed to meet study deadlines were defined as withdrawn. Unacceptable loss to follow-up was prespecified at discontinuation greater than one-third and the number, percentage and characteristics of withdrawn participants were carefully monitored to assess

potential attrition bias. Panellists had the right to withdraw at any time; however, as specified in the Panellist Information Sheet (Appendix 11), panellists were made aware that data collected up until the point of withdrawal could not be erased.

Questionnaires:

All questionnaires were hosted on Google Forms (Alphabet, Inc.), chosen due to its customisability, anonymity, advanced security measures and automated spreadsheet generation. Paper-based alternatives were offered to any panellists who felt uncomfortable using this interface. Itemised in full in Appendix 12, questionnaires consisted of closed and free text items. These assessed the appropriateness of candidate immunosuppressed diagnoses and procedures for inclusion in a COVID-19 specific phenotype for 'adult immunosuppression' and their respective levels of risk for severe infection outcomes – assessed internally (through a Higher vs Lower COVID-19 risk immunosuppressed binary) and against a baseline (through a spectrum of excess vulnerability compared to the immunocompetent).

Candidate immunosuppressed terms are listed with their sources in Table 3.1 below [45-64]; these were extracted from Green Book [65] and, to address criticisms of its completeness made in the previous chapter of this thesis, comparable international classifications of immunosuppression.

Table 3.1: List of candidate immunosuppressed terms and their sources

Candidate Term	Source(s)
Actively treated malignancy	Green Book Chapter 14a; National Institutes of Health
AIDS-defining illness	National Cancer Institute
Anorexia Nervosa	National Cancer Institute
Aplastic anaemia	Australian Immunisation Handbook
Asplenia (anatomic/ functional)	Centers for Disease Control and Prevention; Infectious Diseases Society of America; International Classification of Diseases, 10th Revision (ICD-10); Immunisation Guidelines for Ireland
Autoimmune skin diseases (e.g. Psoriasis, Dermatitis herpetiformis, Vitiligo, Pemphigus, Scleroderma, Dermatomyositis, etc.)	Green Book Chapter 14a; John's Hopkins Medicine; USA Social Security
Bone marrow transplantation	Green Book Chapter 14a
Burn injuries	Infectious Diseases Society of America
Cerebrospinal fluid leak	Infectious Diseases Society of America
Chronic kidney disease	Centers for Disease Control and Prevention
Chronic Obstructive Pulmonary Disease	Panellist recommendation
Chronic stress	Wider determinant of immunosuppression
Cochlear implant	Infectious Diseases Society of America
Cystic Fibrosis	Panellist recommendation
Dialysis	Canadian Immunization Guide; Centers for Disease Control and Prevention
Down Syndrome	New Zealand Immunisation Handbook
Drug-Managed HIV	Centers for Disease Control and Prevention; Green Book Chapter 14a
Endocrine Autoimmune disorders (e.g. Type 1 diabetes mellitus, Hashimoto's thyroiditis, Graves' disease, Addison's disease etc.)	Global Autoimmune Institute
Gastrointestinal Autoimmune Diseases (e.g. Inflammatory Bowel Syndrome, Celiac disease, Ulcerative colitis, Autoimmune hepatitis)	Green Book Chapter 14a
Generalised malignancies (metastasis)	Centers for Disease Control and Prevention
Genetic disorders affecting the immune system (e.g. SCID, complement disorder, IRAK-4, NEMO, inherited blood disorders)	Green Book Chapter 14a; ICD-10
Haematological malignancies	Green Book Chapter 14a
Haematological Autoimmune Disorders (e.g. Evan's syndrome, Immune thrombocytopenic purpura, Antiphospholipid syndrome, VEXAS etc.)	Green Book Chapter 28a; Centers for Disease Control and Prevention; Global Autoimmune Institute

Candidate Term	Source(s)
HIV infection all stages	Green Book Chapter 14a
Islet transplantation	National Institutes of Health
Liver disease (including cirrhotic)	Panellist recommendation
Malnutrition	National Cancer Institute
Multi-organ transplantation	British Columbia Centre for Disease Control; National Institutes of Health
Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome	Panellist recommendation
Nephrotic syndrome	Centers for Disease Control and Prevention
Neurological Autoimmune Conditions (e.g. Multiple sclerosis, Myasthenia gravis, Autoimmune encephalitis, Guillain-Barré syndrome etc.)	Global Autoimmune Institute
Obesity	Panellist recommendation
Ophthalmologic autoimmune conditions (e.g. Uveitis, Graves' ophthalmopathy etc.)	Global Autoimmune Institute
Pregnancy	Wider determinant of immunosuppression
Preterm births	Panellist recommendation
Renal Autoimmune Diseases (e.g. Lupus nephritis, Glomerulonephritis, IgA nephropathy etc.)	British Columbia Centre for Disease Control; Global Autoimmune Institute
Rheumatologic Disorders (e.g. Systemic lupus erythematosus, Rheumatoid Arthritis, Sjögren's syndrome, Idiopathic inflammatory myopathies, Ankylosing spondylitis, Vasculitides, Gout etc.)	Green Book Chapter 14a; World Health Organisation Vaccine Prioritisation Roadmap; USA Social Security
Sickle cell disease	Infectious Diseases Society of America
Skin graft recipients	Panellist recommendation
Sleep deprivation	Wider determinant of immunosuppression
Solid organ transplantation	Green Book Chapter 14a
Solid tumours	World Health Organisation Interim Recommendations
Stem cell transplantation	Green Book Chapter 14a
Stunting	National Cancer Institute
Type 2 diabetes mellitus	National Cancer Institute
Underlying aberrant immunity (e.g. graft-vs-host disease, graft rejection, absent or incomplete immune reconstitution, neutropenia absolute neutrophil count (ANC), lymphopenia absolute lymphocyte count (ALC)	American Society of Hematology
Unmanaged HIV	National Institutes of Health

Terms without dedicated diagnostic codes were operationalised (e.g. Anorexia nervosa and Stunting as operationalisations of Malnutrition, cited by the National Institute of Cancer [50]). Wider determinants of immunosuppression, including Pregnancy [66], Chronic stress [67] and Sleep deprivation [68], were also appraised. Panellists had the opportunity to recommend candidate immunosuppressed terms in the first round of consensus building (see 'Panellist recommendation'). In Round 2, these suggestions had their appropriateness for inclusion evaluated in turn; those that were deemed appropriate for inclusion by ≥75% of panellists were carried forward for phenotyping.

Medication classes were excluded from consideration to align with our secondary objective of producing a digitally practical COVID-19 risk stratified phenotype for 'adult immunosuppression'. As alluded to in the previous chapter and elaborated upon in the next, prescription data are insufficiently codified in CMRs to support medication-inclusive phenotyping [69]: essential details including drug type, brand, dose, polypharmacy, patient weight and prescription timing or discontinuation are not reliably available [70]. Medical diagnoses and procedures are better codified by comparison [71]. However, a series of clinical statements were presented to panellists to build consensus on medication variables that could be operationalised without prescription data (e.g. Drug-managed HIV, inferable within CMRs thanks to the near universal uptake of antiretroviral medications in developed contexts [72]). These statements also aimed to settle longstanding disputes within the immunosuppressed literature, including the exchangeability of key immunosuppressed terms, the universality of patient prioritisation and the medication time and dose thresholds that confer immunosuppression.

Questionnaire items were adapted or refined between rounds if panellists provided feedback that the steering group judged in keeping with study objectives. For example, in later versions reference populations were made explicit, the phrasing and operationalisation of candidate diagnoses were clarified, and a distinction was made between low dose (≤ 20mg per day) and very low dose (≤ 10mg per day) prednisolone in clinical consensus statements. Apart from 'Higher vs Lower risk' categorisations, all questionnaire items were Likert based. Answers at Likert poles (e.g. 'Strongly agree' and 'Somewhat agree' versus 'Strongly disagree' and 'Somewhat disagree') were combined to assess consensus direction. Middle Likert options and free text boxes allowed panellists to report any uncertainty they had in their answers. Panellists could not skip questions and were instructed not to share any identifiable information about themselves or patients while completing free text items.

Phenotyping:

Between rounds of consensus building and in preparation for final discussion, panellists were presented with the results of the preceding round and draft COVID-specific phenotypes for 'adult immunosuppression' developed by the steering group. These drafts were intended to best reflect collected data. Initially, two types of phenotypes were proposed:

1) **COVID-19 Risk Categorised Phenotypes:** A Higher vs Lower COVID-19 risk binary that categorised candidate immunosuppressed terms by risk allocation data

2) **COVID-19 Risk Stratified Phenotypes:** A multi-level COVID-19 risk hierarchy that stratified candidate immunosuppressed terms by excess vulnerability compared to the immunocompetent data

For drafts of the Risk Categorised phenotype, Higher versus Lower Risk allocation was initially determined by majority vote but distinguished the terms within each category that exceeded the ≥75% consensus level. This approach was rejected by panellists, however, and the ≥75% standard was instated for categorisation from the second round. This created a 'Contested' category for terms that did not meet this threshold. Initial labelling of these terms as 'Moderate Risk' was also rejected, with panellists requesting they be reported as 'No consensus'.

Drafts of the Risk Stratified phenotype aimed to create phenotype levels with shared excess COVID-19 vulnerability compared to the immunocompetent and common clinical denominators. This was also balanced with due consideration for population size; unbalanced phenotype levels would affect the viability of comparative analysis at implementation. Recommended by panellists, a cluster analysis of candidate terms' final vulnerability scores was performed as an additional check on the accuracy of risk stratified phenotype structure. This employed hierarchical cluster analysis – based on standardised panel vulnerability scores, Euclidian distance for dissimilarity and Ward's minimum variance for clustering – to assess candidate terms' similarity. A dendrogram was produced to illustrate these shared vulnerability profiles; candidate terms positioned closest together were most alike in panel-appraised vulnerability and, thereby, appropriate for inclusion in the same phenotype risk strata.

Final discussion groups sought to gather detailed feedback on these draft phenotypes and unresolved clinical statements. Meetings were hosted and recorded on Zoom (Zoom Video Communications, Inc); to protect panellist anonymity, panellists were supported to turn their cameras off and display their unique identifiers (IDs). Those unable to attend were invited to submit written feedback. Meeting transcripts and summaries informed the final DESTINIES phenotype that panellists then ratified via Google Form.

Data management:

Protecting panellists' right to privacy and informed consent was paramount in this work; all activities adhered to the Data Protection Act, 2018 [74]. Only the minimum required amount of identifying information was collected during this study and panellists were informed that all study data - including consent forms, completed surveys, feedback forms and discussion audio files and transcripts – would be retained for a maximum of 18 months before being destroyed. Panellist anonymity was protecting using unique IDs. Panellists were also instructed not to share any personally identifying information when completing free-text data entry or participating in final discussion groups, including that of patients previously or currently in their charge. During final discussion groups, panellists were also supported to disable their cameras and participate via their assigned IDs.

3. Results:

Recruitment:

As per Table 3.2, 64 panellists were successfully recruited to the DESTINIES Consortium; their characteristics are summarised below. All clinical specialisms of

relevance to immunosuppression were represented in this panel. There was over-representation amongst rheumatologists and those working in Europe and North America; the African and South American continents were largely and completely missing by comparison.

Table 3.2: Characteristics of the DESTINIES Consortium

		n
Country	Canada	1
	Denmark	1
	France	2
	Germany	2
	Ireland	1
	Israel	5
	Italy	2
	Mexico	1
	Netherlands	3
	Nigeria	1
	Singapore	1
	Spain	1
	Sweden	1
	Switzerland	1
	United Kingdom	29
	United States	12
Gender	Female	28
	Male	36
Affiliation	Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP)	2
	Coalition for Epidemic Preparedness Innovations (CEPI) Scientific Advisory Committee (SAC)	2
	European Medicines Agency (EMA) Vaccines Working Party	1
	European Alliance of Associations for Rheumatology (EULAR)	18
	Food and Drug Administration (FDA) Vaccine Advisory Panel	4
	Former WHO Global Advisory Committee on Vaccine Safety	1
	The Global Immunocompromised Health Coalition	7
	Joint Committee on Vaccination and Immunisation	3
	Panellist recommendation	5
	Nuffield Department of Medicine, University of Oxford	4
	Nuffield Department of Primary Care Health Sciences, University of Oxford	1
	UK Scientific Group for Emergencies (SAGE)	1
	Van Tam Independent Advisory Group	15
Discipline	**Generalist**	
	Immunology	3
	Infectious Diseases	14
	Vaccinology	9
	Specialist	
	Autoimmunity	4
	Clinical Informatics	3
	Dermatology	1
	Gastroenterology	1
	Haematology	1
	HIV	3
	Nephrology	2
	Oncology	2
	Primary Immunodeficiencies	1
	Rheumatology	16
	Transplantation	4

Detail on round-by-round panellist attrition is provided in Appendix 13. There was substantial withdrawal between online data collection and final discussion. While this was not detrimental to the evidence base that informed the DESTINIES phenotype, this did reduce the pool of panellists that were available to ratify it.

Questionnaires:

Outputs from every questionnaire presented to panellists are tabulated in Appendix 14. Final data on candidate terms' 1) appropriateness for inclusion in a COVID-19 risk stratified digital phenotype for 'adult immunosuppression', 2) excess vulnerability to severe COVID-19 outcomes compared to the immunocompetent and 3) categorisations into higher vs lower risk for severe COVID-19 outcomes within the immunosuppressed patient spectrum are provided below in Tables 3.3, 3.4 and 3.5a, b and c respectively. Tables 3.3 and 3.4 present data by clinical category to facilitate comparisons within common clinical denominators.

Disagreement persisted over the appropriateness of almost all immune mediated inflammatory disorder (IMID), anatomical barrier defect, and wider determinant terms. Candidates that met ≥75% panel agreement as inappropriate for inclusion were removed from final phenotypes; this included Chronic Stress and Sleep Deprivation. In keeping with our diagnosis and procedural approach to phenotyping, Actively Treated Malignancy patients were also dropped from drafts. Synonymous or overlapping candidates were also removed: HIV infection all stages was made redundant by the retention of Drug-managed HIV, Untreated HIV and AIDS-defining illness, for example. Finally, no candidate diagnosis suggested by panel members in Round 1 (Obesity, Skin graft recipients, Myalgic encephalomyelitis/ chronic fatigue

syndrome [ME/CFS]), Liver disease [including cirrhotic), Cystic fibrosis, Preterm births) met the ≥75% consensus level for appropriateness; they were dropped from phenotyping as a result.

Despite the superficial agreement between panellists' appraisals of appropriateness and vulnerability, there are important areas of departure. For example, amongst malignancy and transplantation candidate terms, near universal appropriateness ratings contrasted with heterogeneous vulnerability ratings.

Table 3.3: Final panel determinations on the appropriateness of candidate diagnoses for a COVID-specific phenotype of 'adult immunosuppression' (staggered over multiple pages)

	Diagnosis	Not appropriate %	Somewhat inappropriate %	Unsure %	Somewhat appropriate %	Appropriate %	Sum Inappropriate %	Sum Appropriate %	Determination
Malignancy	Actively treated malignancy	0.0	0.0	1.7	20.0	78.3	0.0	98.3	*Appropriate*
	Haematological malignancies	0.0	0.0	0.0	5.0	95.0	0.0	100.0	*Appropriate*
	Generalised malignancies (metastasis)	0.0	1.7	6.7	26.7	65.0	1.7	91.7	*Appropriate*
	Solid tumours	0.0	5.0	13.3	41.7	40.0	5.0	81.7	*Appropriate*
Transplantation	Bone marrow transplantation	0.0	0.0	0.0	3.3	96.7	0.0	100.0	*Appropriate*
	Islet transplantation	1.7	3.3	16.7	33.3	45.0	5.0	78.3	*Appropriate*
	Multi-organ transplantation	0.0	0.0	1.7	1.7	96.7	0.0	98.3	*Appropriate*
	Solid organ transplantation	0.0	0.0	0.0	3.3	96.7	0.0	100.0	*Appropriate*
	Stem cell transplantation	0.0	0.0	0.0	1.7	98.3	0.0	100.0	*Appropriate*
Primary & Acquired Immunodeficiency	AIDS-defining illness	0.0	1.7	0.0	18.3	80	1.7	98.3	*Appropriate*
	Down Syndrome	0.0	11.7	21.7	45.0	21.7	11.7	66.7	Contested
	Drug-managed HIV	13.3	38.3	21.7	20.0	6.7	51.7	26.7	Contested
	Genetic disorders affecting the immune system	0.0	3.3	3.3	18.3	75.0	3.3	93.3	*Appropriate*
	HIV infection all stages	5.0	46.7	11.7	26.7	10.0	51.7	36.7	Contested
	Underlying aberrant immunity	0.0	1.7	1.7	28.3	68.3	1.7	96.7	*Appropriate*
	Untreated HIV	1.7	3.3	3.3	31.7	60.0	5	91.7	*Appropriate*

	Diagnosis	Not appropriate %	Somewhat inappropriate %	Unsure %	Somewhat appropriate %	Appropriate %	Sum Inappropriate %	Sum Appropriate %	Determination
Immune mediated inflammatory disorders	Autoimmune skin disorders	0.0	25.0	31.7	36.7	6.7	25.0	43.3	Contested
	Endocrine autoimmune disorders	3.3	35.0	25.0	31.7	5.0	38.3	36.7	Contested
	Gastrointestinal autoimmune disorders	0	18.3	18.3	53.3	10	18.3	63.3	Contested
	Hematologic autoimmune disorders	1.7	13.3	26.7	43.3	15	15.0	58.3	Contested
	Myalgic encephalomyelitis/ chronic fatigue syndrome	45	21.7	28.3	3.3	1.7	66.7	5.0	Contested
	Neurologic autoimmune disorders	0.0	16.7	21.7	51.7	10.0	16.7	61.7	Contested
	Ophthalmologic autoimmune disorders	6.7	38.3	25.0	23.3	6.7	45.0	30.0	Contested
	Renal autoimmune disorders	0.0	10.0	16.7	50.0	23.3	10.0	73.3	Contested
	Rheumatologic disorders	0.0	15.0	8.3	58.3	18.3	15.0	76.7	*Appropriate*
Disorders affecting haematopoiesis	Aplastic anaemia	1.7	13.3	8.3	33.3	43.3	15.0	76.7	*Appropriate*
	Asplenia (anatomic/ functional)	8.3	10.0	11.7	35.0	35.0	18.3	70.0	Contested
	Chronic kidney disease	1.7	15.0	18.3	46.7	18.3	16.7	65.0	Contested
	Dialysis	0.0	6.7	6.7	45.0	41.7	6.7	86.7	*Appropriate*
	Liver disease (including cirrhotic)	0.0	16.7	11.7	50.0	21.7	16.7	71.7	Contested
	Nephrotic disease	1.7	15.0	15.0	43.3	25.0	16.7	68.3	Contested
	Sickle cell disease	8.3	16.7	23.3	33.3	18.3	25.0	51.7	Contested
Lung disorders	Chronic obstructive pulmonary disease	6.7	23.3	13.3	43.3	13.3	30.0	56.7	Contested
	Cystic fibrosis	5.0	16.7	8.3	35.0	35.0	21.7	70.0	Contested
Anatomical barrier defects	Burn injuries	11.7	28.3	20.0	31.7	8.3	40.0	40.0	Contested
	Cerebrospinal fluid leak	18.3	26.7	28.3	15.0	11.7	45.0	26.7	Contested
	Cochlear implant	31.7	31.7	20.0	8.3	8.3	63.3	16.7	Contested
	Skin graft recipients	16.7	23.3	26.7	26.7	6.7	40.0	33.3	Contested

	Diagnosis	Not appropriate %	Somewhat inappropriate %	Unsure %	Somewhat appropriate %	Appropriate %	Sum Inappropriate %	Sum Appropriate %	Determination
Wider determinants of immunosuppression	Anorexia nervosa	41.67	15	23.3	16.7	3.3	56.7	20.0	Contested
	Chronic stress	58.3	18.3	15.0	6.7	1.7	76.7	8.3	*Inappropriate*
	Malnutrition	30.0	16.7	21.7	26.7	5.0	46.7	31.7	Contested
	Obesity	18.3	33.3	16.7	26.7	5.0	51.7	31.7	Contested
	Pregnancy	16.7	20.0	10.0	41.7	11.7	36.7	53.3	Contested
	Preterm births	3.3	20.0	21.7	31.7	23.3	23.3	55.0	Contested
	Sleep deprivation	60.0	18.3	16.7	3.3	1.7	78.3	5.0	*Inappropriate*
	Stunting	45.0	25.0	23.3	5.0	1.7	70.0	6.7	Contested
	Type 2 diabetes mellitus	10.0	35.0	16.7	31.7	6.7	45.0	38.3	Contested

Table 3.4: Candidate diagnoses' excess vulnerability to severe COVID-19 outcomes compared to the immunocompetent (staggered over multiple pages)

	Diagnosis	No additional vulnerability %	Slightly elevated vulnerability %	Significantly elevated vulnerability %	High vulnerability %	Extremely high vulnerability %	Sum minimal additional vulnerability %	Sum major additional vulnerability %	Determination
Malignancy	Actively treated malignancy	1.7	13.3	16.7	40.0	28.3	15.0	68.3	Contested
	Haematological malignancies	0.0	8.3	21.7	40.0	30.0	8.3	70.0	Contested
	Generalised malignancies (metastasis)	0	1.7	6.7	26.7	65.0	1.7	91.7	*Major additional vulnerability*
	Solid tumours	0	15	31.7	36.7	16.7	15.0	53.3	Contested
Transplantation	Bone marrow transplantation	0.0	0.0	6.7	8.3	85.0	0.0	93.3	*Major additional vulnerability*
	Islet transplantation	5.0	8.3	28.3	33.3	25.0	13.3	58.3	Contested
	Multi-organ transplantation	0.0	0.0	5.0	10.0	85.0	0.0	95.0	*Major additional vulnerability*
	Solid organ transplantation	0.0	0.0	10.0	13.3	76.7	0.0	90.0	*Major additional vulnerability*
	Stem cell transplantation	0.0	0.0	5.0	10.0	85.0	0.0	95.0	*Major additional vulnerability*
Primary & Acquired Immunodeficiency	AIDS-defining illness	0.0	3.3	21.7	26.7	48.3	3.3	75.0	*Major additional vulnerability*
	Down Syndrome	5.0	21.7	41.7	21.7	10.0	26.7	31.7	Contested
	Drug-managed HIV	38.3	43.3	15.0	3.3	0.0	81.7	3.3	*Minimal additional vulnerability*
	Genetic disorders affecting the immune system	0.0	3.3	8.3	30.0	58.3	3.3	88.3	*Major additional vulnerability*
	HIV infection all stages	5.0	48.3	21.7	20.0	5.0	53.3	25.0	Contested
	Underlying aberrant immunity	0.0	11.7	10.0	36.7	41.7	11.7	78.3	*Major additional vulnerability*
	Untreated HIV	1.7	13.3	26.7	41.7	16.7	15.0	58.3	Contested

	Diagnosis	No additional vulnerability %	Slightly elevated vulnerability %	Significantly elevated vulnerability %	High vulnerability %	Extremely high vulnerability %	Sum minimal additional vulnerability %	Sum major additional vulnerability %	Determination
Immune mediated inflammatory disorders	Autoimmune skin disorders	8.3	60.0	21.7	8.3	1.7	68.3	10.0	Contested
	Endocrine autoimmune disorders	16.7	50.0	23.3	10.0	0.0	66.7	10.0	Contested
	Gastrointestinal autoimmune disorders	6.7	51.7	26.7	15.0	0.0	58.3	15.0	Contested
	Hematologic autoimmune disorders	8.3	31.7	36.7	18.3	5.0	40.0	23.3	Contested
	Myalgic encephalomyelitis/ chronic fatigue syndrome	70.0	26.7	1.7	1.7	0.0	96.7	1.7	*Minimal additional vulnerability*
	Neurologic autoimmune disorders	6.7	45.0	33.3	15.0	0.0	51.7	15.0	Contested
	Ophthalmologic autoimmune disorders	28.3	51.7	13.3	6.7	0.0	80.0	6.7	*Minimal additional vulnerability*
	Renal autoimmune disorders	5.0	23.3	38.3	28.3	5.0	28.3	33.3	Contested
	Rheumatologic disorders	3.3	26.7	43.3	23.3	3.3	30.0	26.7	Contested
Disorders affecting haematopoiesis	Aplastic anaemia	10.0	26.7	20.0	36.7	6.7	36.7	43.3	Contested
	Asplenia (anatomic/ functional)	20.0	30.0	23.3	21.7	5.0	50.0	26.7	Contested
	Chronic kidney disease	1.7	28.3	40.0	30.0	0.0	30.0	30.0	Contested
	Dialysis	0.0	21.7	28.3	35.0	15.0	21.7	50.0	Contested
	Liver disease (including cirrhotic)	8.3	33.3	36.7	18.3	3.3	41.7	21.7	Contested
	Nephrotic disease	3.3	35.0	33.3	26.7	1.7	38.3	28.3	Contested
	Sickle cell disease	13.3	35.0	28.3	21.7	1.7	48.3	23.3	Contested
Lung disorders	Chronic obstructive pulmonary disease	10.0	21.7	35.0	25.0	8.3	31.7	33.3	Contested
	Cystic fibrosis	8.3	23.3	35.0	20.0	13.3	31.7	33.3	Contested

	Diagnosis	No additional vulnerability %	Slightly elevated vulnerability %	Significantly elevated vulnerability %	High vulnerability %	Extremely high vulnerability %	Sum minimal additional vulnerability %	Sum major additional vulnerability %	Determination
Anatomical barrier defects	Burn injuries	43.3	28.3	20.0	8.3	0.0	71.7	8.3	Contested
	Cerebrospinal fluid leak	55.0	28.3	6.7	8.3	1.7	83.3	10.0	*Minimal additional vulnerability*
	Cochlear implant	66.7	16.7	6.7	8.3	1.7	83.3	10.0	*Minimal additional vulnerability*
	Skin graft recipients	41.7	33.3	10.0	13.3	1.7	75.0	15.0	*Minimal additional vulnerability*
Wider determinants of immunosuppression	Anorexia nervosa	45.0	41.7	11.7	1.7	0.0	86.7	1.7	*Minimal additional vulnerability*
	Chronic stress	63.3	31.7	3.3	1.7	0.0	95.0	1.7	*Minimal additional vulnerability*
	Malnutrition	31.7	46.7	16.7	5.0	0.0	78.3	5.0	*Minimal additional vulnerability*
	Obesity	21.7	43.3	18.3	13.3	3.3	65.0	16.7	Contested
	Pregnancy	6.7	43.3	23.3	25.0	1.7	50.0	26.7	Contested
	Preterm births	16.7	38.3	30.0	13.3	1.7	55.0	15.0	Contested
	Sleep deprivation	70.0	26.7	1.7	1.7	0.0	96.7	1.7	*Minimal additional vulnerability*
	Stunting	61.7	31.7	5.0	1.7	0.0	93.3	1.7	*Minimal additional vulnerability*
	Type 2 diabetes mellitus	15.0	48.3	20.0	16.7	0.0	63.3	16.7	Contested

Table 3.5a: Panel categorisations for higher vs lower risk for severe COVID-19 outcomes within the immunosuppressed patient spectrum, higher risk

Diagnosis	Higher Risk (n)	Higher Risk (%)	Lower Risk (n)	Lower Risk (%)	Determination
Bone marrow transplant	59	98.3	1	1.7	Higher Risk
Haematological malignancies	59	98.3	1	1.7	Higher Risk
Multi-organ transplant	59	98.3	1	1.7	Higher Risk
Solid organ transplant	59	98.3	1	1.7	Higher Risk
Stem cell transplant	59	98.3	1	1.7	Higher Risk
Actively treated malignancies	56	93.3	4	6.7	Higher Risk
AIDS-defining illness	56	93.3	4	6.7	Higher Risk
Genetic diseases (PIDs)	56	93.3	4	6.7	Higher Risk
Untreated HIV	55	91.7	5	8.3	Higher Risk
Generalised malignancies (metastasis)	54	90.0	6	10.0	Higher Risk
Underlying aberrant immunity	53	88.3	7	11.7	Higher Risk
Islet transplant	52	86.7	8	13.3	Higher Risk
Dialysis	50	83.3	10	16.7	Higher Risk
Renal autoimmune	46	76.7	14	23.3	Higher Risk
Aplastic anaemia	45	75.0	15	25.0	Higher Risk
Solid tumours	45	75.0	15	25.0	Higher Risk

Table 3.5b: Panel categorisations for higher vs lower risk for severe COVID-19 outcomes within the immunosuppressed patient spectrum, lower risk

Diagnosis	Higher Risk (n)	Higher Risk (%)	Lower Risk (n)	Lower Risk (%)	Determination
Cerebrospinal fluid leak	14	23.3	46	76.7	Lower Risk
Anorexia nervosa	12	20.0	48	80.0	Lower Risk
Cochlear implants	11	18.3	49	81.7	Lower Risk
Stunting	8	13.3	52	86.7	Lower Risk
Drug-managed HIV	7	11.7	53	88.3	Lower Risk
Chronic stress	6	10.0	54	90.0	Lower Risk
Sleep deprivation	6	10.0	54	90.0	Lower Risk
ME/CFS	4	6.7	56	93.3	Lower Risk

Table 3.5c: Panel categorisations for higher vs lower risk for severe COVID-19 outcomes within the immunosuppressed patient spectrum, no consensus

Diagnosis	Higher Risk (n)	Higher Risk (%)	Lower Risk (n)	Lower Risk (%)	Determination
Chronic kidney disease	44	73.3	16	26.7	No consensus
Rheumatological disorders	44	73.3	16	26.7	No consensus
Nephrotic syndrome	43	71.7	17	28.3	No consensus
Chronic Obstructive Pulmonary Disease	42	70.0	18	30.0	No consensus
Cystic fibrosis	42	70.0	18	30.0	No consensus
Haematologic autoimmune disorders	41	68.3	19	31.7	No consensus
Down syndrome	39	65.0	21	35.0	No consensus
Liver disease (including cirrhotic)	39	65.0	21	35.0	No consensus
Sickle cell disease	39	65.0	21	35.0	No consensus
HIV infection (all levels)	37	61.7	23	38.3	No consensus
Asplenia (functional or anatomic)	36	60.0	24	40.0	No consensus
Neurologic autoimmune disorders	36	60.0	24	40.0	No consensus
Pregnancy	33	55.0	27	45.0	No consensus
Preterm births	33	55.0	27	45.0	No consensus
Obesity	29	48.3	31	51.7	No consensus
Gastrointestinal autoimmune disorders	28	46.7	32	53.3	No consensus
Autoimmune skin disorders	23	38.3	37	61.7	No consensus
Endocrine autoimmune disorders	22	36.7	38	63.3	No consensus
Type 2 Diabetes	20	33.3	40	66.7	No consensus
Burn injuries	17	28.3	43	71.7	No consensus
Malnutrition	17	28.3	43	71.7	No consensus
Skin grafts	17	28.3	43	71.7	No consensus
Ophthalmologic autoimmune disorders	16	26.7	44	73.3	No consensus

Panel 1 distinguishes between the clinical statements that did and did not achieve panel consensus.

Panel 1: DESTINIES Consortium appraisals of general and dependency clinical statements
Of the clinical statements presented to panellists, consensus was achieved on the following:
General clinical statements:
≥75% AGREE

- *'Immunosuppression is poorly defined'* (92%)
- *'COVID care for the immunosuppressed – including vaccination and the release of antivirals and other resources – is overly one size fits all'* (82%)

≥75% DISAGREE

- *'COVID-19 no longer poses a real risk to the immunosuppressed'* (97%)
- *'Vulnerability to COVID-19 is similar for all immunosuppressed subgroups'* (97%)

Dependency clinical statements:
≥75% AGREE

- *'A patient would no longer be considered immunosuppressed if…*
  - *their immunosuppressive regimen was discontinued more than 3 years ago'* (90%)
  - *their HIV was drug managed'* (82%)
  - *their immunosuppressive regimen was discontinued more than 1 year ago'* (82%)
  - *their cancer was in remission'* (77%)

≥75% DISAGREE

- *'A patient would no longer be considered immunosuppressed if…*
  - *they had been on immunosuppressive treatment for less than 6 months'* (85%)
  - *their cancer was untreated'* (77%)

However, consensus was not achieved on the following:
General clinical statements:

- *'Our current clinical definition for immunosuppression is too expansive'*
- *'Our current clinical definition for immunosuppression is not expansive enough'*
- *'The terms 'immunosuppression' and 'immunocompromised' can be used interchangeably'*
- *'The needs of the immunosuppressed are sufficiently prioritised in times of public health emergency'*
- *'It is easy to pick out the immunosuppressed subgroups at most risk for COVID-19*
- *'The immunosuppressed subgroups that are at most risk for COVID-19 are the same subgroups at most risk for other infectious diseases (Respiratory syncytial virus, influenza, bacterial pneumonia etc.)'*

Dependency clinical statements:

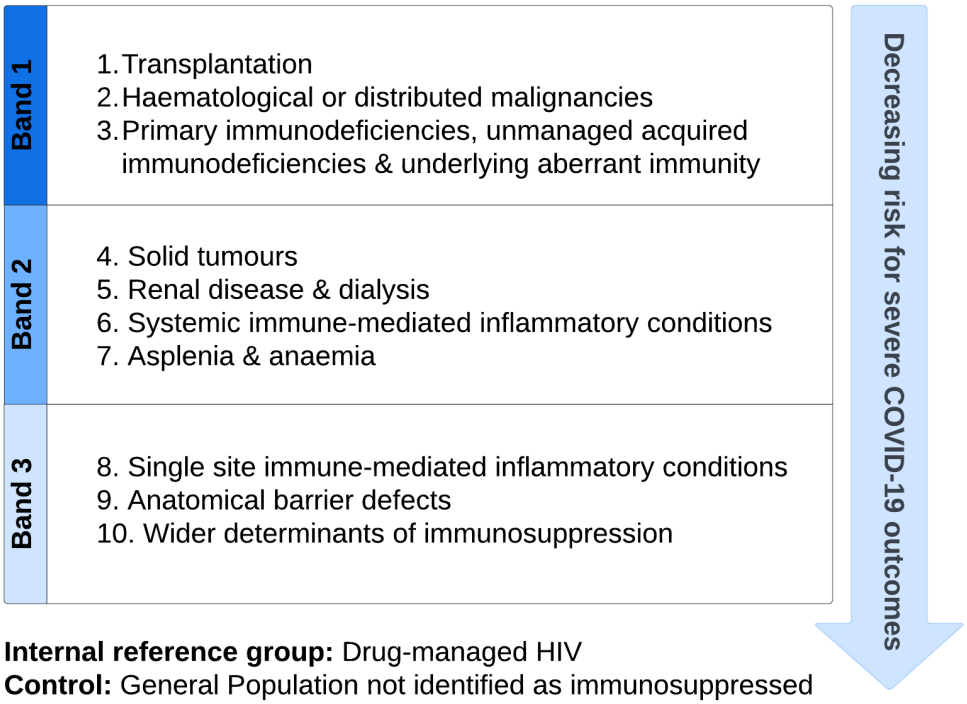
- *'A patient would no longer be considered immunosuppressed if…*
  - *their cancer is classed as Early Stage (Stage I)'*
  - *their inflammatory disease is currently untreated'*
  - *Their immunosuppressive regimen was discontinued more than 6 months ago'*
  - *They are on low dose immunosuppressives (equivalent of ≤ 20 mg of prednisolone)'*
  - *They are on very low dose immunosuppressives (equivalent of ≤ 10 mg of prednisolone)'*

Phenotyping:

A summary document of all points raised during DESTINIES Final Discussion Groups is provided in Appendix 15; a total of twelve were hosted to fit within sociable hours of attending panellists. All iterations of draft Risk Categorised and Risk Stratified phenotypes for adult immunosuppression and their evaluation data are also provided within Appendix 16.

As requested during final discussions, only a single phenotype was ratified for onward use in real-world data (the DESTINIES phenotype; Figure 3.2 and operationalised in Panel 2); this utilised risk bands to reconcile Risk Categorised and Risk Stratified approaches. Phenotype levels and their contents (relative to each level) are presented in descending order of risk for severe COVID-19 outcomes. Band 1 levels were evaluated as at major risk for severe COVID-19 outcomes, Band 2 levels as at moderate risk for severe COVID-19 outcomes and Band 3 levels as at minimal risk for severe COVID-19 outcomes. Italicised text denotes key exclusions; these were restricted to those that would be implementable within CMRs.

Figure 3.2: The DESTINIES phenotype



Internal reference group: Drug-managed HIV
Control: General Population not identified as immunosuppressed

Panel 2: Operationalisation of the DESTINIES phenotype

1. Transplantations:

Hematopoietic stem cell transplantation (Bone Marrow/ Stem Cell transplantation)
Multi-Organ Transplantation
Solid Organ Transplantation
Islet Transplantation

2. Haematological or distributed malignancies

Haematological Malignancies
Generalised Malignancies (metastasis)
Medical records with remission codes excluded

3. Primary immunodeficiencies, unmanaged acquired immunodeficiencies & underlying aberrant immunity

Genetic disorders of the immune system (Primary Immunodeficiencies: e.g. SCID)
AIDS-defining Illness (HIV-related conditions including tuberculosis, Kapsi's sarcoma, candidiasis, histoplasmosis, isosporiasis, recurrent pneumonia etc.) & Unmanaged HIV
Underlying aberrant immunity (e.g. graft-vs-host disease, graft rejection, absent or incomplete immune reconstitution, neutropenia ANC, lymphopenia ALC, secondary hypogammaglobinaemia etc.)
Down syndrome

4. Solid tumours

Medical records with remission codes excluded

5. Renal Disease & Dialysis

Dialysis
Renal Autoimmune Conditions (e.g. Lupus nephritis, Glomerulonephritis, IgA nephropathy etc.)
Chronic Kidney Disease (Late Stage, 4+)
Nephrotic Syndrome
Excluding Chronic Kidney Disease < Stage 4

6. Systemic immune-mediated inflammatory conditions

Rheumatological autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, idiopathic inflammatory myopathies, ankylosing spondylitis, vasculitides, gout etc.)
Haematological autoimmune diseases (e.g. Evan's syndrome, immune thrombocytopenic purpura, antiphospholipid syndrome, autoimmune neutropenia, VEXAS etc.)
Gastrointestinal autoimmune conditions (e.g. celiac disease, Crohn's disease, ulcerative colitis, autoimmune gastritis, microscopic colitis, autoimmune pancreatitis, autoimmune hepatitis etc.)
Neurological autoimmune conditions (e.g. multiple sclerosis, myasthenia gravis, neuromyelitis optica etc.)

7. Anaemia & asplenia

Severe anaemia (e.g. aplastic anaemia, pernicious anaemia, autoimmune haemolytic anaemia etc.)
Sickle cell disease
Asplenia (functional or anatomic)
Generic/ mild cases of anaemia excluded

8. Single site immune-mediated inflammatory conditions

Autoimmune skin conditions (e.g. psoriasis, dermatitis herpetiformis, vitiligo, pemphigus, scleroderma, dermatomyositis etc.)
Endocrine autoimmune conditions (e.g. Type 1 diabetes mellitus, Hashimoto's thyroiditis, Graves' disease, Addison's disease etc.)
Ophthalmological autoimmune conditions (e.g. Uveitis, Graves' ophthalmopathy etc.)

9. Anatomical Barrier Defects

Severe burn Injuries
Cerebrospinal Fluid Leak
Cochlear Implant
Mild/ moderate burns excluded (< Stage 3)

10. Wider determinants of immunosuppression

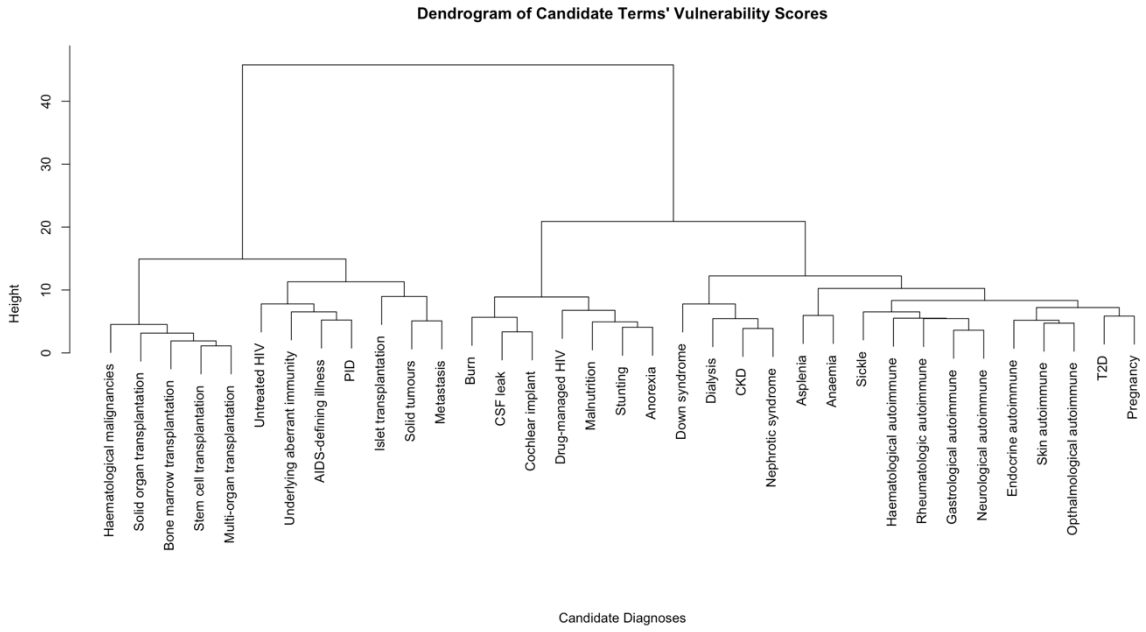
Pregnancy (final trimester)
Type 2 Diabetes
Malnutrition (operationalised as anorexia nervosa & stunting)
Excluding pregnancies earlier than 3rd trimester

Internal reference group: Drug-managed HIV
Control: General Population not identified as immunosuppressed

To reflect panel consensus that *'a patient would no longer be considered immunosuppressed if their HIV was drug-managed'*, Drug-manged HIV was removed from the main body of the phenotype. This will be trialled as an internal reference group for comparative research – offering a point of relative immunocompetence and a better demographic and vaccine uptake match to the immunosuppressed than the general population control.

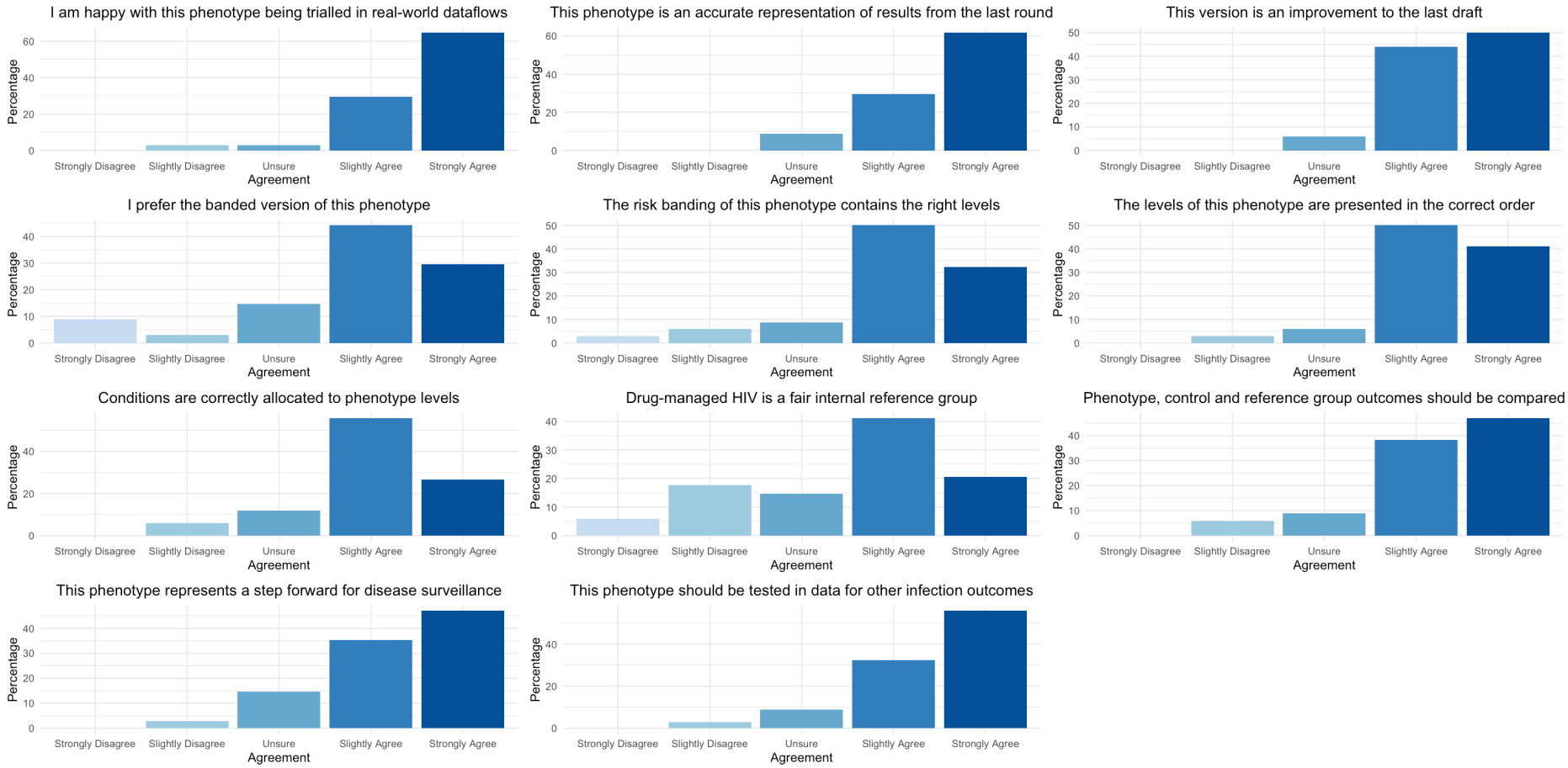
A dendrogram of the cluster analysis of final vulnerability scores that served as an additional check on phenotype structure is provided in Figure 3.3. Risk stratified phenotype levels were sufficiently consistent with dendrogram clusters to be presented to panellists for final evaluation and ratification.

Figure 3.3: A dendrogram of cluster analysed excess vulnerability scores



Final ratification data are illustrated in Figure 3.4 below and reported in full within Appendix 17.

Figure 3.4: DESTINIES Consortium ratification of the DESTINIES phenotype



Panellists agreed with near unanimity that the DESTINIES phenotype was an improvement from previous drafts (94%), warranted being trialled in real-world data (94%) and represented study results accurately (91%). Phenotype contents and cadence also exceeded 75% consensus and panellists agreed on the exploratory value of comparing phenotype, reference and control group data for COVID-19 (85%) and other infection outcomes (Respiratory syncytial virus [RSV], pneumonia, seasonal influenza etc; 88%). With 24% disagreement, there were reservations around the use of Drug-managed HIV as an internal reference group; implementation studies, such as those summarised in the subsequent chapter, will determine its retention in this capacity.

4. Discussion:

Principal findings and their implications:

This study delivered the following outputs: a COVID-19 specific, internationally ratified and digitally practical phenotype for ‘adult immunosuppression’, current international consensus on immunosuppressed diagnoses and procedures at higher and lower risk for severe COVID-19 outcomes and agreement on a wide range of hitherto contended clinical statements. Subject to validation in real-world data, these outputs hold significant promise for COVID-19 surveillance and targeted patient support. More granular intelligence can inform the allocation of COVID-specific medical resources (booster vaccinations, monoclonal antibodies, convalescent plasma, antivirals etc) and non-pharmaceutical interventions including shielding, improved ventilation and continued mask wearing in public spaces.

Those identified with consensus as at greatest risk for severe COVID-19 outcomes included Haemopoietic transplant and Solid organ transplant recipients, those with malignancies (Solid tumour and Haematological) and Primary Immunodeficiency, Aplastic anaemia, Renal autoimmune and Dialysis patients. Meanwhile, Drug-managed HIV and the majority of Anatomical barrier defect and Wider determinants of immunosuppression candidates were deemed at lowest risk of severe COVID-19 within the immunosuppressed spectrum. This has strong concordance with findings in the previous chapter and confirms the high-risk status of primary immunodeficiencies that evaded rapid scoping review.

Despite multiple rounds of data collection and discussion, panellists failed to agree on either the appropriateness or COVID-19 risk profiles of certain candidate terms, however. Immune mediated inflammatory disorders were especially affected. There was also significant heterogeneity within common clinical categories. This served as a reminder for the complexity and idiosyncrasy of immunosuppression and the dynamic nature of their vulnerability: panellists continually caveated the influence of individual medication and demographic factors (e.g. age or comorbidity) when making their appraisals – caveats that are too nuanced to be codified in a CMR-compatible phenotype at this moment in time.

Consensus was achieved on the following clinical statements: that immunosuppression was poorly defined, that COVID-19 continued to endanger these patients, that this threat was not experienced equally across the patient spectrum and that COVID-19 care was still insufficiently targeted to protect those most at risk. Agreement was also reached on the reversal of immunosuppressed

status if a patient's HIV was sufficiently drug-managed, if a patient's cancer went into remission and if their immunosuppressive medications had been discontinued for over one year. Meanwhile, adherence to an immunosuppressive regimen for six months or longer was sufficient for conferring immunosuppression. Panellists noted exceptions to these areas of agreement, however – citing the long-term, even lifelong immunosuppression associated with rituximab and other B-Cell depleting therapies, and the non-reversal of immunosuppressed status if a cancer treated via haemopoietic transplantation achieved remission. Drug equivalence statements were rejected outright; immunosuppressive regimens were considered completely non-comparable and, thereby, non-standardisable.

As discussed elsewhere, the heterogeneity of COVID-19 risk profiles within common clinical categories demonstrates the importance of constructing digital phenotypes that do not collapse higher risk diagnoses or procedures into a more moderate category average. The DESTINIES phenotype achieves this, elevating Metastasising cancer, Unmanaged HIV and Systemic immune-mediated inflammatory disease from their respective clinical categories. When implemented in real-world data, this will reduce the likelihood that sub-trends of clinical importance are erased and, in so doing, retain a higher degree of visibility on the infection outcomes of those at greatest risk for severe or critical infection.

Viewing the immunosuppressed as a minor and thus low-priority group leads to underinvestment in their interests with severe health consequences [74]. The holistic interpretation of immunosuppression offered by the DESTINIES phenotype has the benefit of alerting policymakers, pharmaceutical companies and the wider public to

the scale of vulnerability in their communities. That said, panellists warned against prioritising all DESTINIES phenotype contents for enhanced care; this would not be economically viable in any public health system [75]. If validated in real-world data, risk banding and dependency clinical statements should direct resources, with stock and shielding notices prioritised for those confirmed as at highest risk. This is intended to prevent the over-scoping that strained resource allocation during the acute phase of the COVID-19 pandemic [76].

Finally, this work is the first to address international inconsistencies in how immunosuppression is defined and risk assessed through the lens COVID-19. Consortium members acknowledged that this was an exceedingly difficult exercise with significant heterogeneity and uncertainty to navigate; achieving consensus in any domain was considered an accomplishment, bringing clarity to long-disagreed topics in the field. Completed late 2024, its timeliness serves as a reminder of the ongoing threat COVID-19 poses to the immunosuppressed; these patients' interests must not be deprioritised even now the acute stage of the pandemic has passed. This adds to a growing chorus from leadership in industry [77] and non-profits [78] to renew investment in COVID-19 protections for the immunosuppressed. The calibre, global scope and gender-balance of consortium members are further strengths of this work.

Comparison to existing literature:

Consensus studies regarding the immunosuppressed ordinarily focus upon a single clinical issue within specific condition, medication class or procedure known to confer immunosuppression [79; 80; 81]. Although the COVID-19 pandemic necessitated

some exercises that handled these patients as a singular entity – namely building consensus on vaccination strategy [82] - to the best of the doctoral candidate's knowledge, this exercise is the first to field international perspectives on the very composition of this group and their respective risks for critical illness. Maintaining both broad and narrowed criterion for immunosuppression is not without precedent, however: this was the approach taken by Evans and colleagues (2023) to clarify COVID-19 outcomes in the immunosuppressed during the omicron era [41].

That said, the DESTINIES Study is unique in its ratification of the removal of drug-managed HIV from immunosuppressed criteria. This result is momentous given the longstanding vulnerability of this population and demonstrates the necessity of drug equity initiatives, including the World Health Organisation's 90:90:90 initiative [83]. Panel ratification of Wider determinants of immunosuppression, Anatomical barrier defects and the demarcation between Systemic and Single site immune-mediated inflammatory conditions added scope and detail to existing definitions of immunosuppression.

Limitations:

Despite these achievements, the DESTINIES Study suffered from the following limitations. As highlighted within the study protocol [1], the Delphi method is not underpinned by standardised reporting guidelines. This creates considerable inconsistency in how these studies are conducted and enables a high degree of flexibility and iteration during investigations. Such revisionism – including the changes that were made to DESTINIES' questionnaires and statistical analysis plans based on panel feedback - could be criticised as unscientific. Likewise, providing

panellists with interim data to inform said feedback may inadvertently have produced groupthink or pressure for dissenting views to conform.

Panellists were also frustrated by their inability to provide medicated versus unmedicated appraisals of candidates' COVID-19 risk. For example, the immunosuppressive nature of certain medical conditions, such as asthma, is entirely predicated on medication. While panellists appreciated the difficulties and poor accuracy associated with operationalising a medication-inclusive phenotype in real-world data, they questioned the comprehensiveness of the DESTINIES phenotype without these considerations. The subjectivity or vagueness of certain candidate terms (e.g. Underlying aberrant immunity) also caused concern. These issues blocked consensus on the evaluations of several candidate terms. It is therefore our recommendation that a separate, but similar, eDelphi exercise be arranged to build international consensus on the types of medications and prescription-specific factors that confer immunosuppression and their respective COVID-19 risk profiles. Subject to validation in real-world data, this could augment the present DESTINIES phenotype, providing parallel axes for COVID-19 risk appraisal and onwards segmentation of surveillance dataflows.

The highly generalised nature of the clinical statements put to panellists was also detrimental to consensus building. Many topics were extremely context dependent. Panellists were especially resistant to identifying a standardised medication dosage or time point where immunosuppressed status would be reversed; this will be communicated to the authors of clinical guidelines that attempt this [65].

Panel composition can also be criticised in several ways: a recruitment strategy that targeted public health agencies was not purposive enough to secure a fully representative panel. The absence or underrepresentation of certain continents were detrimental; low- or middle-income country (LMIC) contexts and considerations were insufficiently addressed. Representativeness was also eroded by attrition between Round 2 and Final Discussion. These in-person discussion groups were affected by scheduling conflicts and often coincided with annual leave. It was an oversight to not remind those struggling to accommodate their in-person timeslots that written participation would be accepted. Further, choosing to exclusively recruit hospital-based specialists for this exercise – and omitting the general practitioner perspective - may have artificially inflated COVID-19 risk assessments: hospital-based specialists only encounter highest risk patients or those experiencing worst COVID-19 outcomes. Finally, despite approaching the patient champions of target entities, none agreed to participate in this work. Patient ratification is essential for go-forward usage of the DESTINIES phenotype. This has since been addressed through the recruitment of a DESTINIES Immunosuppressed Patient Panel. Elaborated upon in the next chapter, this thesis concluded with a consultation exercise and ratifying vote amongst this panel; patient feedback was obtained on the DESTINIES phenotype and the results of its initial implementation in real-world data assets.

As a collective, these limitations currently preclude the DESTINIES phenotype from supporting clinical decision-making; it must be validated within real-world dataflows and ratified by patients before its surveillance can inform care. Likewise, without testing, this phenotype cannot be considered generalisable to other disease domains. The idiosyncrasies of COVID-19 infection, especially the protective value

of certain immunosuppressed states and medications [85] against critical outcomes, mean that the risk hierarchy that surfaced in this exercise may not hold for other infection types.

5. Chapter Commentary:

Over the course of two online questionnaires, one discussion group and a final ratifying vote, this exercise has resolved several points of contention in the immunosuppressed literature and has produced a COVID-19 specific, internationally aligned and digitally practical means of identifying immunosuppressed patients in real-world data and COVID-19 risk stratifying their respective infection outcomes.

The limitations of this consensus building exercise and those of the eDelphi study design more generally have been outlined at length. However, further consideration should be given to the statistical and temporal vulnerability of this exercise and its resultant DESTINIES phenotype. Consensus building as a process is often more subjective than data driven [85]. Working in silos, specialists are less able to compare the prognoses of their charges versus other risk groups and patients they encounter in clinical settings may not reflect the average disease course of this population. Counteracting this with heterogeneous expertise, as the DESTINIES Study attempted to, can have the unintended consequence of diluting focus and complicating consensus building. This decision quality trade-off has been well-documented [86] and can be rectified by triangulating eDelphi results with other qualitative methods (interviews, focus groups etc.) – something that fell outside the scope of this thesis. Consensus building also often fails to stand the test of time: clinical understanding of COVID-19 evolves rapidly, creating redundancies amongst

successful past consensus exercises, for example [87]. Ongoing and high-resolution disease surveillance is there necessary for ensuring findings persist and recommendations remain robust.

The subsequent chapter aims to address these criticisms, utilising real-world COVID-19 infection and vaccination data to check the validity of DESTINIES Study consensus and preceding literature reviews. Agreement between the immunosuppressed subgroups predicted by literature review and eDelphi to be at greatest risk for severe COVID-19 and those observed to have the poorest outcomes via historical surveillance data will be assessed. As mentioned, a final consultation exercise will seek to ratify the value of thesis findings from the patient perspective before thesis findings and recommendations are laid out in full.

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4

How do prototype digital phenotypes for adult immunosuppression perform in real-world infection and vaccination datasets? Output from the segmentation of linked and non-linked UK primary care data, secondary analysis of global surveys and a patient engagement exercise.

Introduction: Disease surveillance efforts typically monitor immunosuppressed patient outcomes as an aggregate; this erases sub-trends of potentially urgent clinical importance.

Method: A pilot phenotype and eDelphi-ratified phenotype for adult immunosuppression were both operationalised in COVID-19 infection and vaccination databases to assess whether their predictions for COVID-19 risk were borne out in real-world observations. The pilot phenotype was implemented in secondary linked UK disease surveillance, including serosurveillance (pp. 148 to 181). The eDelphi phenotype was first trialled in international survey data (pp. 182 to 220) before being operationalised in full in UK primary care data (pp. 220 to 258). A patient engagement exercise (pp. 258 to 267) was hosted to report these findings and approve the eDelphi phenotype for ongoing use in UK disease surveillance.

Results: These exercises returned nuanced information about the distinct COVID-19 infection and vaccine experiences of immunosuppressed subgroups. There was strong concordance between exercises, including extreme risk in transplantation and haematological malignancy patients. However, predictions for Chronic kidney disease & dialysis, single-organ immune mediated inflammatory disease, drug-managed HIV and primary immunodeficiency patients were not replicated in all instances. Risk assessments were duly updated. 89% of patient panellists approved the eDelphi phenotype for disease surveillance purposes.

Discussion: Collectively, these exercises provide proof of concept for the value of risk stratified immunosuppressed disease surveillance, yielding new insights on differential vaccine benefit-risk in this population. Although limited by inconsistent data access, consistent findings for subgroups at greatest risk for COVID-19 across diverse data sources strengthens our confidence in the clinical validity of our conclusions. The eDelphi phenotype is the first to be endorsed for national disease surveillance by both patients and clinical experts.

Elements of this chapter have been published [1, 2, 3, 4].

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1. Introduction:

Defined by the World Health Organisation as the '*systematic ongoing collection, collation and analysis of data for public health purposes and the timely dissemination of health information for action'* [5], public health surveillance is foundational to disease management and control [6]. However, immunosuppressed patients often remain underserved by traditional surveillance systems, despite their disproportionate vulnerability to severe infection outcomes [7; 8]. The convention of aggregating data within passive or routine surveillance flows privileges the interests of the general population over complex or rare groups [9]. Meanwhile, previous attempts to enhance surveillance for protected populations have received criticism for their inability to mitigate key risks such as reidentification and subsequent stigmatisation and discrimination [10; 11; 12]. Patient informed consent for such targeted efforts is also difficult to confirm when the purpose, methods and analytics of disease surveillance are not fully transparent or well-understood [13].

The absence of immunosuppressed patients from largescale clinical development trials [14] and the underpowering of more specialised efforts [15] makes disease

surveillance systems especially important for these patients, however. It is essential that these systems become better able to detect distinct infection or vaccine outcomes to inform proportionate care and mitigation strategies [16]. That said, any innovation to disease surveillance or pharmacovigilance systems on behalf of the immunosuppressed must occur with their consultation and full endorsement [17].

This chapter presents the conversion of literature reviews and eDelphi study findings into segmented COVID-19 surveillance and pharmacovigilance for immunosuppressed patients. Serving as the apex of this thesis, this work will test the real-world validity of literature and eDelphi consensus for the immunosuppressed subgroups at greatest risk of severe COVID-19 outcomes. Four exercises are described to this end: a pilot of a rapid scoping-review informed phenotype for COVID-19 risk in adult immunosuppressed patients within COVID-19 vaccine effectiveness surveillance data, a pilot of the DESTINIES phenotype for COVID-19 risk in adult immunosuppressed patients within immune mediated inflammatory disease (IMID) COVID-19 pharmacovigilance data, a full operationalisation of this latter phenotype within primary care data and an immunosuppressed patient consultation exercise that leveraged findings from the above.

2. Differentiating COVID-19 vaccine surveillance with a rapid scoping review-informed phenotype for COVID-19 risk in adult immunosuppressed patients (pilot phenotype):

i. Method:

This work was completed between December 2022 and September 2024 and utilised secondary care-linked Oxford-Royal College of General Practitioners' Research and Surveillance Centre (RSC) data. It aimed to assess whether implementing a pilot COVID-19 risk stratified phenotype for adult immunosuppression offered any improvements to prevailing vaccine effectiveness dataflows.

Surveillance partner to UKHSA for over 60 years [3], RSC intelligence is made up of a confluence of pseudonymised primary care and biological sampling (serology, virology) data as well as diverse linkages to secondary care and health registry data (Secondary Uses Service [SUS], Hospital Episode Statistics [HES], National Immunisation Management System [NIMS], Second Generation Surveillance System [SGSS], Office of National Statistics [ONS] mortality etc.). Managed by the Clinical Informatics and Health Outcomes Research Group (CIHORG) [18] the doctoral candidate works within, these data are updated daily or twice weekly to produce real-time, nationally representative and holistic surveillance of infection and vaccine outcomes in the United Kingdom. RSC data are held securely within Oxford Clinical Information Digital Hub (ORCHID) at the University of Oxford's Nuffield Department of Primary Care Health Sciences [19]. This trusted research environment (TRE) also possesses internal tools to facilitate the curation of clinical code sets and digital

phenotypes, converting conceptual taxonomies into those capable of identifying, extracting and segmenting specific populations in CMRs.

Prior to this doctoral programme, the RSC handled immunosuppressed data as an undifferentiated risk group. This aggregation made its surveillance entirely unsuitable for informing more targeted approaches to patient care, health protections or vaccine protocols. This became especially apparent during the COVID-19 pandemic where despite RSC dataflows' scale (n = 17.3 million patients as of 2021), detail and timeliness, its aggregation of immunosuppressed data concealed urgent sub-trends in infection outcome and vaccine benefit-risk data. As per Figure 4.1[4], RSC data could not identify the common clinical denominators of the immunosuppressed that failed to respond to COVID-19 vaccination; potential root causes, such as shared diagnoses, medications, dosages or comorbidities, had to be investigated manually on a record-by-record basis – something enormously time and resource intensive. Likewise, aggregated RSC estimates of immunosuppressed COVID-19 vaccine effectiveness have been subject to wide and frequently overlapping confidence intervals - communicating very little to policymakers (Figure 4.2[3]).

Figure 4.1: Spike (S) antibody levels (au/ml) after dose 2 or 3 of COVID-19 vaccination in Nucleocapsid(N)-negative individuals, by primary course manufacturer and last dose received, coloured red for members of the immunosuppressed risk group (or coloured grey for non-members). The green dashed line is the assay positive/negative seroconversion cut-off at 0.8au/ml. Antibody levels are on a logarithmic scale (Whitaker et al, 2023)

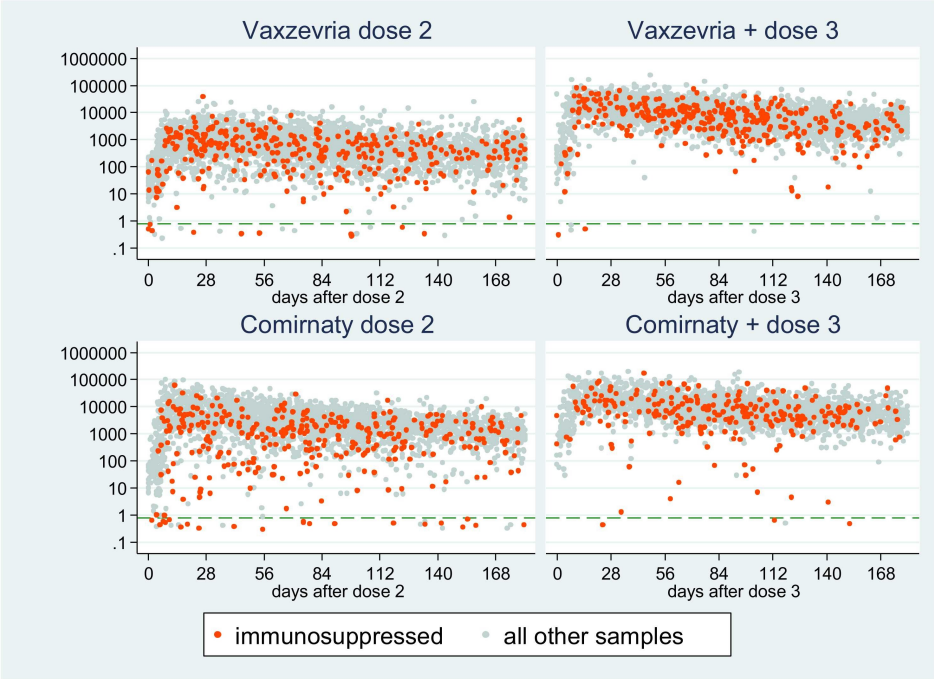
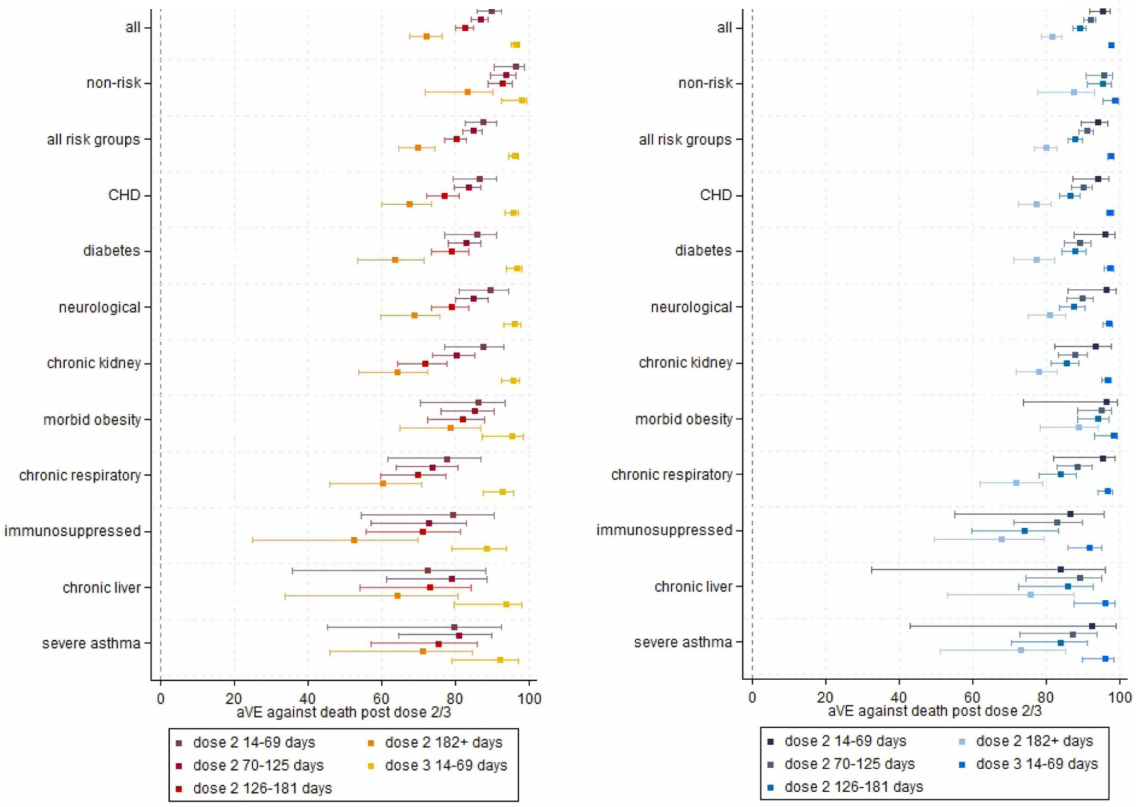


Figure 4.2: Cohort adjusted vaccine effectiveness (aVE) against death within 28-days of a positive SARS-CoV-2 test. Left panel: Vaxzevria primary course, right panel: Comirnaty primary course (Whitaker et al, 2022).



As signposted in Chapter 2, the doctoral candidate utilised rapid scoping review findings to risk stratify these data. However, after receiving conflicting supervisory advice on the ethical approvals that would be necessary for accessing and handling secondary-linked data herself, late-stage applications were made to Central University Research Ethics Committee (CUREC). Although approved (R92502/RE001) and utilised to analyse summary data, indefinite delays to NHS Data Access Request Service (DARS) consideration and ongoing conflicts between Surveillance and Research data permissions meant UKHSA stakeholders were tasked with executing much of the pilot analysis detailed below within their own servers. Said work was permitted for these actors under Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, under Sections 3(i) (a) to (c), 3(i)(d) (i) and (ii) and 3(3) [20]. Resultant summary outputs were then tested, visualised, interpreted and written up in equal partnership with the doctoral candidate.

UKHSA stakeholders have approved this work's inclusion in the doctoral candidate's thesis in its entirety, however, recognising her leadership over its underpinning methodology (pilot phenotype development, curation and implementation), final analysis and dissemination. For the sake of transparency and academic integrity, analysis conducted exclusively by UKHSA colleagues will be clearly indicated in the results that follow.

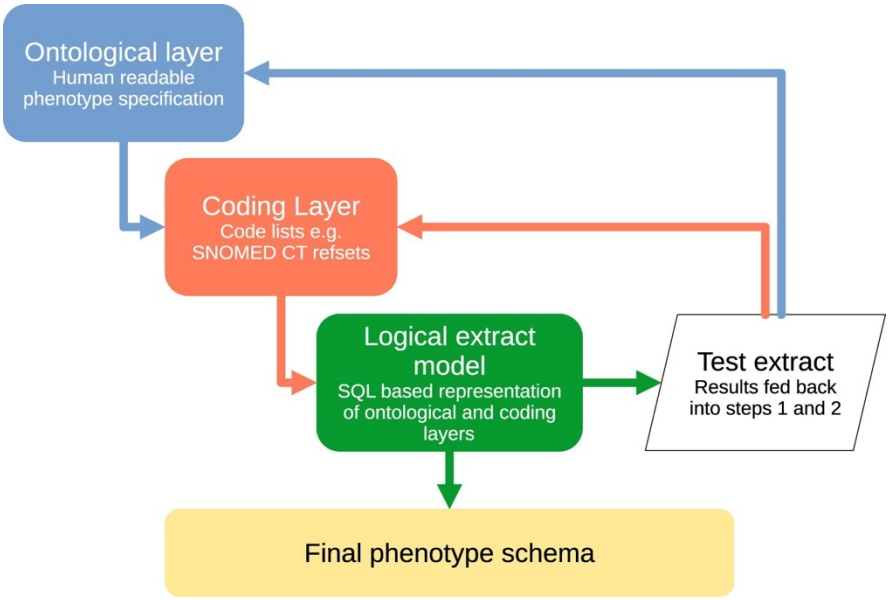
Pilot phenotype curation and implementation:

In-house RSC clinical experts were called upon to support the conversion of rapid scoping review findings into an initial means of identifying and risk stratifying the

RSC immunosuppressed population and their secondary care-linked COVID-19 infection and vaccine outcomes. The five-part conceptual hierarchy that resulted was then converted into an ORCHID-ready pilot phenotype for COVID-19 risk in the adult immunosuppressed following the three-stage method depicted in Figure 4.3 [21]. This conversion process encompasses:

1) An ontological layer – a human-readable description of key clinical concepts within a given hierarchy
2) A coding layer – where hierarchy layers are clinically codified (discrete alphanumeric labels that represent medical diagnoses, events, procedures and prescriptions) to create a machine-readable valueset.
3) A logical data extract layer – where the ontological rules that dictate phenotype eligibility are converted into Structured Query Language (SQL; Microsoft) expressions. This transforms a valueset or flat list into a hierarchical phenotype and enables nuanced or conditional data extraction. The resultant extract is then tested for face validity against reference populations; any discrepancies are used to refine the phenotype at either the Ontological or Coding Layer. This iterative approach maximises the accuracy and value of the Final phenotype schema.

Figure 4.3: RSC standard practice for instituting a novel digital phenotype in ORCHID dataflows



To be compatible with ORCHID, digital phenotypes must be curated with Systematised Nomenclature of Medicine Clinical Terms (SNOMED CT) diagnostic and Dictionary of Medicines and Devices (dm+d) prescription terms [22]. UKHSA currently commissions the University of Nottingham based Primary Care Information Services (PRIMIS) to produce SNOMED CT and dm+d reference sets for disease surveillance purposes [23]; these resources act as repositories for specific clinical populations' constituent medical codes to standardise and expedite research. PRIMIS version 1.3.3 and 2.3 were consequently key resources for the Coding Layer of the pilot phenotype.

That said, PRIMIS assets are undifferentiated and highly sensitive to redundancy as SNOMED CT and dm+d vocabularies update regularly (monthly and weekly, respectively). PRIMIS clinical risk groups are also highly porous, with codes relevant for immunosuppression dispersed amongst numerous other reference sets. An RSC

data curation tool, SNOMED CT Concept ID [21], was used to manually quality assure these reference sets, updating clinical terms or scraping relevant codes from wider PRIMIS risk groups where necessary. Furthermore, supertype and theme variables specific to the ORCHID TRE, known as Themes Access Dynamic Data Services [TADDS] variables, augmented our Coding Layer and reduced the vulnerability of our pilot phenotype to redundancy. TADDS variables denote specific disease or medication types and are more readily updated with Expression Constraint Language (ECL).

The Logical Extract Model Layer instituted the time conditions cited in Green Book Chapter 14a guidelines [24] and relevant literature [25] into our pilot phenotype; this ensured that those deemed insufficiently immunosuppressed during a study period (e.g. legacy cancer patients and those yet to receive at least 6 months of immunosuppressive therapy) were excluded from consideration. Hierarchical principles were applied to ensure that, once implemented within ORCHID, our pilot phenotype would extract medical records into the highest risk group they were eligible for. This mutual exclusivity ensured patients would not contribute their data to multiple phenotype levels.

Once curated and quality assured by multiple members of the RSC clinical team, the pilot phenotype was used to extract and segment a linked dataset of English primary care, immunisation, death registration, hospitalisation and biological sampling data within ORCHID. These data, including a serological subset, were utilised in the exercises that follow.

Differentiated immunosuppressed COVID-19 vaccine effectiveness surveillance:
A combination of test-negative case control (TNCC) and retrospective cohort analyses were conducted to differentiate COVID-19 vaccine effectiveness between pilot phenotype levels. These study designs were selected to reflect available data and replicate previous UKHSA surveillance work against the same outcomes [4; 26; 27]. Coinciding with the August 2021 and Spring 2022 booster campaigns, both TNCC- and retrospective cohort-based investigations utilised data collected between December 2021 to May 2022 to estimate 1st, 2nd, and ≥3rd dose effectiveness.

Descriptive statistics comparing age, gender and ethnicity composition between immunosuppressed subgroups and those not identified as immunosuppressed were tabulated. Key COVID-19 infection outcomes (positive test within +/-10 days of symptomatic GP visit, death within 28 days of positive COVID-19 test, hospital stay of ≥2 days within 14 days of positive COVID-19 test, hospital stay of any length within 14 days of positive COVID-19 test, severe outcomes [hospital stay of any length and/or death within 28 days of positive COVID-19 test]) were also reported. Hospitalisation for COVID-19 was qualified by hospital admission ≤ 2 days before or ≤ 14 days after testing positive. Patients with an acute respiratory hospitalisation code, any COVID-19 discharge code and use of oxygen or admission to intensive care were included in this outcome. COVID-19 mortality included death within 28 days of a positive test and/ or acute respiratory death with a primary COVID-19 code on the death certificate.

The TNCC utilised multivariable logistic regression to establish vaccine effectiveness of most recent dose against medically attended COVID-19 (testing positive for

COVID-19 within +/- 10 days of a symptomatic GP appointment). TNCC study design was permissible here as both cases and controls attended their GP, controlling for potential differences in health-seeking behaviours between participants. Vaccination status was ascertained either at the time of test or GP consultation date and effectiveness was calculated as 1-odds ratio, where OR is the odds of vaccination in cases compared to controls. Covariates adjusted for included NHS region and age group (10-year bands).

The retrospective cohort study utilised multivariate Poisson regression to establish vaccine effectiveness of most recent dose against severe COVID-19 outcomes (hospitalisation of ≥2 days within 14 days or death within 28 days of testing positive for SARS-CoV-2). This study design enabled direct calculation of outcome incidence rates (IRs) for both vaccinated and unvaccinated individuals. Effectiveness here was calculated as 1-risk ratio (RR), where RR is the attack rate of the vaccinated group over the attack rate of the unvaccinated group. In this retrospective cohort analysis, vaccine status was utilised as a time-varying covariate with effectiveness estimates produced in three-month periods (14 to 89 days, 90 to 179 days and >180 days). An initial 14-day delay was incorporated to accommodate immune response to latest dose. Covariates adjusted for included NHS region, age group (5-year bands), sex, IMD quintile, household size, ethnicity, shielded list membership, smoking status, CMMS and history of previous COVID-19 infection.

Vaccine effectiveness work was completed on STATA v14.2 (StataCorp LLC) by UKHSA colleagues; the doctoral candidate provided quality assurance and supported interpretation, visualisation of summary outputs and final write-up.

Differentiated immunosuppressed COVID-19 serosurveillance:

Serological analysis provided an additional means of differentiating vaccine response amongst the immunosuppressed. This utilised a subset of the linked ORCHID data specified: blood samples volunteered by RSC patients over the age of 18 years that were collected as part of routine phlebotomy in member practices between October 2021 and September 2022. CMR-linkages established volunteers' immunosuppressed status at the start of the study period (as defined by the pilot phenotype) as well as their COVID-19 infection and vaccination history.

Descriptive analysis first differentiated this study set by immunosuppressed category, their respective age-sex distributions and vaccine uptake (≥ 3 doses). Samples' anti-spike (S) antibody and nucleocapsid (N) antibody concentrations were then measured with a Roche Elecsys assay. Statistical analysis of resulting data was completed by UKHSA collaborators using STATA v14.2 (StataCorp LLC); the doctoral candidate participated in their interpretation and write-up.

N antibody seropositivity is a marker of natural exposure to a pathogen, though it is noted that some individuals never produce this response or levels wane into negative ranges over time. The positive/negative cut off was defined at 1au/ml (manufacturer instructions), although UKHSA colleagues also determined an equivocal range with a lower limit of 0.4 au/ml [28]. Due to low sample sizes amongst the immunosuppressed, comparisons of N seropositivity for COVID-19 by case history were only performed for those identified and not identified as immunosuppressed by the pilot phenotype. Descriptive statistics of N antibody

seropositivity were reported in 3-month intervals to gauge whether COVID-19 infection levels were underreported in any time period or population.

S antibodies are those generated after vaccination or infection. Isolating vaccine-induced S antibody seroconversion from that produced by natural infection requires only analysing S antibody positive samples with simultaneously low N antibody levels (<0.4 au/ml) and no history of a past positive viral test. Linear regression models of log S antibody levels against immunosuppression status and pilot phenotype level were then fitted with explanatory terms for age, sex, and an interaction between dose and time since last dose (log time since last dose was used after comparison of model fit with various transformations). The geometric ratio of immunosuppressed S antibody seroconversion versus those with no immunosuppression (as defined by the pilot phenotype) was also calculated. S antibody response measurements for all samples were collected, converted to the natural logarithm, averaged into a mean for each study category before producing a ratio against the non-immunosuppressed baseline result. This ratio was then exponentiated to convert back from the logarithmic scale and interpreted. Results were adjusted for age, sex, COVID-19 vaccine dose and time since inoculation. For illustrative purposes, a prediction for average S antibody response at 91 days post dose 3 (geometric mean au/ml) was calculated from the fitted regression model for each study group and reported with its associated 95% confidence interval.

ii. Results:

Pilot phenotype curation and implementation:

This work was conducted by the doctoral candidate and CIHORG colleagues.

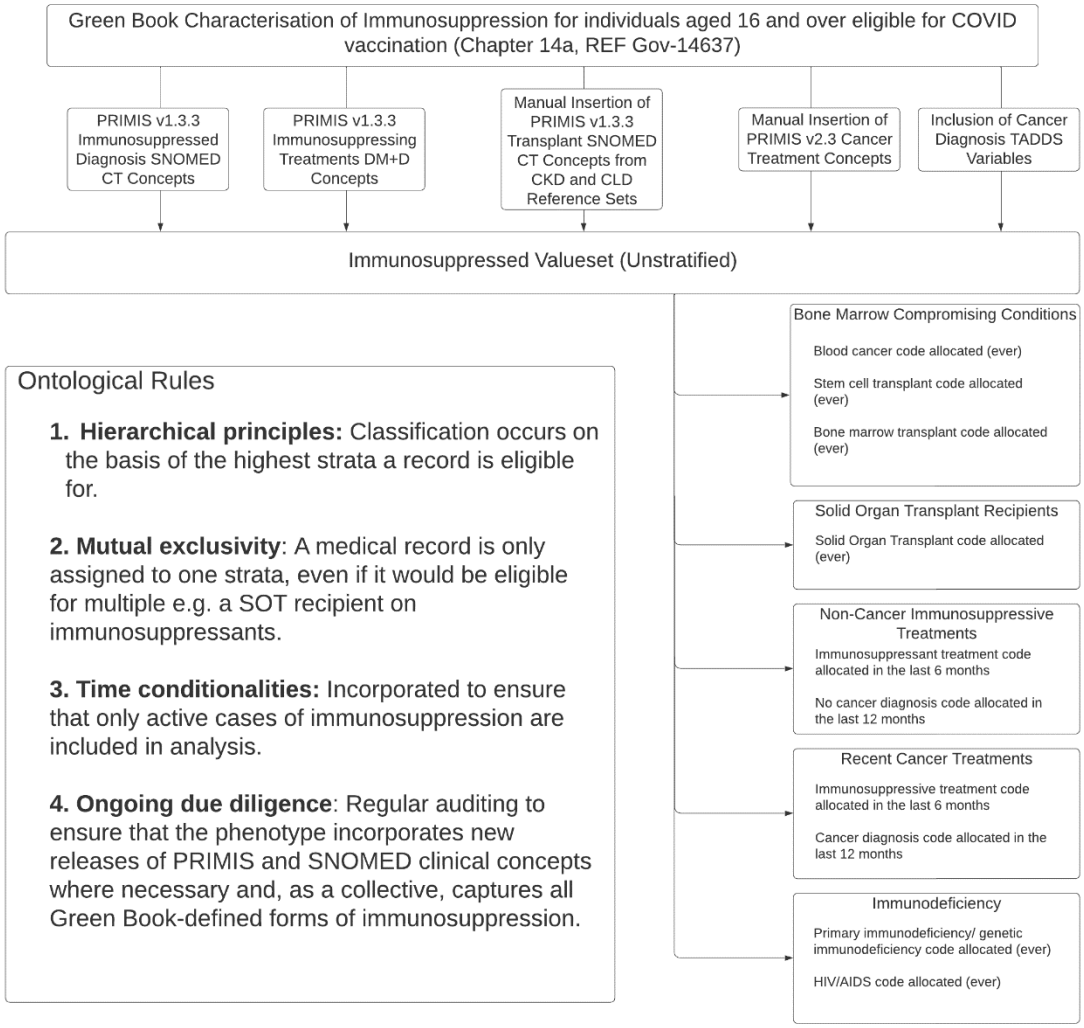
Initially, the following three patient clusters proved most valuable for segmenting rapid scoping review results: 1) those with bone marrow compromising conditions, 2) those receiving ongoing immunosuppressing treatments and/or procedures and 3) those with primary or acquired immunodeficiencies. In consultation with RSC clinicians, this initial tripartite model was expanded to five levels to prevent oversimplification – distinguishing solid organ transplant recipients and immunosuppressive regimens related and unrelated to cancer in recognition of their unique vulnerability to COVID-19 and easy confusion in medical databases, respectively (the same immunosuppressive medications can be prescribed as cancer and non-cancer purposes, for example). These five levels are operationalised with their respective time and medication conditions in Table 4.1 below; they are presented in descending order of COVID-19 risk, as informed by rapid scoping review.

Table 4.1: Operationalising the pilot phenotype for COVID-19 risk in the adult Immunosuppressed population

Phenotype Level		Composition	Conditions
i.	Bone Marrow Compromising Conditions	Haematological malignancy and Bone Marrow/Stem Cell Transplantation	Diagnostic code allocated ever
ii.	Solid Organ Transplant Recipients	Solid Organ Transplantation	Diagnostic code allocated ever
iii.	Non-Cancer Related Immunosuppressives	Immunosuppressives unrelated to cancer	No cancer diagnosis code allocated in last 12 months; immunosuppressive prescription code allocated in last 6 months
iv.	Recent Cancer Treatments	Systemic cancer treatments including cancer-related immunotherapy, chemotherapy and radical radiotherapy	No cancer diagnosis code allocated in last 12 months; immunosuppressive prescription code allocated in last 6 months
v.	Immunodeficiency	Genetic immunodeficiencies and HIV/AIDS	Diagnostic code allocated ever

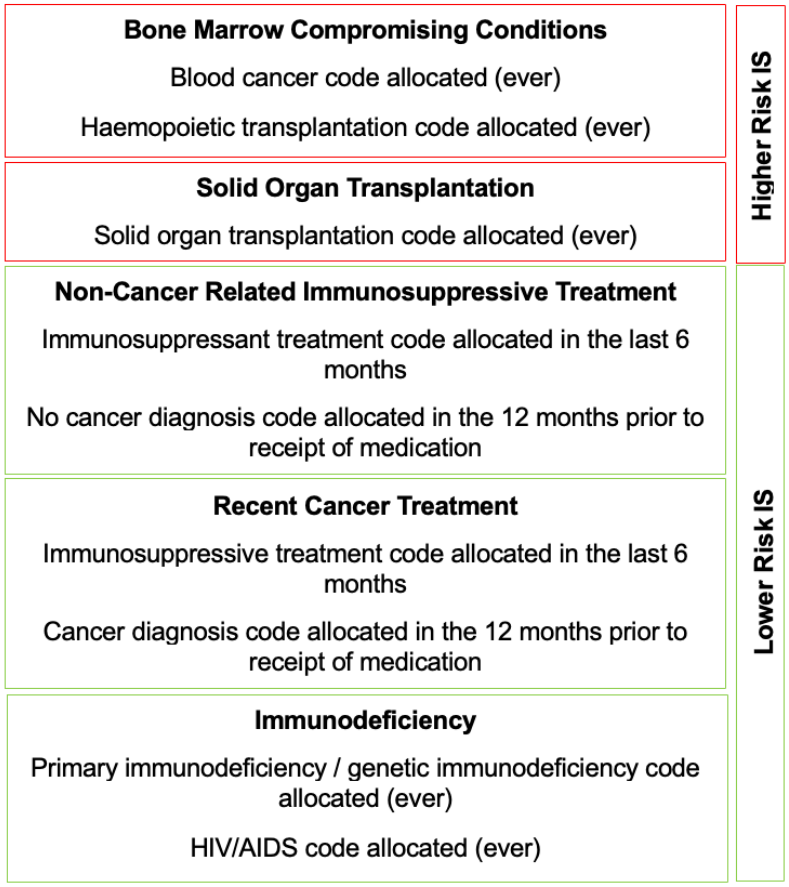
The test valueset can be obtained in the publication of this work [1]; its data sources and development are depicted in Figure 4.4, including the manual insertion of the chronic kidney and liver transplantation codes that were omitted by both PRIMIS immunosuppressed reference sets.

Figure 4.4: Clinical logic flow of the pilot phenotype for COVID-19 risk in the adult immunosuppressed population



These five levels were organised into the higher and lower COVID-19 risk immunosuppressed binary illustrated in Figure 4.5 below. Said binary facilitated lower resolution but higher-powered comparisons within the immunosuppressed population.

Figure 4.5: Repurposing pilot phenotype levels into an immunosuppressed COVID-19 risk binary



Differentiated immunosuppressed COVID-19 vaccine effectiveness surveillance

Summary outputs of the implementation of this pilot phenotype within the secondary linked ORCHID sentinel surveillance dataset are provided in Table 4.2; these descriptive data were compiled by UKHSA collaborators with onwards interpretation and analysis performed by the doctoral candidate. Immunosuppressed status was accurate as of the 19th of December, 2021. Five years of medical data prior to this date were cross-referenced for 'ever' coded immunosuppressed categories; eighteen months of medical record data prior to this date were utilised for time-sensitive categories – the maximum amount that could have elapsed and met both 6-month prescription and 12-month diagnostic criteria.

The pilot phenotype identified <2% of the total secondary-linked dataset as immunosuppressed. Sample sizes were seen to vary substantially between subgroups, however, and the catchment of Recently Treated Cancer was surprisingly low. The dominance of Non-Cancer Related Immunosuppressives by comparison suggests records may have been misallocated between these two medication-specific phenotype levels – important context for the results that follow.

While interquartile ranges overlapped, the immunosuppressed were generally older than those not identified as immunosuppressed. A greater proportion were over the age of 65 years in every subgroup, indicating potential comorbidities beyond immunosuppression. Age adjustment in modelling was crucial as a result. Primary or Acquired Immunodeficiency patients or those receiving immunosuppressive medications of any description were also more likely to be female than other phenotype levels and those not identified as immunosuppressed. Meanwhile, the proportion of patients from ethnic minority backgrounds were higher in Solid Organ Transplant and Primary and Acquired Immunodeficiency subgroups. Although vaccine uptake was consistently high in the immunosuppressed, Primary & Acquired Immunodeficiencies had nearly twice as many unvaccinated patients than its counterparts.

Table 4.2: Descriptive data produced by implementing the pilot phenotype for COVID-19 risk in the adult immunosuppressed population in secondary-linked ORCHID data

		0: Non-IS		1: Bone Marrow Compromised		2: SOTs		3: Non-cancer related immunosuppressives		4: Recently treated cancer		5: Primary & Acquired Immunodeficiencies	
		n	%	n	%	n	%	n	%	n	%	n	%
Number/ percentage of study population		11,982,594	98.14	78103	0.64	11114	0.09	89935	0.74	5095	0.04	42714	0.35
Median age (IQR)		46 (31-62)		70 (56-79)		57 (45-66)		63 (57-75)		67 (57-75)		55 (43-67)	
Age (>65)		2,602,347	21.7	47802	61.2	3218	28.95	41275	45.89	2934	57.59	12368	28.96
Gender (Female)		5,940,710	49.6	35880	45.94	4543	40.88	55058	61.22	3148	61.79	21719	50.85
Minority ethnic group		1,789,761	17.2	6297	8.78	2073	20.36	7766	9.27	341	7.17	8566	21.65
Vaccination status at end of study	Unvaccinated	1,997,173	16.7	3431	4.39	530	4.77	2098	2.33	167	3.28	3452	8.08
	One dose	331,987	2.8	694	0.89	133	1.2	567	0.63	59	1.16	686	1.61
	Two doses	1,746,411	14.6	4128	5.29	744	6.69	4412	4.91	395	7.75	3997	9.36
	≥Three doses	7,907,023	65.7	69850	89.4	9707	87.3	82858	92.1	4474	87.8	34579	81
GP attended COVID-19 (positive test within +/- 10 days of symptomatic appointment)		175,519	0.01	2971	0.04	657	0.06	3340	0.04	180	0.04	1326	0.03
Hospital stay of 2 days or more within 14 days of testing positive for COVID-19		18,242	0.2	844	1.08	235	2.11	476	0.53	83	1.63	164	0.38
Hospital stay of any length within 14 days of testing positive for COVID-19		34,645	0.3	1785	2.29	737	6.63	1458	1.62	216	4.24	448	1.05
Death within 28 days of testing positive for COVID-19		5,741	0.1	351	0.45	47	0.42	137	0.15	60	1.18	49	0.11
Severe outcomes (any death or hospital stay of any length within 28-days of testing positive for COVID-19)		37,307	0.3	1982	2.54	753	6.78	1529	1.7	254	4.99	484	1.13

Further analysis and visualisation of this summary data revealed substantial discrepancies between homogenous patterns of vaccine uptake within the immunosuppressed population and their COVID-19 infection outcomes (Figures 4.6 and 4.7).

Figure 4.6: COVID-19 vaccine uptake by immunosuppressed subgroup, as defined by the pilot phenotype for COVID-19 risk in the adult immunosuppressed

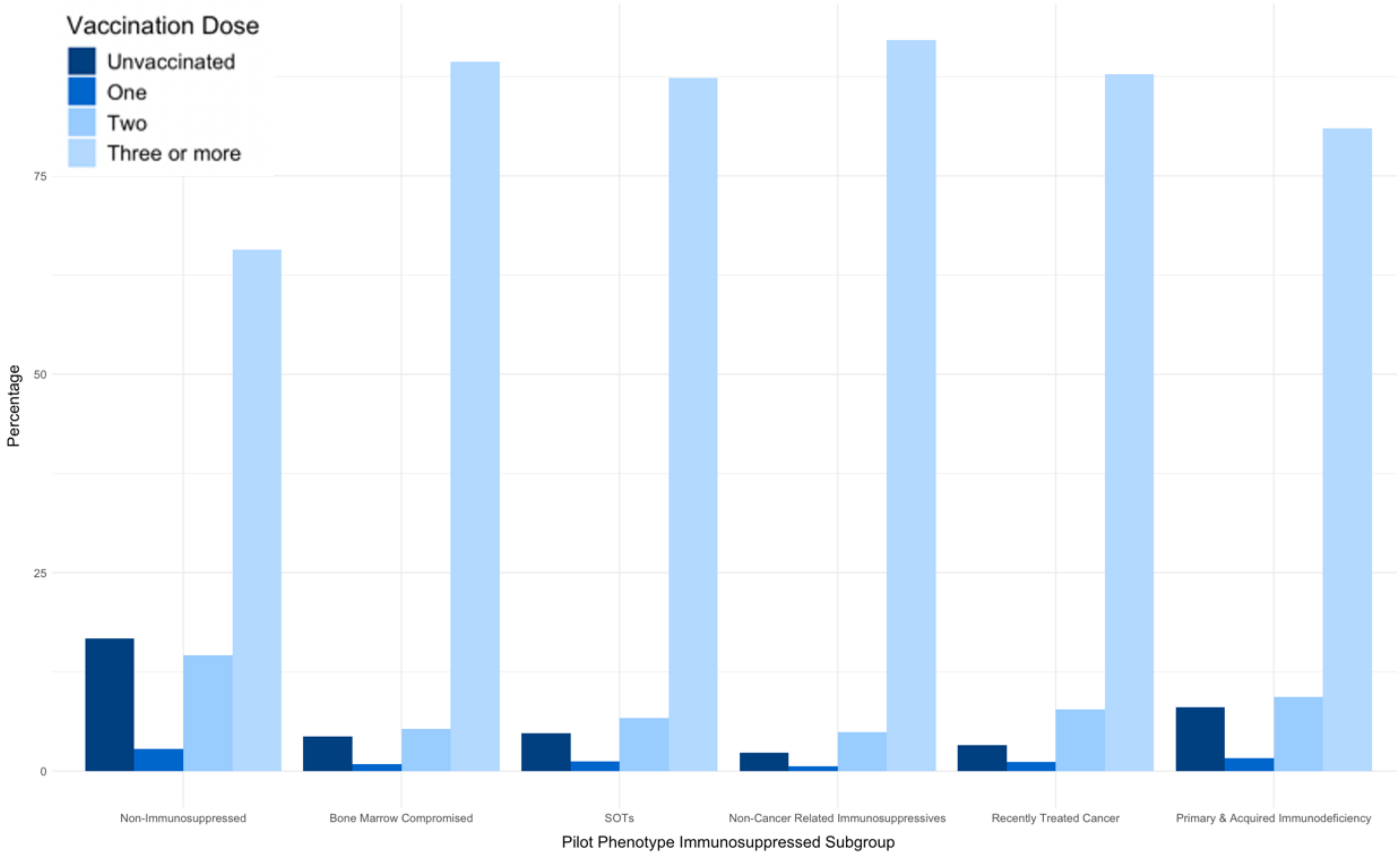
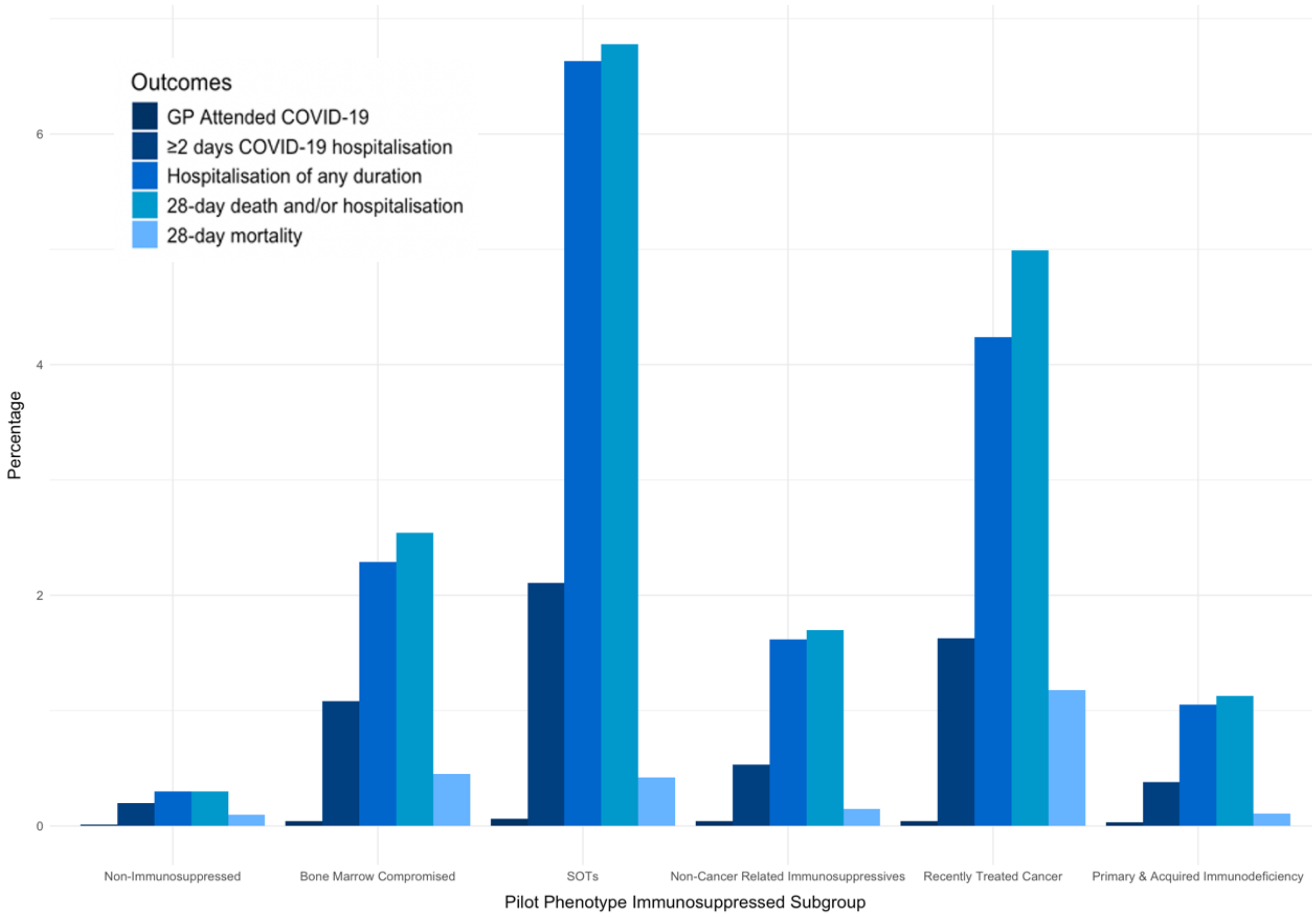


Figure 4.7: COVID-19 infection outcomes by immunosuppressed subgroup, as defined by the pilot phenotype for COVID-19 risk in the adult immunosuppressed population

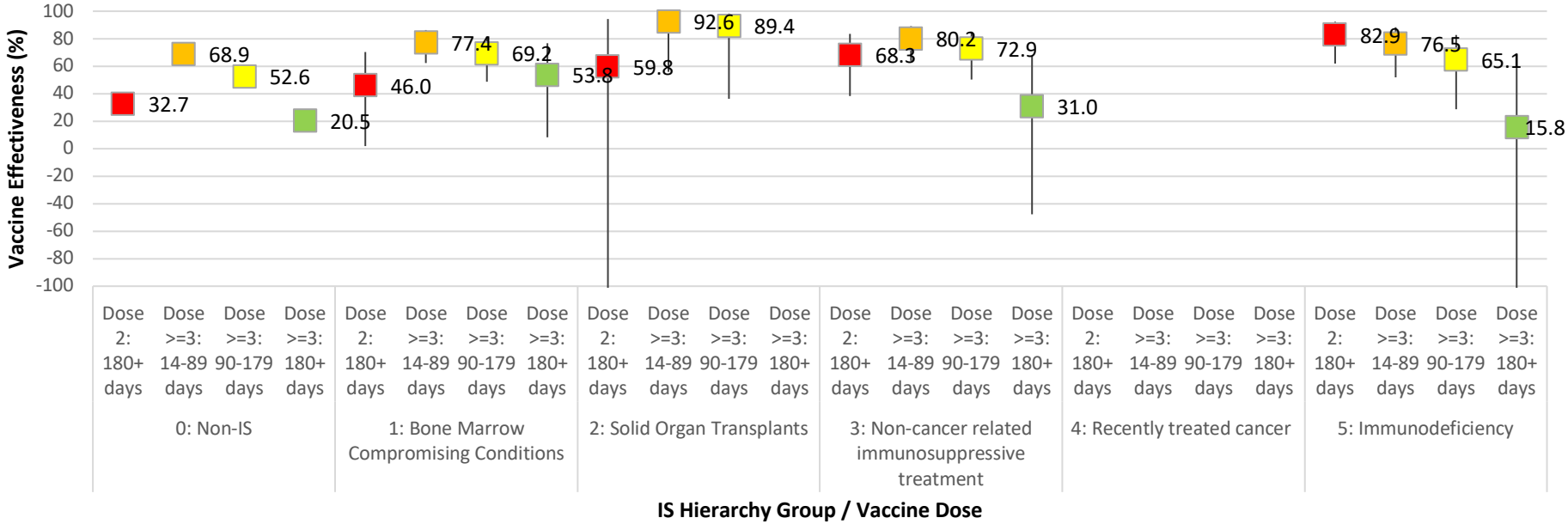


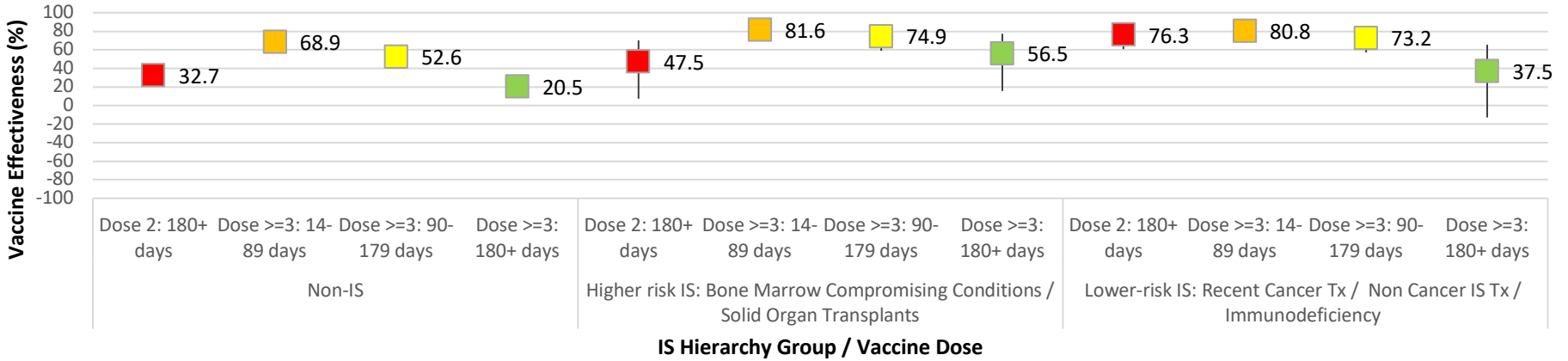
Despite broadly similar levels of GP attended COVID-19, severe infection outcomes varied between phenotype subgroups. All immunosuppressed subgroups were at heightened risk for subsequent hospitalisation and/or mortality; contradicting the cadence of risk anticipated by the pilot phenotype, however, these outcomes were most concentrated within Solid Organ Transplant recipients and Recently Treated Cancer patients.

Vaccine effectiveness against medically attended COVID-19:

Whether immunosuppressed data was handled as a binary (higher versus lower COVID-19 risk) or differentiated by pilot phenotype levels, dose 2 and 3 vaccine effectiveness against medically attended COVID-19 infection was broadly similar in these patients to non-immunosuppressed data (Figure 4.8). Small sample sizes affected the fidelity of analysis differentiated by certain immunosuppressed subgroups, however; all results for Recently Treated Cancer patients as well as 180 days after dose three for Solid Organ Transplantation patients are suppressed as meaningful analysis could not be performed. That said, vaccine effectiveness was seen to peak for Bone Marrow Compromised, Solid Organ Transplant and Non-Cancer Related Immunosuppressives at 14 to 89 days after dose three or more. Vaccine waning was observed irrespective of immunosuppressed status or subgroup with universal declines in vaccine effectiveness seen 180 days after dose three or more. Vaccine effectiveness against medically attended COVID-19 were surprisingly low amongst the non-immunosuppressed – lower, in fact, than the immunosuppressed in certain instances. It is possible that higher numbers of unvaccinated non-immunosuppressed patients could be driving these discrepancies (skewing the odds ratio data that underpin logistic regression-based estimates for vaccine effectiveness) or indicate higher levels of clinical vulnerability in the non-immunosuppressed population than was anticipated. The minimal adjustment of these data may also have contributed to these unexpected outputs.

Figure 4.8: TNCC estimates for vaccine effectiveness against medically attended COVID-19 within +/- 10 days of a positive test in immunosuppressed subgroups by dose and timepoint





Vaccine effectiveness against COVID-19 hospitalisation and/or mortality:

When calculated against severe outcomes, vaccine effectiveness was considerably more varied amongst immunosuppressed subgroups (Figure 4.9). However, small sample sizes – both in terms of experimental groups and severe COVID-19 outcomes – produced broad confidence intervals in some circumstances, with estimates often crossing zero.

Solid organ transplantation and immunodeficiency patients produced especially depressed results, with converse patterns of waning and boosting over time and dosing. Results amongst Bone Marrow Compromised, Non-Cancer Related Immunosuppressives and Recently Treated Cancer were more aligned with results returned amongst those not identified as immunosuppressed. Here, lowest VE against COVID-19 hospitalisation and/or mortality were typically observed at 180 days after vaccine dose two and showed some signs of waning in all groups bar bone marrow compromised patients. Any discrepancies between immunosuppressed and non-immunosuppressed outcomes were erased when data was handled as a COVID-19 risk binary, however (Figure 4.10).

Figure 4.9: Retrospective cohort estimates for vaccine effectiveness against severe COVID-19 in immunosuppressed subgroups by dose and timepoint

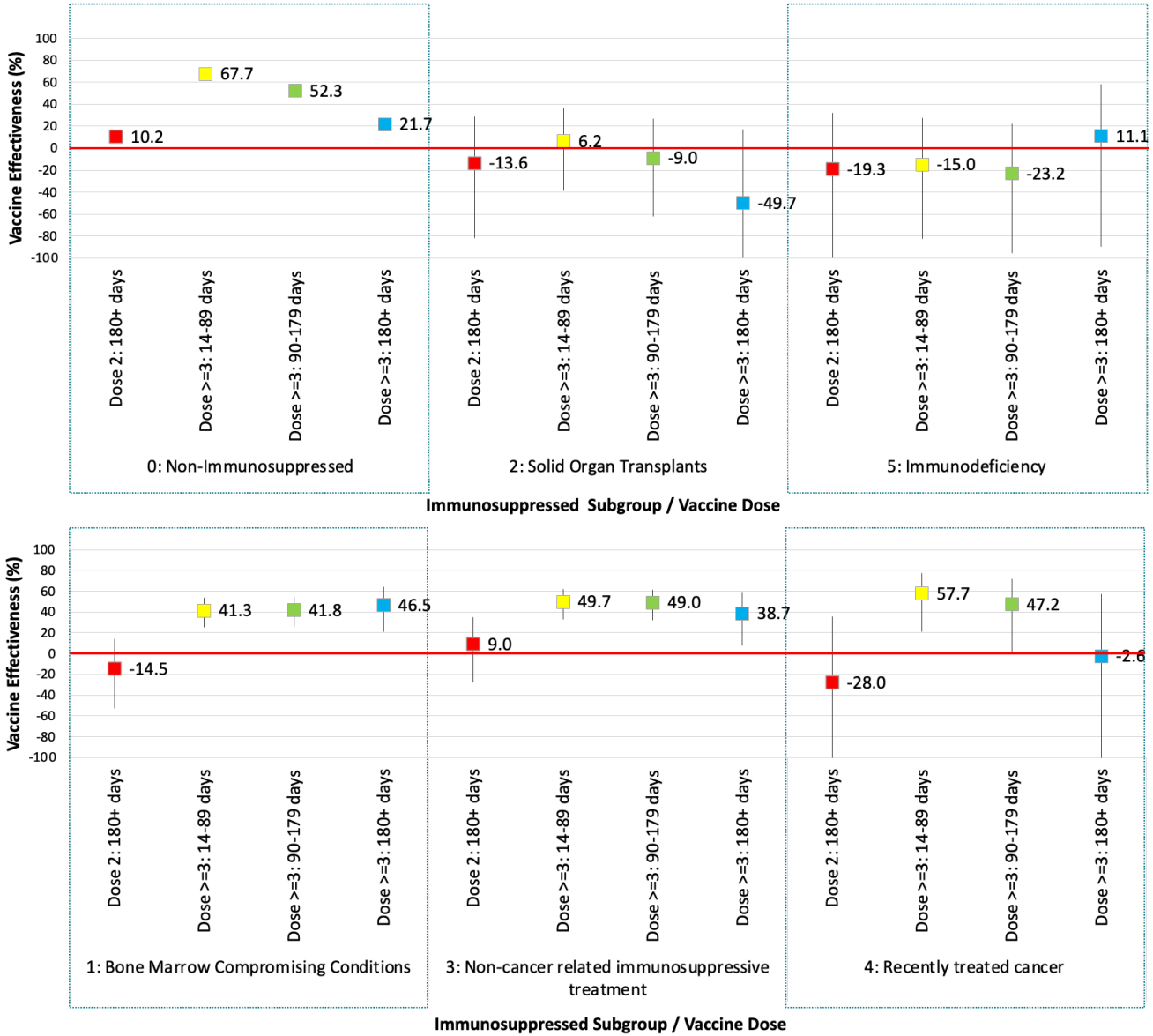
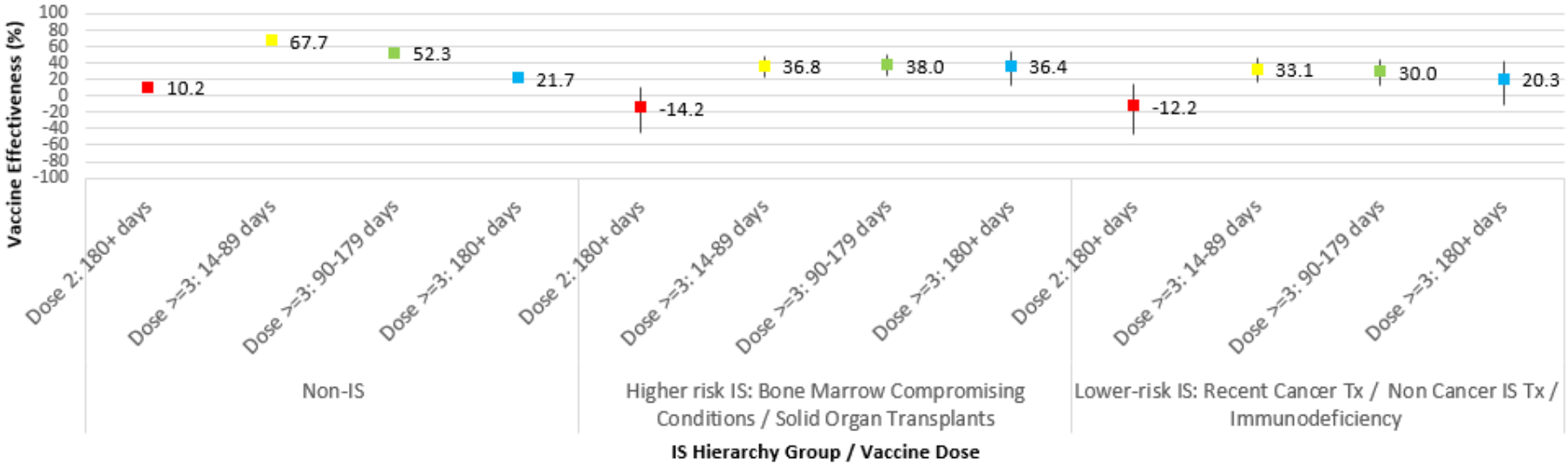


Figure 4.10: Retrospective cohort estimates for vaccine effectiveness against severe COVID-19 in non-immunosuppressed and higher and lower immunosuppressed subgroups by dose and timepoint



Differentiated immunosuppressed COVID-19 serosurveillance:

Table 4.3 provides descriptive information about the serological samples volunteered by RSC patients over the age of 18 years between October 2021 and September 2022. Men were disproportionately represented in the Solid organ transplant subgroup whereas women were disproportionately represented in Recently Treated Cancer and Primary & acquired immunodeficiencies groups. With overlapping IQRs, study category ages were broadly similar; Bone marrow compromised patients were older on average, however. Small sample sizes in certain groups (Bone Marrow Compromised and Solid Organ Transplantation) affected the rigour and comparability of subsequent reporting.

Table 4.3: Descriptive analysis of serosurveillance cohort

	Non-IS	BMC	SOTs	Non-Cancer IS	Recently Treated Cancer	Primary & Acquired IDs
n	14,398	220	24	855	28	109
Age, Median (IQR)	65 (53 - 74)	74 (65.5 - 81)	64 (53 - 66)	66 (57 - 73)	65 (60.5 - 71.5)	65 (56 - 74)
Female (%)	7436 (52%)	92 (42%)	2 (8%)	526 (62%)	22 (79%)	77 (71%)
n ≥3 vaccine doses	12086 (84%)	203 (92%)	22 (92%)	775 (91%)	25 (89%)	102 (94%)

N antibody seropositivity:

Table 4.4 below details the N antibody seropositivity of all volunteer samples, segmenting data by year quarter, immunosuppressed status and immunosuppressed subgroup. These data suggest natural exposure to COVID-19 was more prevalent amongst those without immunosuppression; similar levels of N antibody seroconversion seen at the beginning of data sampling diverge significantly by the end of the study period. Seroconversion by this measure was especially compromised amongst solid organ transplant recipients, though extremely low sample sizes severely undermine confidence in these data.

Table 4.4: N antibody seropositivity by immunosuppressed status

	Non-IS		All IS		BMC		SOTs		Non-Cancer IS		Recently Treated Cancer		Primary & Acquired IDs	
	n > 0.4 ml/au / n total	%	n > 0.4 ml/au / n total	%	n > 0.4 ml/au / n total	%	n > 0.4 ml/au / n total	%	n > 0.4 ml/au / n total	%	n > 0.4 ml/au / n total	%	n > 0.4 ml/au / n total	%
2021 Q4	430/2551	17	33/233	14	6/37	16	0/4	0	20/167	12	1/6	17	6/19	32
2022 Q1	1519/5164	29	102/433	24	15/66	23	0/10	0	75/313	24	0/10	0	12/34	35
2022 Q2	1669/3393	49	113/300	38	24/62	39	2/5	40	77/197	39	1/7	14	8/29	28
2022 Q3	1993/3290	61	99/270	37	21/55	38	2/5	40	59/178	33	3/5	60	14/27	52

Table 4.5 compares N antibody seroconversion data between immunosuppressed and non-immunosuppressed patients without a recorded history of SARS-CoV-1 infection prior to date of sampling. Amongst the non-immunosuppressed, discrepancies can clearly be seen between CMR records and blood-based indications of COVID-19 exposure with more than half of samples returning detectable levels of N antibodies by the end of the study period. These data could be used to support the assertion of under-reporting of infection amongst the non-immunosuppressed. Immunosuppressed samples, meanwhile, were significantly less likely to return detectable levels of N antibodies than the non-immunosuppressed – consistent with their medical records. This discrepancy between the non-immunosuppressed and immunosuppressed reached statistical significance from 2022 Q1 onwards ($p (\leq 0.05$ from this date). However, it cannot be determined whether these data are reflective of non-exposure amongst the immunocompromised or poor N antibody seroconversion and accelerated waning in response.

Table 4.5: Antibody results in individuals who had no report of a positive viral test prior to sampling date

	Not identified as immunosuppressed			**Immunosuppressed**			***p-value***
	<0.4 negative	>0.4 equiv / positive	% equiv / positive	<0.4 negative	>0.4 equiv / positive	% equiv / positive	
2021 Q4	2,117	384	15%	200	32	14%	0.568
2022 Q1	3,608	1,068	23%	330	71	18%	0.018
2022 Q2	1,708	1,127	40%	182	73	29%	<0.001
2022 Q3	1,279	1,440	53%	159	62	28%	<0.001

Table 4.6 compares N antibody seroconversion data between immunosuppressed and non-immunosuppressed patients with a recorded history of SARS-CoV-1 infection prior to date of sampling. Consistent with N antibody waning or non-seroconversion, by 2022 Q2, immunosuppressed patients return significantly less N antibody positive blood samples post-COVID-19 infection than their non-immunosuppressed counterparts (p = (≤ 0.05 from this point onwards). Small samples amongst the immunosuppressed affect the strength of these findings, however.

Table 4.6: N antibody results in individuals who had reported a positive viral test prior to sampling date

	Not identified as immunosuppressed			**Immunosuppressed**			***p-value***
	<0.4 negative	>0.4 equiv / positive	% equiv / positive	<0.4 negative	>0.4 equiv / positive	% equiv / positive	
2021 Q4	4	46	92%	0	1	-	-
2022 Q1	37	451	92%	1	31	97%	0.499
2022 Q2	16	542	97%	5	40	89%	0.015
2022 Q3	18	553	97%	12	37	76%	0.002

S antibody seropositivity:

As per Table 4.7 below, after adjusting for age, sex, COVID-19 vaccine dose and time since inoculation, S antibody levels were universally lower for all

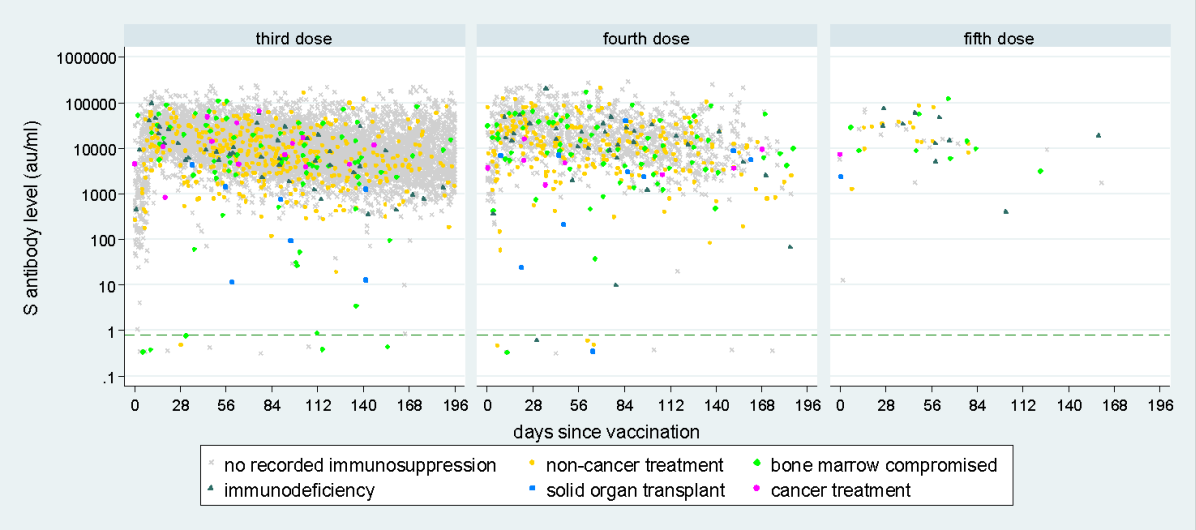
immunosuppressed subgroups compared to those not identified as immunosuppressed. Geometric mean antibody levels were lowest amongst solid organ transplant patients by a large margin.

Table 4.7: Geometric mean ratio of S antibody response in immunosuppressed subgroups compared with those with no record of immunosuppression, doses 3-5 during the period September 2021 to August 2022. As an illustrative example, the table also gives the predicted geometric mean S antibody level (au/ml) at 91 days post dose 3.

	Geometric mean ratio of S antibody response	Predicted geometric mean S antibody level (au/ml) at 91 days post dose 3
Not identified as immunosuppressed	ref	9276 (9028 - 9530)
All immunosuppressed	0.54 (0.49 - 0.58)	4981 (4579 - 5418)
Bone marrow compromised	0.44 (0.36 - 0.53)	4047 (3360 - 4876)
Solid organ transplant	0.04 (0.02 - 0.06)	342 (197 - 595)
Treatment unrelated to Cancer	0.57 (0.34 - 0.93)	5232 (3192 - 8574)
Recently treated Cancer	0.6 (0.55 - 0.67)	5596 (5083 - 6161)
Primary & Acquired Immunodeficiency	0.49 (0.38 - 0.64)	4549 (3516 - 5884)

Reassuringly, plots of S antibody production (au/ml) by study category (Figure 4.11) indicate that most immunosuppressed subgroups had seroconverted by their third dose of COVID-19 vaccination. Lingering issues of poor or non-response were seen amongst Solid Organ Transplant and Bone Marrow Compromised patients, though small sample sizes affect confidence in this assessment. No non-responders were detectable by dose 5.

Figure 4.11: S antibody level against time since COVID-19 vaccination doses 3-5, points coloured by immunosuppression status



iii. Discussion:

Principal findings and their implications:

This pilot phenotype and the rapid scoping review that informed it were both conducted as hypothesis generating exercises and should be judged accordingly. Despite the limitations to be catalogued, this pilot phenotype was the first to operationalise UK specifications for immunosuppression hierarchically and created a clinically meaningful and medical health record compatible – if imperfectly so – basis for extracting and segmenting this vulnerable population. Unconditional phenotype levels provided valuable intelligence for UKHSA stakeholders on the distinct COVID-19 vaccine and infection experiences of immunosuppressed subgroups. As laid out in the previous chapter, the DESTINIES phenotype incorporated this best practice by only phenotyping with unconditional and standalone procedural and diagnostic codes as well as ontological rules that could be easily operationalised within CMRs.

Immunosuppressed patients were seen to be at substantially greater risk of critical COVID-19 infection outcomes than their non-immunosuppressed counterparts. Moreover, by segmenting immunosuppressed data, stark contrasts could be revealed between homogenised COVID-19 vaccine uptake (reflective of the universalised vaccine roll-out for clinical risk groups in the UK [29]) and varied infection outcomes. Solid Organ Transplant and Recently Treated Cancer patients were seen to be especially vulnerable. Such data makes a clear case for selectively enhancing COVID-19 care for the immunosuppressed, allocating vaccine boosters and passive forms of immunisation on a needs-basis.

Explorations of differential vaccine effectiveness amongst the immunosuppressed revealed broadly similar results to the non-immunosuppressed standard when appraised against medically attended COVID-19 via TNCC and considerably more varied results when appraised against severe COVID-19 (hospitalisation and/or mortality) via retrospective cohort study. Solid Organ Transplantation and Primary & Acquired Immunodeficiency patients returned especially depressed vaccine effectiveness against severe outcomes, though small sample sizes affected our analysis. Evidence was provided for vaccine waning over time almost universally.

In serological estimations of vaccine response, both N and S antibody seroconversion were depressed amongst the immunosuppressed compared to the non-immunosuppressed baseline. Although small sample sizes again undermined our confidence in reporting, Solid Organ Transplant patients were especially affected in this. That said, nearly all patients had successfully seroconverted by dose 3 according to S antibody plots; no non-responders were identified by dose 5.

Meanwhile, conflicts between non-immunosuppressed patients' medical history for COVID-19 and sera N antibody levels are suggestive of under-reporting of infection in this group – perhaps explained by higher levels of asymptomatic disease in these patients. Immunosuppressed sera were more consistent with their medical history, by comparison.

Comparisons to existing literature:

This work benefitted from underpinning collaboration between RSC clinical experts and UKHSA epidemiologists. Constituent clinical codes were quality assured by multiple clinicians and data analysts for accuracy and comprehensiveness – augmenting existing reference lists that did not withstand these tests of face validity. UKHSA collaborators obtained the necessary approvals to link primary care data with biological samples and secondary outcomes to produce a more holistic appraisal of vaccine response in the immunosuppressed than comparable investigations [30, 31]. N versus S antibody serological analysis provided a unique view of natural versus vaccinated immune response in these patients, for example.

This first experiment represents a step forward from the aggregated surveillance dataflows that preceded it; this pilot phenotype has unlocked higher resolution surveillance of immunosuppressed patients than prevailing passive offerings [32] and is less resource intensive to implement than active alternatives [33].

This pilot phenotype identified just under 2% of the study cohort as immunosuppressed, a figure that is in line with comparable literature [7; 34], if a slight underestimate. Discrepancies between Recently Treated Cancer and Non-

Cancer Related Immunosuppressives sample sizes are suggestive of misallocation, however – affecting the confidence of our findings for these subgroups specifically.

Conflicts seen between universal vaccine uptake and highly variable COVID-19 infection outcomes amongst immunosuppressed subgroups suggests contemporary vaccine programmes were insufficient for protecting all patients. Targeted care and enhanced vaccination protocols may have proven beneficial. This assessment is corroborated by the depressed vaccine effectiveness against COVID-19 hospitalisation and/or death reported amongst those with transplants or immunodeficiencies as well as the disproportionate levels of poor seroconversion seen in Solid Organ Transplant and Bone Marrow Compromised subgroups. Said findings, including the eventual resolution of poor seroconversion in later vaccine doses, are in line with outputs of both the INFORM study group [7] and OCTAVE and OCTAVE DUO serological analysis – multicentre, randomised, controlled, phase 3 trials cross-referencing humoral and T-cell responses to COVID-19 vaccines amongst key immunosuppressed subgroups [35; 36].

Likewise, the challenges this work encountered when utilising prescription data for surveillance purposes have been replicated elsewhere [37; 38] and are informative for those working within clinical informatics. We discovered that, at present, prescription information available in CMRs are insufficiently detailed or accurate to allow for medication-based differentiation of clinical outcomes. This finding leant further support to our decision to proceed with an exclusively diagnostic and procedural approach to phenotyping immunosuppression.

Limitations:

Despite these advantages, this clinical value of this work was limited in several respects. Firstly, in its current form, the pilot phenotype produced significant misallocations between medication-specific layers during extraction; medical record keeping was not contemporaneous enough to accomplish the dual medication-diagnosis conditions requested with absolute accuracy. This undermined confidence in all findings reported for Recently Treated Cancer and Non-Cancer Related Immunosuppressive subgroups.

Secondly, instituting time conditions in phenotype-based extracts proved unnecessarily complicated and accident-prone. In this exercise, mandating the presence of a cancer diagnosis code within 12 months of receiving an immunosuppressive prescription code inadvertently allocated all treated cancers that received a diagnosis code outside of this window to the Non-Cancer Related Immunosuppressive subgroup. Indeed, with hindsight, the Recently Treated Cancer level of the pilot phenotype should be relabelled Recently Treated Recently Diagnosed Cancer from the inflexibility of these time conditionalities. Moreover, since this work was conducted, these recommended timings have been updated with clinical logic now conferring immunosuppression upwards of 12 months or 24 months after the discontinuation of chemo/radiotherapy and Chimeric Antigen Receptor T-Cells (CAR-T) therapy, respectively [39].

Furthermore, despite the innovation this pilot phenotype offers, its segmentation was informed by an extremely superficial evidence base. Single study estimates led to misrepresentations of clinical risk. The systematic review, meta-analysis and

consensus building exercise that informed the DESTINIES phenotype were direct responses to this criticism. Said exercises also revealed the heightened vulnerability of those with primary immunodeficiencies to severe COVID-19 – a patient group that was deprioritised in the pilot phenotype. Likewise, this work's access to five years of medical history may have proven insufficient for accurately assigning immunosuppressed status. Ongoing medical conditions and older diagnoses or procedures – most notably transplantations – would not have been identified as immunosuppressed by the pilot phenotype. This also calls the validity of our control group into question. Finding a time interval that can balance the need to include ongoing forms of immunosuppression while excluding legacy conditions will be key going forwards.

The mutual exclusivity of the pilot phenotype can also be criticised as artificial; immunosuppressive conditions typically receive treatment, for example [40]. Although valuable for simplifying analysis and interpretation, this phenotype's hierarchical sort erased important comorbidity information and made it extremely difficult to assess the respective contributions of immunosuppressive medication or diagnosis to patient risk for severe COVID-19 outcomes. The extensional nature of this pilot phenotype, manually codifying levels, makes it susceptible to redundancies and inaccuracies as PRIMIS and underpinning terms update. An intensional, concept hierarchy- or rule-based and machine-readable process would have improved this phenotype's resilience to redundancy and resulted in a more readily sharable asset [21].

The representativeness of RSC data is imperfect. As a source of primary care electronic records, this data asset can only offer information about patients registered within general practice [3]. The unregistered are rendered invisible. Furthermore, RSC membership is sparse amongst the East of the England, Scottland and Wales and is concentrated amongst more affluent regions, including London and the South East of England [3].

Finally, the comparability of immunosuppressed and immunocompetent vaccine effectiveness outputs can be called into question. By calculating vaccine effectiveness at specific timepoints since last dose and not calendar month or week, these outputs fail to control for asynchronous exposures to COVID-19 variants. Lower-dose performance against Omicron is not a fair comparison to higher-dose performance against Omicron or Delta variants, for example.

3. Operationalising the DESTINIES phenotype to differentiate the COVID-19 infection and vaccination experiences of Systemic, Single Organ and Overlap Immune Mediated Inflammatory Disease (IMID) patients:

i. Method:

The COVID-19 Vaccination in Autoimmune Disease (COVAD) Study was established to enhance pharmacovigilance for immune-mediated inflammatory disorders (IMID), including autoimmune patients. Its first iteration, COVAD 1, successfully collected information about the COVID-19 infection and first and second vaccine dose experiences of a global cohort of over >19,000 IMID patients and

general population comparators. COVAD 1 Study design, ethical approvals, recruitment, data collection and initial analysis have been described elsewhere [41].

This programme of work presents a secondary analysis of COVAD 1 data, utilising DESTINIES phenotype IMID subgroups – including a novel 'Overlap IMID' subgroup in acknowledgement of potential multi-morbidities - to differentiate respondents' data. Consistent with the cadence of the DESTINIES phenotype, this work tested the hypothesis that the COVID-19 vaccine and infection outcomes of IMID patients would be significantly poorer than general population controls, with worst outcomes concentrated amongst those with generalised pathologies. It was anticipated that the localised nature of Single Organ IMID would produce less adverse vaccine events and severe cases of COVID-19 than those reported amongst their Overlap and Systemic counterparts. However, the influence of wider explanatory variables (age, gender, ethnicity, country economic status, vaccine dose, self-reported health, physical activity status and medication history) over the likelihood of being hospitalised for COVID-19 or reporting side effects post-inoculation were also evaluated.

A protocol for this work is publicly available [2]; this details the twenty-two diagnoses COVAD 1 respondents could self-select and the consensus building process that informed their allocation into Overlap, Systemic and Single Organ IMID subgroups this research utilises (Table 4.8). Seven expert rheumatologists from the original DESTINIES panel participated in this process; the shift in language they requested from Single Site (ratified by the whole DESTINIES panel in Chapter 2) to Single Organ IMID brought this work into closer alignment with existing clinical systems [42]. This is default language from this point in the thesis onwards.

Table 4.8: Final allocation of COVAD 1 IMIDs into Single Organ, Systemic and Overlap subgroups

Single Organ IMID	Systemic IMID	Overlap IMID
Declaring one or more of the following: - Type 1 diabetes - Thyroid (hypothyroid or hyperthyroid) - Myasthenia gravis - Multiple sclerosis - Pernicious anaemia - Haemolytic anaemia/ idiopathic thrombocytopenic purpura (ITP) - Inclusion Body Myositis	*Declaring one or more of the following:* - Scleroderma - Rheumatoid arthritis - Sjögren's syndrome - Systemic lupus erythematosus - Overlap Myositis with lupus or Sjogren or Systemic sclerosis or Rheumatoid arthritis - Polymyalgia rheumatica - Ankylosing Spondylitis or Psoriatic arthritis - Vasculitis - Mixed Connective Tissue Disease - Anti-synthetase syndrome - Juvenile dermatomyositis - Dermatomyositis - Polymyositis - Crohn's disease or ulcerative colitis (Inflammatory bowel disease/IBD) - Necrotizing myositis	Declaring a combination of both Single Organ *and* Systemic IMID diagnoses.

COVAD 1 data were collected between March and December, 2021; secondary analysis was performed by the doctoral candidate between August and December 2024 after material transfer requests and the study protocol were reviewed and approved by the COVAD Steering Group. A full data dictionary, including the survey question set and an inventory of participating countries and respondents' spoken languages, is provided in Appendix 18.

Data cleaning removed all incomplete survey responses, the unvaccinated and those that either failed to provide information about their IMID status or disclosed conditions outside of the twenty-two specified. To preserve usable data, Google Translate (Alphabet, Inc.) was cross-referenced to check the eligibility of responses given in languages other than English.

Descriptive analysis assessed whether there were notable demographic differences between IMID subgroups and the general population; age, sex, ethnicity, country

economic status, self-reported activity levels, health and IMID status were tabulated. Following its successful implementation in the systematic literature review, country economic status was once again operationalised using World Bank Country classifications [43]: 'Higher' referred to those identified as high income, 'Lower' referred to countries identified as either low, lower-middle or upper-middle income.

Summary data were also produced by study category on vaccination symptoms, pre-vaccination use of steroidal and non-steroidal medications (or discontinuation thereof), vaccine uptake and side effects (minor and major). Descriptive statistics were also provided for COVID-19 infection data (presence of symptoms, symptom type, duration and severity) across study categories. Participants could report side effects from either their first or second COVID-19 vaccine dose; data were not collected on which dose these reports were associated with, however. Mild vaccine side effects were operationalised as 'injection site (arm) pain and soreness', 'muscle pain in all arms and legs', 'body ache', 'fever', 'chills', 'nausea/vomiting', 'headache', 'rash', 'fatigue', 'diarrhoea', 'abdominal pain', 'high pulse rate or palpitations', 'rise in blood pressure', 'fainting', 'difficulty in breathing', 'dizziness', 'chest pain' and 'other'. Major vaccine side effects were operationalised as 'anaphylaxis (shock)', 'marked difficulty in breathing', 'tongue swelling or throat closure', 'severe diffuse body rash (hives)', 'required hospitalisation' and 'other'. These symptoms were tabulated separately by vaccine type to investigate whether disproportionate adverse events were observable for specific technologies (messenger ribonucleic acid [mRNA], adenoviral, inactivated virus, protein subunit) or mixed schedules.

Incidence rate ratios (IRRs) of both mild and major vaccine side effects were estimated for each IMID subgroup against the general population baseline via Poisson regression. This analysis occurred at the aggregated and disaggregated level, differentiating data by side effect class (mild versus major vaccine side effects) and specific type (fever, anaphylaxis etc.) to test for significant differences in both the severity and symptomology of adverse events that IMID patients reported. Results were presented with their corresponding 95% Confidence Intervals. Likelihood ratio tests were performed using the Chi-Square method to determine the overall influence of study categorisation on these outputs. Subgroup analyses were also performed to assess whether results attenuated by vaccine dose, country economic status and the use of steroidal or non-steroidal medications prior to vaccination. Insufficient data was available to conduct these subgroup analyses for each side effect type, however. Because the control group were unmedicated, Single Organ IMID respondents served as the reference category when differentiating IRRs by steroidal and non-steroidal status; here, the Chi-Square method was utilised to assess the influence of IMID categorisation on outcomes of interest.

Amongst COVID-19 infections, IRRs for COVID-19 symptoms and for hospitalisation (with and without oxygen support) were produced for each IMID subgroup against the general population reference via Poisson regression. As before, analysis was aggregated (symptomatic vs non-symptomatic) and disaggregated (taking each COVID-19 symptom in turn). These IRRs were reported with their respective 95% confidence intervals with likelihood ratio tests again performed via the Chi-Square method. Subgroup analyses of aggregated symptom data were repeated as before.

Age-sex matching was not attempted to preserve sample sizes and adequately power comparisons. Instead, multivariable logistic regressions were performed to assess the relative influence of demographic, health, medication and vaccine variables over a respondents' likelihood of reporting i) previous hospitalisation for COVID-19 (a composite of hospitalisation with or without supplemental Oxygen) and ii) adverse events post-inoculation (a composite of mild and major side effects). Survey responses that did not provide information on either vaccine side effects or hospitalisation did not contribute to this analysis.

For COVID-19 hospitalisation, the following models were run at the whole cohort level and then separately for IMID (aggregated and categorised) and general control data.

- Model 1 (demographics): age, sex, ethnicity and country economic status
- Model 2 (demographics + prior health): age, sex, ethnicity, country economic status, health status and medication status
- Model 3 (demographics + prior health + vaccination): age, sex, ethnicity, country economic status, health status, medication status and vaccine dose.

For COVID-19 vaccine side effects, the following models were run as before:

- Model 1 (demographics): age, sex, ethnicity and country economic status
- Model 2 (demographics + prior health): age, sex, ethnicity, country economic status, health status and medication status
- Model 3 (demographics + prior health + vaccination): age, sex, ethnicity, country economic status, health status, medication status, vaccine dose and pre-vaccine symptoms and medication suspensions.

Each factor had constituent levels' influence over the likelihood of reporting previous COVID-19 hospitalisation or vaccine side effects analysed in turn. This was estimated by measuring the change in likelihood of these outcomes created by exchanging reference level with test level data. The reference levels for each factor were pre-specified. The influence of Study Category over these outcomes were assessed amongst aggregated IMID and whole cohort data; Single Organ IMID data was the reference category in the former, general population data was the reference category in the latter. To support the interpretation of these data, resultant coefficients were exponentiated and reported as Odds Ratios with their associated 95% Confidence Intervals and *p-values*. Statistical significance was set at $p \leq 0.05$.

ii. Results:

A total of 19,200 respondents attempted to complete the COVAD 1 survey. After removing the unvaccinated and those that either failed to complete the survey or to provide data on their IMID status, data from 12,223 respondents were carried forward for analysis as per Methods. Tables 4.9a and b provides the output of initial descriptive analysis; 'Not stated' entries summarise where data was either skipped or inappropriate for completion (e.g. general population controls being unable to answer questions regarding the severity of their IMID symptoms).

Table 4.9a: Descriptive analysis of cohort demographics and health status

		Control	IMID all	Overlap	Systemic	Single organ
Cohort (n)		5550	6673	688	4757	1228
Age (mean, SD)		37.35 (13.98)	49.85 (15.05)	52.53 (13.5)	48.99 (14.4)	51.66 (18.0)
Gender	Do not wish to disclose	29 (0.5)	28 (0.4)	3 (0.4)	15 (0.3)	10 (0.8)
	Female	3026 (54.5)	4582 (68.7)	558 (81.1)	3315 (69.7)	709 (57.7)
	Male	1670 (30.1)	1013 (15.2)	50 (7.3)	678 (14.3)	285 (23.2)
	Not stated	825 (14.9)	1050 (15.7)	77 (11.2)	749 (15.7)	224 (18.2)
Ethnicity	African American or of African origin (Black)	33 (0.6)	70 (1.0)	4 (0.6)	60 (1.3)	6 (0.5)
	Asian	1336 (24.1)	1269 (19.0)	88 (12.8)	1010 (21.2)	171 (13.9)
	Caucasian (White)	1961 (35.3)	3451 (51.7)	437 (63.5)	2362 (49.7)	652 (53.1)
	Do not wish to disclose	350 (6.3)	231 (3.5)	21 (3.1)	176 (3.7)	34 (2.8)
	Hispanic	757 (13.6)	403 (6.0)	42 (6.1)	256 (5.4)	105 (8.6)
	Native American/ Indigenous/Pacific Islander	25 (0.5)	21 (0.3)	4 (0.6)	16 (0.3)	1 (0.1)
	Not stated	825 (14.9)	1050 (15.7)	77 (11.2)	749 (15.7)	224 (18.2)
	Other	263 (4.7)	178 (2.7)	15 (2.2)	128 (2.7)	35 (2.9)
Country economic status	Higher	1060 (19.1)	3541 (53.1)	454 (66.0)	2489 (52.3)	598 (48.7)
	Lower	3665 (66.0)	2082 (31.2)	157 (22.8)	1519 (31.9)	406 (33.1)
	Not stated	825 (14.9)	1050 (15.7)	77 (11.2)	749 (15.7)	224 (18.2)
Self-reported Health Data						
Self-reported health rating	Poor	44 (0.9)	404 (6.9)	74 (11.7)	282 (6.7)	48 (4.5)
	Fair	311 (6.2)	1651 (28.1)	240 (37.8)	1179 (28.2)	232 (21.9)
	Good	1615 (32.2)	2326 (39.6)	237 (37.3)	1704 (40.7)	385 (36.4)
	Very good	1968 (39.2)	1128 (19.2)	70 (11.0)	770 (18.4)	288 (27.2)
	Excellent	1085 (21.6)	366 (6.2)	14 (2.2)	248 (5.9)	104 (9.8)
Self-reported ability to complete daily tasks	Not at all	82 (1.6)	199 (3.4)	19 (3.0)	119 (2.8)	61 (5.8)
	A little	107 (2.1)	708 (12.1)	107 (16.9)	449 (10.7)	152 (14.4)
	Moderately	336 (6.7)	1322 (22.5)	177 (27.9)	987 (23.6)	158 (14.9)
	Mostly	779 (15.5)	1593 (27.1)	168 (26.5)	1212 (29.0)	213 (20.2)
	Completely	3719 (74.0)	2053 (34.9)	164 (25.8)	1416 (33.9)	473 (44.7)

Table 4.9b: Descriptive analysis of cohort COVID-19 infection and vaccination experiences

		Control	IMID all	Overlap	Systemic	Single organ
IMID status prior to vaccine	I am not sure	0 (0.0)	560 (9.1)	58 (8.9)	343 (7.8)	159 (14.5)
	Disease active & worsening	0 (0.0)	494 (8.1)	70 (10.7)	288 (6.6)	136 (12.4)
	Disease active but stable & manageable	0 (0.0)	2985 (48.7)	330 (50.5)	2176 (49.7)	479 (43.7)
	Disease active & improving	0 (0.0)	451 (7.4)	53 (8.1)	356 (8.1)	42 (3.8)
	Disease inactive/ in remission	0 (0.0)	1531 (25.0)	136 (20.8)	1149 (26.2)	246 (22.5)
	Other	0 (0.0)	107 (1.7)	6 (0.9)	68 (1.6)	33 (3.0)
	Not stated	5550 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IMID symptoms prior to vaccination	No	3 (0.1)	3059 (45.8)	230 (33.4)	2109 (44.3)	720 (58.6)
	Yes	0 (0.0)	3265 (48.9)	442 (64.2)	2409 (50.6)	414 (33.7)
	Not stated	5547 (99.9)	349 (5.2)	16 (2.3)	239 (5.0)	94 (7.7)
Non-steroid medication use prior to vaccination	No	1 (<0.01)	1841 (27.6)	137 (19.9)	884 (18.6)	820 (66.8)
	Yes	1 (<0.01)	4243 (63.6)	516 (75.0)	3452 (72.6)	275 (22.4)
	Not stated	5548 (100.0)	589 (8.8)	35 (5.1)	421 (8.9)	133 (10.8)
Steroid use prior to vaccination	No	1 (<0.01)	4338 (65.0)	432 (62.8)	2903 (61.0)	1003 (81.7)
	Yes	1 (<0.01)	1790 (26.8)	221 (32.1)	1477 (31.0)	92 (7.5)
	Not stated	5548 (100.0)	545 (8.2)	35 (5.1)	377 (7.9)	133 (10.8)
Discontinued medications prior to vaccine	No	1 (<0.01)	3967 (59.4)	438 (63.7)	3075 (64.6)	454 (37.0)
	Yes	0 (0.0)	877 (13.1)	117 (17.0)	727 (15.3)	33 (2.7)
	Not stated	5549 (100.0)	1829 (27.4)	133 (19.3)	955 (20.1)	741 (60.3)
Vaccine doses received	1	1427 (25.7)	2010 (30.1)	202 (29.4)	1434 (30.1)	374 (30.5)
	2	4123 (74.3)	4663 (69.9)	486 (70.6)	3323 (69.9)	854 (69.5)
Vaccine type	Adenoviral	1696 (30.6)	2009 (30.1)	209 (30.4)	1408 (29.6)	392 (31.9)
	Inactivated virus	1801 (32.5)	852 (12.8)	48 (7.0)	642 (13.5)	162 (13.2)
	Mixture	7 (0.1)	16 (0.2)	2 (0.3)	14 (0.3)	0 (0.0)
	mRNA	2000 (36.0)	3753 (56.2)	424 (61.6)	2664 (56.0)	665 (54.2)
	Protein subunit	4 (0.1)	11 (0.2)	0 (0.0)	8 (0.2)	3 (0.2)
	Unsure	42 (0.7)	32 (0.5)	5 (0.7)	21 (0.4)	6 (0.5)
Mild vaccine side effects	No	1359 (24.5)	1475 (22.1)	116 (16.9)	1060 (22.3)	299 (24.3)
	Yes	4191 (75.5)	5198 (77.9)	572 (83.1)	3697 (77.7)	929 (75.7)
Major vaccine side effects	No	5493 (99.0)	6523 (97.8)	666 (96.8)	4662 (98.0)	1195 (97.3)
	Yes	57 (1.0)	150 (2.2)	22 (3.2)	95 (2.0)	33 (2.7)
COVID-19 Infection Data						
Past COVID-19 infection	No	4511 (81.3)	5845 (87.6)	603 (87.6)	4165 (87.6)	1077 (87.7)
	Yes	1039 (18.7)	828 (12.4)	85 (12.4)	592 (12.4)	151 (12.3)
COVID-19 symptoms	No	92 (1.7)	57 (0.9)	4 (0.6)	41 (0.9)	12 (1.0)
	Yes	947 (17.1)	771 (11.6)	81 (11.8)	551 (11.6)	139 (11.3)
	Not stated	4511 (81.3)	5845 (87.6)	603 (87.6)	4165 (87.6)	1077 (87.7)
Average duration of COVID-19 symptoms in days (mean, SD)		14.15 (18.6)	18.89 (21.63)	23.41 (22.7)	17.87 (20.9)	20.35 (23.7)
Hospitalised for COVID	No	956 (17.2)	668 (10.0)	64 (9.3)	480 (10.1)	124 (10.1)
	Hospitalised	52 (0.9)	96 (1.4)	12 (1.7)	65 (1.4)	19 (1.5)
	Hospitalised w/Oxygen support	30 (0.5)	64 (1.0)	9 (1.3)	47 (1.0)	8 (0.7)
	Data omitted	4511 (81.3)	5845 (87.6)	603 (87.6)	4165 (87.6)	1077 (87.7)

Although respondent numbers in the IMID group and general population control were well balanced, sample sizes within IMID subgroups were extremely heterogeneous. Systemic IMID respondents (n = 4757) outnumbered those in the Overlap (n = 688)

and Single Organ (n = 1228) subgroups. These discrepancies must be considered when interpreting any significant differences between these subgroups.

Key demographic variables differed considerably between study categories. IMID respondents were, on average, less ethnically diverse and more likely to be female compared to individuals in the control group. In contrast, general population respondents were significantly likelier to originate from countries of lower economic status than those within IMID subgroups. These disparities justified the inclusion of all demographic variables in subsequent logistic regressions.

Unsurprisingly, IMID respondents of any category were likelier to self-report ill-health and physical limitations than general control counterparts. Within IMID subgroups, Overlap and Systemic patients saw elevated levels of steroidal or non-steroidal medications and were likelier to report poorer health and pre-vaccination IMID symptoms than those with Single Organ IMID diagnoses. These patients were also less likely to discontinue their medications prior to COVID-19 vaccination than Single Organ IMID counterparts.

COVID-19 vaccine uptake was consistent across all study categories; at the time of data collection, the majority of respondents had received two doses. Of all vaccine types available, the uptake of adenoviral and mRNA substrates dominated; inactivated viral alternatives were rarely taken up by IMID patients. Mild vaccine side effects were seen to be reassuringly similar across IMID subgroups. Elevated reporting in Systemic and Overlap IMID subgroups were marginal. Major vaccine side effects were far more pronounced in IMID respondents, however. Side effect

counts in Overlap IMID respondents trebled that of general population respondents. That said, absolute numbers of these major adverse reactions remained exceedingly low; overall this exercise suggests the COVID-19 vaccine was generally well tolerated in all study categories.

COVID-19 infection levels and numbers of symptomatic cases were both considerably lower amongst IMID patients than the general population. That said, infection outcomes were far more severe: across all IMID subgroups, symptom duration were longer, and hospitalisations of any form were elevated beyond control reports. Hospitalisations without Oxygen support varied little between IMID subgroups; hospitalisations with Oxygen support, however, were concentrated amongst Overlap and Systemic IMID subgroups.

The IRRs produced in Table 4.10 and Table 4.11 enabled more detailed comparisons of clinical outcomes between IMID subgroups. Appendix 19 hosts disaggregated data on IMID COVID-19 symptom and vaccine side effect reporting compared to the general population control – providing IRRs for each specific vaccine side effects and infection symptoms, including asymptomatic reports. Mild and major vaccine side effects are also tabulated by vaccine type.

Table 4.10: Incidence rate ratios of key clinical events against the general population control by IMID subgroup (whole cohort, side effects as yes/no binary)

		Overlap	Systemic	Single organ	Control	Chi² *p-value*
Cohort		688	4757	1228	5550	
Past COVID-19 infection	Yes	85	592	151	1039	<0.001
IRR		0.66	0.66	0.66	/	*
Lower CI		0.53	0.60	0.55	/	
Upper CI		0.82	0.74	0.78	/	
p-value		<0.001 *	<0.001 *	<0.001 *	/	
Mild vaccine side effects	Yes	572	3697	929	4191	0.1424
IRR		1.10	1.03	1.00	/	
Lower CI		1.01	0.98	0.93	/	
Upper CI		1.20	1.08	1.07	/	
p-value		0.03 *	0.20	0.96	/	
Major vaccine side effects	Yes	22	95	33	57	<0.001
IRR		3.11	1.94	2.62	/	*
Lower CI		1.86	1.41	1.69	/	
Upper CI		5.01	2.71	4.00	/	
p-value		<0.001 *	<0.001 *	<0.001 *	/	

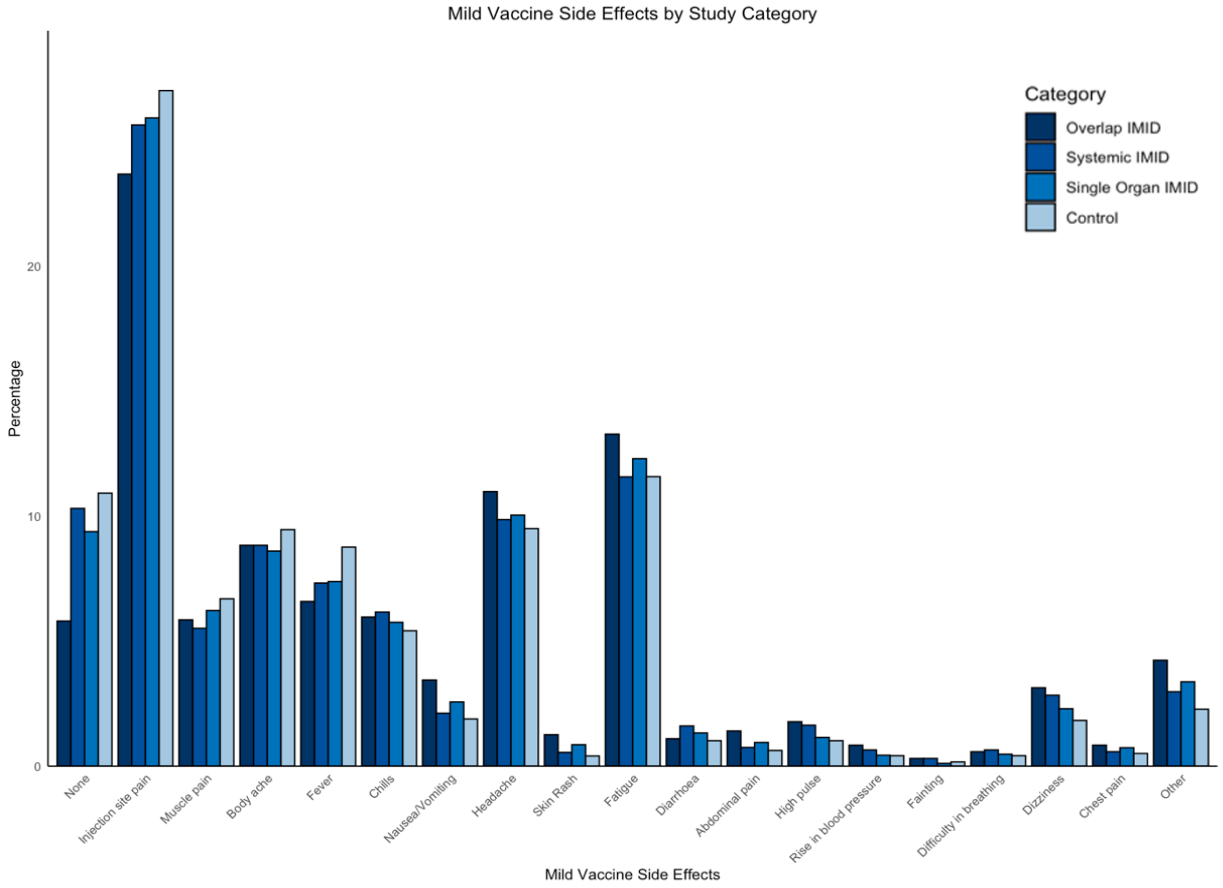
Table 4.11: Incidence rate ratios of key clinical events against the general population control by IMID subgroup (COVID-19 cases only, symptoms as yes/no binary)

		Overlap	Systemic	Single organ	Control	Chi² *p-value*
COVID-19 Cases		85	592	151	1039	
COVID-19 symptoms	Yes	81	552	139	947	0.96
IRR		1.05	1.02	1.01	/	
Lower CI		0.83	0.92	0.84	/	
Upper CI		1.30	1.13	1.20	/	
p-value		0.70	0.67	0.91	/	
Hospitalised w/o Oxygen support	Yes	12	65	19	52	<0.001
IRR		2.82	2.19	2.51	/	*
Lower CI		1.44	1.53	1.45	/	
Upper CI		5.10	3.17	4.17	/	
p-value		<0.001 *	<0.001 *	<0.001 *	/	
Hospitalised w/Oxygen support	Yes	9	47	8	30	<0.001
IRR		3.67	2.75	1.83	/	*
Lower CI		1.64	1.75	0.78	/	
Upper CI		7.41	4.39	3.81	/	
p-value		<0.001 *	<0.001 *	0.13	/	

When aggregated, only Overlap IMID patients reported levels of mild vaccine side effects that deviated significantly from those experienced by controls (IRR: 1.10, p = 0.03). However, once incidence calculations were disaggregated and utilised all symptoms reported (Appendix 19), reports of nausea/ vomiting, rash, fatigue, diarrhoea, abdominal pain, high pulse rate and dizziness were seen to be statistically

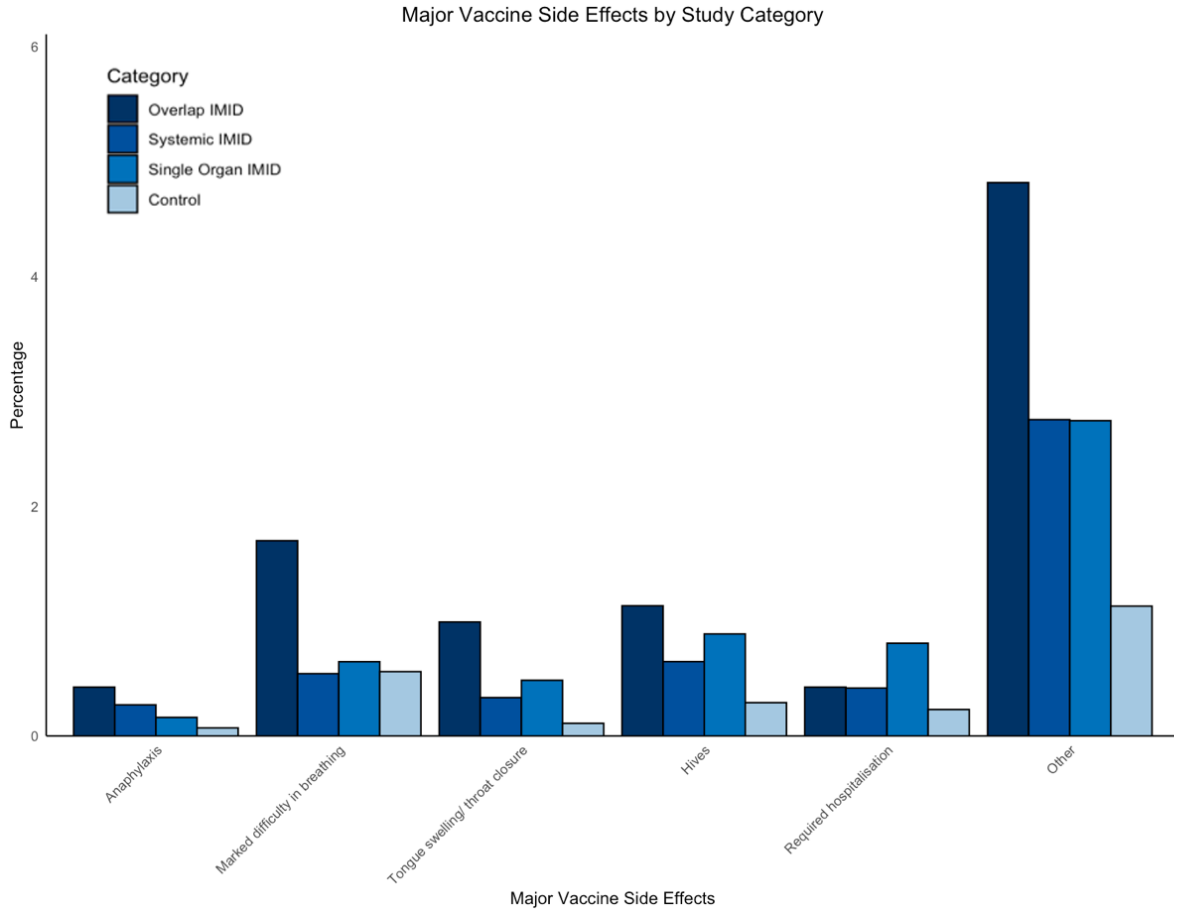
more commonplace amongst IMID subgroups. Distributions of specific mild COVID-19 vaccine side effects are visualised by Study Category in Figure 4.12.

Figure 4.12: Distribution of mild COVID-19 vaccine side effects by study category



Whether reported as an aggregate or disaggregated (Appendix 19), major vaccine side effects were disproportionately high amongst IMID subgroups compared to controls (Chi^2 $p<0.001$). Despite the comparability between reports of asymptomatic vaccine response between IMID subgroups and the general population control, incidences of anaphylaxis, marked difficulty breathing, tongue swelling, severe rash, hospitalisation and other severe symptoms were disproportionate in some – usually all – IMID respondents compared to the reports of controls. Distributions of specific major COVID-19 vaccine side effects are visualised by Study Category in Figure 4.13; asymptomatic data is omitted for interpretability and scale.

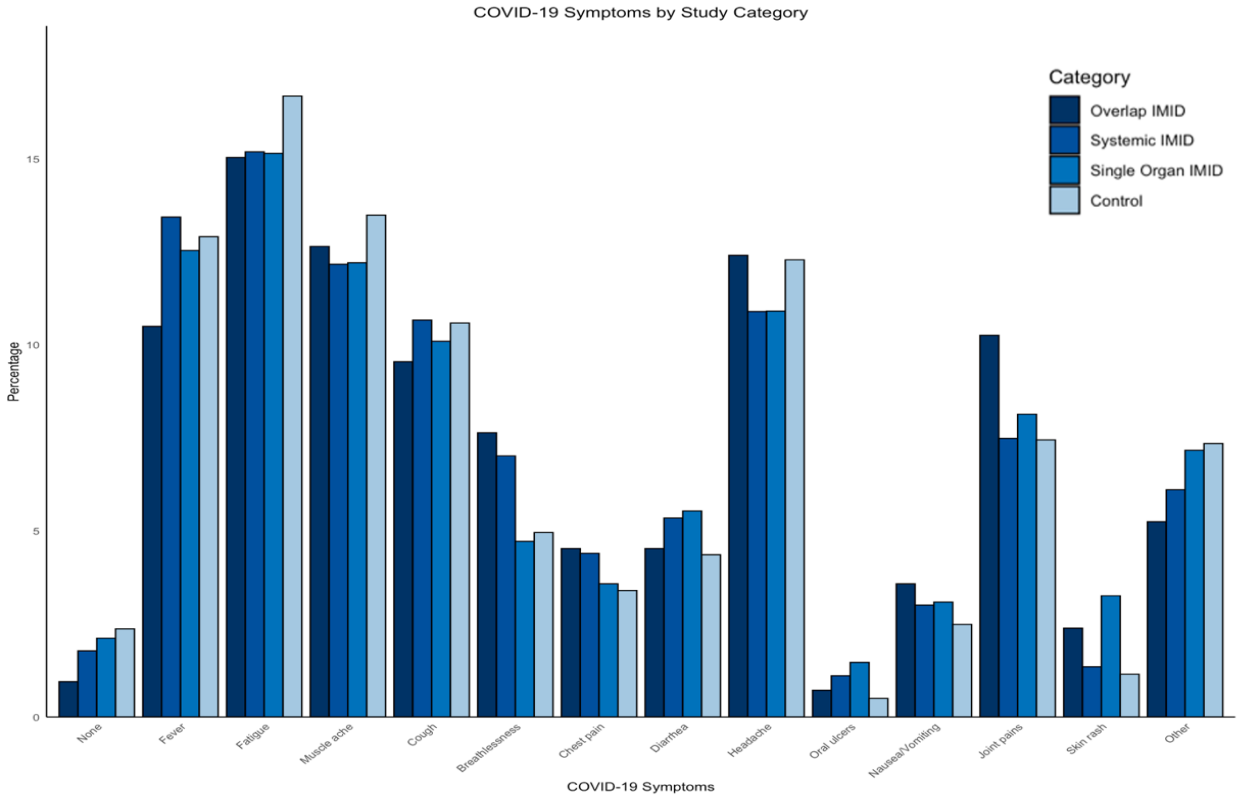
Figure 4.13: Distribution of major COVID-19 vaccine side effects by study category



When differentiating vaccine side effects by vaccine type, mild vaccine side effects were seen to be more commonplace amongst mRNA and adenoviral recipients irrespective of study category (Appendix 19) – though this may be attributable to the disproportionate uptake of these classes amongst the study cohort. Tentative evidence is also supplied for reduced mild adverse events amongst recipients of inactivated viral vaccines. Disaggregating major vaccine side effects in this way proved less insightful due to the extremely low numbers of these events and the uptake of certain vaccine types.

When looking to COVID-19 infection rates (Table 4.10) and their outcomes (Table 4.11), IMID patients saw significantly reduced incidences of COVID-19 infection compared to the general population (IRR: 0.66, $p<0.001$ for Overlap, Systemic and Single Organ IMID subgroups; Chi^2 $p<0.001$). As an aggregated outcome, symptomatic COVID-19 cases were not statistically dissimilar between IMID and control groups. However, once symptoms were disaggregated (Appendix 19), patterns of statistical significance became observable: breathlessness (Overlap IRR: 1.54, $p = 0.02$; Systemic IRR: 1.42, $p = <0.001$), chest pain (Systemic IRR: 1.29, $p = 0.04$), oral ulcers (Systemic IRR: 2.21, $p = 0.006$; Single Organ IRR: 2.91, $p = 0.007$), joint pains (Overlap IRR: 1.38, $p = 0.049$) and skin rashes (Overlap IRR: 2.08, $p = 0.04$; Single Organ IRR: 2.83, $p < 0.001$) were all elevated in experimental groups. Disaggregated COVID-19 symptoms are visualised by study category in Figure 4.14 below.

Figure 4.14: Distribution of COVID-19 symptoms by study category



Irrespective of oxygen support, incidences of hospitalisation (Table 4.11) were consistently elevated amongst IMID subgroups compared to general population controls. This disparity reached statistical significance in all instances for Overlap and Systemic IMID respondents (hospitalisation without Oxygen support Overlap IMID IRR: 2.82, $p<0.001$; hospitalisation without Oxygen support Systemic IMID IRR: 2.19, $p<0.001$; hospitalisation with Oxygen support Overlap IMID IRR: 3.67, $p<0.001$; hospitalisation with Oxygen support Systemic IRR: 2.75, $p<0.001$) and for hospitalisation without Oxygen support amongst Single IMID respondents (IRR: 2.51, $p<0.001$).

Subgroup analyses of COVID-19 vaccine and infection outcome IRRs by medication type, vaccine dose and country income are tabulated below (Table 4.12) to assess whether previously reported IRRs attenuated by these explanatory variables.

Table 4.12: Incidence rate ratios of key clinical events against the general population control by IMID subgroup, subgroup analyses (staggered over multiple pages)

Subgroup	Cohort			Overlap	Systemic	Single organ	Control	Chi² *p-value*
Non-steroidal medications	Medicated (all)	n		516	3452	275	NA	
		Past COVID-19 infection	Yes	59	431	37	NA	0.720
			IRR	0.85	0.93	/	NA	
			Lower CI	0.57	0.67		NA	
			Upper CI	1.29	1.32		NA	
			p-value	0.44	0.66		NA	
		Mild vaccine side effects	Yes	428	2706	216	NA	0.557
			IRR	1.06	1.00	/	NA	
			Lower CI	0.90	0.87		NA	
			Upper CI	1.25	1.15		NA	
			p-value	0.51	0.98		NA	
		Major vaccine side effects	Yes	14	63	10	NA	0.099
			IRR	0.75	0.50	/	NA	
			Lower CI	0.33	0.27		NA	
			Upper CI	1.73	1.04		NA	
			p-value	0.48	0.04 *		NA	
Non-steroidal medications	Medicated (COVID-19 cases)	n		59	431	37	NA	
		Symptomatic	Yes	58	406	33	NA	0.903
			IRR	1.10	1.06	/	NA	
			Lower CI	0.72	0.75		NA	
			Upper CI	1.71	1.53		NA	
			p-value	0.66	0.76		NA	
		Hospitalised for COVID-19 w/o Oxygen Support	Yes	10	51	11	NA	0.034
			IRR	0.57	0.40	/	NA	*
			Lower CI	0.24	0.22		NA	
			Upper CI	1.35	0.80		NA	
			p-value	0.20	0.005 *		NA	
		Hospitalised for COVID-19 w/ Oxygen Support	Yes	6	35	3	NA	0.883
			IRR	1.25	1.00	/	NA	
			Lower CI	0.33	0.36		NA	
			Upper CI	5.94	4.16		NA	
			p-value	0.75	1.00		NA	

Subgroup	Cohort			Overlap	Systemic	Single organ	Control	Chi² *p-value*
Non-steroidal medications	Unmedicated (all)	n		137	884	820	NA	
		Past COVID-19 infection	Yes	20	104	89	NA	0.496
			IRR	1.35	1.08	/	NA	
			Lower CI	0.81	0.82		NA	
			Upper CI	2.14	1.44		NA	
			p-value	0.23	0.58		NA	
		Mild vaccine side effects	Yes	115	670	612	NA	0.521
			IRR	1.12	1.02	/	NA	
			Lower CI	0.91	0.91		NA	
			Upper CI	1.37	1.13		NA	
			p-value	0.25	0.78		NA	
		Major vaccine side effects	Yes	6	18	16	NA	0.268
			IRR	2.24	1.04	/	NA	
			Lower CI	0.81	0.53		NA	
			Upper CI	5.46	2.07		NA	
			p-value	0.09	0.90		NA	
Non-steroidal medications	Unmedicated (COVID-19 cases)	n		20	104	89	NA	
		Symptomatic	Yes	17	92	82	NA	0.939
			IRR	0.93	0.96	/	NA	
			Lower CI	0.53	0.71		NA	
			Upper CI	1.51	1.29		NA	
			p-value	0.76	0.78		NA	
		Hospitalised for COVID-19 w/o Oxygen Support	Yes	1	9	6	NA	0.804
			IRR	0.74	1.28	/	NA	
			Lower CI	0.04	0.46		NA	
			Upper CI	4.34	3.83		NA	
			p-value	0.78	0.64		NA	
		Hospitalised for COVID-19 w/ Oxygen Support	Yes	2	9	3	NA	0.269
			IRR	2.97	2.57	/	NA	
			Lower CI	0.39	0.77		NA	
			Upper CI	17.91	11.57		NA	
			p-value	0.23	0.16		NA	

Subgroup	Cohort			Overlap	Systemic	Single organ	Control	Chi² *p-value*
Steroidal medications	Medicated (all)	n		221	1477	92	NA	
		Past COVID-19 infection	Yes	26	176	17	NA	0.260
			IRR	0.64	0.64	/	NA	
			Lower CI	0.35	0.40		NA	
			Upper CI	1.19	1.10		NA	
			p-value	0.15	0.08		NA	
		Mild vaccine side effects	Yes	178	1127	67	NA	0.729
			IRR	1.11	1.05	/	NA	
			Lower CI	0.84	0.83		NA	
			Upper CI	1.47	1.35		NA	
			p-value	0.48	0.71		NA	
		Major vaccine side effects	Yes	5	30	9	NA	0.002
			IRR	0.23	0.21	/	NA	
			Lower CI	0.07	0.10		NA	*
			Upper CI	0.67	0.46		NA	
			p-value	<0.001 *	<0.001 *		NA	
Steroidal medications	Medicated (COVID-19 cases)	n	n	26	176	17	NA	
		Symptomatic	Yes	24	163	16	NA	0.998
			IRR	0.98	0.98	/	NA	
			Lower CI	0.53	0.61		NA	
			Upper CI	1.88	1.71		NA	
			p-value	0.95	0.95		NA	
		Hospitalised for COVID-19 w/o Oxygen Support	Yes	5	25	7	NA	0.078
			IRR	0.47	0.34	/	NA	
			Lower CI	0.14	0.16		NA	
			Upper CI	1.46	0.86		NA	
			p-value	0.19	0.01 *		NA	
		Hospitalised for COVID-19 w/ Oxygen Support	Yes	5	27	2	NA	0.824
			IRR	1.63	1.30	/	NA	
			Lower CI	0.35	0.39		NA	
			Upper CI	11.41	8.09		NA	
			p-value	0.56	0.72		NA	

Subgroup	Cohort			Overlap	Systemic	Single organ	Control	Chi² *p-value*
Steroidal medications	Unmedicated (all)	n		432	2903	1003	NA	
		Past COVID-19 infection	Yes	53	365	109	NA	0.400
			IRR	1.13	1.16	/	NA	
			Lower CI	0.81	0.94		NA	
			Upper CI	1.56	1.44		NA	
			p-value	0.47	0.18		NA	
		Mild vaccine side effects	Yes	365	2284	761	NA	0.24
			IRR	1.11	1.00	/	NA	
			Lower CI	0.98	0.96		NA	
			Upper CI	1.26	1.13		NA	
			p-value	0.09	0.39		NA	
		Major vaccine side effects	Yes	15	51	17	NA	0.08
			IRR	2.05	1.04	/	NA	
			Lower CI	1.01	0.61		NA	
			Upper CI	4.11	1.85		NA	
			p-value	0.04 *	0.90		NA	
Steroidal medications	Unmedicated (COVID-19 cases)	n	n	53	365	109	NA	
		Symptomatic	Yes	51	340	99	NA	0.944
			IRR	1.06	1.03		NA	
			Lower CI	0.75	0.82		NA	
			Upper CI	1.48	1.29		NA	
			p-value	0.74	0.83		NA	
		Hospitalised for COVID-19 w/o Oxygen Support	Yes	6	35	10	NA	0.912
			IRR	1.23	1.05		NA	
			Lower CI	0.42	0.54		NA	
			Upper CI	3.32	2.23		NA	
			p-value	0.68	0.90		NA	
		Hospitalised for COVID-19 w/ Oxygen Support	Yes	3	17	4	NA	0.843
			IRR	1.54	1.27	/	NA	
			Lower CI	0.30	0.47		NA	
			Upper CI	7.00	4.41		NA	
			p-value	0.57	0.67		NA	

Subgroup	Cohort			Overlap	Systemic	Single organ	Control	Chi² *p-value*
Vaccine dose	Dose 1 (all)	n		202	1434	374	1427	
		Past COVID-19 infection	Yes	27	250	55	282	0.054
			IRR	0.68	0.88	0.74	/	
			Lower CI	0.45	0.74	0.55		
			Upper CI	0.98	1.05	0.98		
			p-value	0.052	0.15	0.05 *		
		Mild vaccine side effects	Yes	166	1140	293	1154	0.935
			IRR	1.02	0.98	0.97	/	
			Lower CI	0.86	0.91	0.85		
			Upper CI	1.19	1.07	1.10		
			p-value	0.85	0.68	0.63		
		Major vaccine side effects	Yes	3	40	19	22	0.002
			IRR	0.96	1.81	3.30	/	*
			Lower CI	0.23	1.09	1.77		
			Upper CI	2.78	3.09	6.09		
			p-value	0.95	0.03 *	<0.001 *		
Vaccine dose	Dose 1 (COVID-19 Cases)	n		27	250	55	282	0.985
		Symptomatic	Yes	25	233	51	254	
			IRR	1.03	1.03	1.03	/	
			Lower CI	0.66	0.87	0.75		
			Upper CI	1.52	1.24	1.38		
			p-value	0.90	0.71	0.85		
		Hospitalised for COVID-19 w/o Oxygen Support	Yes	3	29	11	18	0.028
			IRR	1.74	1.82	3.13	/	*
			Lower CI	0.41	1.02	1.43		
			Upper CI	5.14	3.33	6.54		
			p-value	0.37	0.05 *	0.003 *		
		Hospitalised for COVID-19 w/ Oxygen Support	Yes	2	23	2	10	0.054
			IRR	2.09	2.59	1.03	/	
			Lower CI	0.32	1.27	0.16		
			Upper CI	7.92	5.71	3.89		
			p-value	0.34	0.01 *	0.97		

Subgroup	Cohort			Overlap	Systemic	Single organ	Control	Chi² *p-value*
Vaccine dose	Dose 2 (all)	n		486	3323	854	4123	
		Past COVID-19 infection	Yes	58	342	96	757	<0.001
			IRR	0.65	0.56	0.61	/	*
			Lower CI	0.49	0.49	0.49		
			Upper CI	0.84	0.64	0.75		
			p-value	<0.001 *	<0.001 *	<0.001 *		
		Mild vaccine side effects	Yes	406	2557	636	3037	0.074
			IRR	1.13	1.04	1.01	/	
			Lower CI	1.02	0.99	0.93		
			Upper CI	1.26	1.10	1.10		
			p-value	0.02 *	0.10	0.80		
		Major vaccine side effects	Yes	19	55	14	35	<0.001
			IRR	4.61	1.95	1.93	/	*
			Lower CI	2.58	1.28	1.01		
			Upper CI	7.96	3.00	3.51		
			p-value	<0.001 *	0.002 *	0.04 *		
Vaccine dose	Dose 2 (COVID-19 cases)	n		58	342	96	757	
		Symptomatic	Yes	56	318	88	693	0.981
			IRR	1.05	1.02	1.00	/	
			Lower CI	0.79	0.89	0.80		
			Upper CI	1.37	1.16	1.24		
			p-value	0.70	0.82	0.99		
		Hospitalised for COVID-19 w/o Oxygen Support	Yes	9	36	8	34	<0.001
			IRR	3.45	2.34	1.86	/	*
			Lower CI	1.56	1.47	0.80		
			Upper CI	6.89	3.76	3.81		
			p-value	<0.001 *	<0.001 *	0.12		
		Hospitalised for COVID-19 w/ Oxygen Support	Yes	7	24	6	20	<0.001
			IRR	4.57	2.66	2.37	/	*
			Lower CI	1.79	1.47	0.87		
			Upper CI	10.32	4.86	5.55		
			p-value	<0.001 *	<0.001 *	0.06		

Subgroup	Cohort			Overlap	Systemic	Single organ	Control	Chi² *p-value*
Country Income	Higher income (all)	n		454	2489	598	1060	
		Past COVID-19 infection	Yes	41	182	42	160	<0.001
			IRR	0.60	0.48	0.47	/	*
			Lower CI	0.42	0.39	0.33		
			Upper CI	0.83	0.60	0.65		
			p-value	0.003 *	<0.001 *	<0.001 *		
		Mild vaccine side effects	Yes	383	2056	431	911	0.020
			IRR	0.98	0.96	0.83	/	
			Lower CI	0.87	0.89	0.75		*
			Upper CI	1.10	1.04	0.94		
			p-value	0.76	0.32	0.003 *		
		Major vaccine side effects	Yes	12	37	10	16	0.419
			IRR	1.75	0.98	1.11	/	
			Lower CI	0.81	0.56	0.49		
			Upper CI	3.68	1.82	2.41		
			p-value	0.14	0.96	0.80		
Country Income	Higher income (COVID-19 cases)	n		41	182	42	160	
		Symptomatic	Yes	40	172	36	153	0.937
			IRR	1.02	0.99	0.90	/	
			Lower CI	0.71	0.80	0.61		
			Upper CI	1.43	1.23	1.27		
			p-value	0.91	0.92	0.56		
		Hospitalised for COVID-19 w/o Oxygen Support	Yes	4	12	5	2	0.009
			IRR	7.80	5.27	9.52	/	*
			Lower CI	1.52	1.44	2.05		
			Upper CI	56.30	33.90	66.50		
			p-value	0.02 *	0.03 *	0.007 *		
		Hospitalised for COVID-19 w/ Oxygen Support	Yes	5	15	3	3	0.022
			IRR	6.5	4.40	3.81	/	*
			Lower CI	1.59	1.45	0.71		
			Upper CI	31.71	18.98	20.58		
			p-value	0.01 *	0.10 *	0.02 *		

Subgroup	Cohort			Overlap	Systemic	Single organ	Control	Chi² *p-value*
Country Income	Lower income (all)	n		157	1519	406	3665	
		Past COVID-19 infection	Yes	33	295	75	748	0.771
			IRR	1.03	0.95	0.91	/	
			Lower CI	0.71	0.83	0.71		
			Upper CI	1.43	1.09	1.14		
			p-value	0.87	0.47	0.41		
		Mild vaccine side effects	Yes	125	1085	324	2685	0.280
			IRR	1.08	0.97	1.09	/	
			Lower CI	0.90	0.91	0.97		
			Upper CI	1.29	1.04	1.22		
			p-value	0.36	0.48	0.15		
		Major vaccine side effects	Yes	6	28	9	32	0.001
			IRR	4.38	2.11	2.54	/	*
			Lower CI	1.65	1.26	1.14		
			Upper CI	9.74	3.51	5.10		
			p-value	<0.001 *	0.003 *	0.01 *		
Country Income	Lower income (COVID-19 cases)	n		33	295	75	748	
		Symptomatic	Yes	30	272	72	676	0.965
			IRR	1.01	1.02	1.06	/	
			Lower CI	0.68	0.89	0.83		
			Upper CI	1.42	1.17	1.34		
			p-value	0.97	0.78	0.63		
		Hospitalised for COVID-19 w/o Oxygen Support	Yes	7	37	8	41	<0.001
			IRR	3.87	2.29	1.95	/	*
			Lower CI	1.59	1.46	0.85		
			Upper CI	8.09	3.57	3.93		
			p-value	<0.001 *	<0.001 *	0.08		
		Hospitalised for COVID-19 w/ Oxygen Support	Yes	2	19	2	23	0.106
			IRR	1.97	2.09	0.87	/	
			Lower CI	0.32	1.13	0.14		
			Upper CI	6.66	3.84	2.93		
			p-value	0.36	0.17 *	0.85		

The impact of steroidal and non-steroidal medications on IRRs of key clinical outcomes could only be assessed within IMID subgroups with Single Organ IMIDs serving as the reference group.

For those receiving non-steroidal medications, significant differences in clinical outcomes compared to the Single Organ baseline were only observed in the hospitalisation without Oxygen support and major vaccine side effect data of medicated Systemic IMID patients (IRR: 0.50, p = 0.04 and IRR: 0.40, p = 0.005, respectively). No significant differences were observable in clinical outcomes for IMID patients not receiving non-steroidal medications. For steroid recipients, significant reductions were reported in major vaccine side effects of Systemic and Overlap IMID patients compared to the Single Organ IMID reference. Significant reductions in hospitalisation without oxygen support were also observable in Systemic IMIDs (IRR: 0.34, p = 0.01) compared to Single Organ counterparts, suggesting that steroidal medications might especially disadvantage these reference patients.

Meanwhile, incidences of COVID-19 cases were significantly reduced amongst all IMID subgroups receiving two vaccine doses (IRRs of 0.65, p<0.001; 0.56, p<0.001; 0.61, p<0.001 for Overlap, Systemic and Single Organ IMIDs, respectively) compared to the general population reference. By comparison, only Single Organ IMID patients receiving one vaccine dose saw this same statistically significant reduction in COVID-19 infection compared to controls (IRR: 0.74, p=0.04). Irrespective of vaccine dose, all vaccine side effects and hospitalisations were elevated amongst IMID patient respondents compared to general population controls – disparities that achieved statistical significance in most cases.

Across all categories, IMID patients from higher economic contexts reported significantly lower incidences of COVID-19 infection than the control group reference

(IRRs: 0.60, p = 0.003; 0.48, p < 0.001; 0.33, p <0.001 for Overlap, Systemic and Single Organ IMIDs respectively); these results were not replicated amongst respondents from lower economic contexts. Meanwhile, disparities between IMID and control group respondents' major vaccine side effects only reached significance amongst those from lower economic countries (IRRs: 4.38, p<0.001; 2.11, p = 0.003; 2.54, p = 0.01 for Overlap, Systemic and Single Organ IMIDs respectively). Irrespective of economic context, hospitalisations for COVID-19 were elevated amongst all IMID respondents compared to controls. This trend was universally statistically significant amongst those from higher economic contexts but inconsistent amongst those reporting from lower economic contexts.

All results from multivariable logistic regression analyses for COVID-19 vaccine side effect and COVID-19 hospitalisation data are provided in Appendix 20; significant results from Model 3 (fully adjusted) are summarised for both outcomes in Table 4.13 and Table 4.14 below.

Table 4.13: Significant predictors of reporting COVID-19 vaccine side effects according to Model 3*

Study Category	Variable Category	Variable	Odds Ratio	Lower 95% CI	Upper 95% CI	*p value*
Control	Intercept		6.39	2.80	14.60	<0.001
	Age		0.96	0.95	0.97	<0.001
	Gender (Ref = Female)	Male	0.57	0.49	0.66	<0.001
	Ethnicity (Ref = Caucasian)	Hispanic	2.30	1.72	3.09	<0.001
	Country economic status (Ref = Higher)	Lower	0.54	0.42	0.68	<0.001
	Health status (Ref = Excellent)	Very good	1.64	1.36	1.99	<0.001
		Good	2.11	1.71	2.60	<0.001
		Fair	2.96	2.00	4.37	<0.001
		Poor	2.66	1.04	6.80	0.041
	Vaccine type (Ref = Unsure)	Adenoviral	4.54	2.06	10.00	<0.001
		mRNA	5.29	2.39	11.70	<0.001
Overlap	Intercept		40.62	1.85	894.02	0.019
	Age		0.97	0.95	0.99	0.001
	Gender (Ref = Female)	Male	0.37	0.18	0.75	0.006
Systemic	Intercept		9.37	2.79	31.41	<0.001
	Age		0.96	0.96	0.97	<0.001
	Gender (Ref = Female)	Male	0.50	0.41	0.61	<0.001
	Ethnicity (Ref = Caucasian)	Do not wish to disclose	2.77	1.70	4.50	<0.001
		Hispanic	1.92	1.26	2.91	0.002
	Country economic status (Ref = Higher)	Lower	0.50	0.38	0.65	<0.001
	Health status (Ref = Excellent)	Very good	2.25	1.57	3.22	<0.001
		Good	2.23	1.58	3.15	<0.001
		Fair	2.86	1.95	4.19	<0.001
		Poor	2.41	1.48	3.92	<0.001
	Physical status (Ref = Completely)	A little	0.61	0.44	0.84	0.002
		Moderately	0.69	0.54	0.88	0.003
	Steroids (Ref = No)	Yes	0.82	0.69	0.98	0.033
	Discontinued medications prior to vaccination (Ref = No)	Yes	1.57	1.09	2.27	0.016
	Symptoms prior to vaccine (Ref = No)	Yes	1.41	1.18	1.69	<0.001

Model 3: incorporating age, sex, ethnicity, country economic status, health status, medication status, medication suspensions, vaccine dose, pre-vaccine symptoms and – where relevant – study category*

Study Category	Variable Category	Variable	Odds Ratio	Lower 95% CI	Upper 95% CI	*p-value*
Single Organ	Age		0.96	0.95	0.97	<0.001
	Gender (Ref = Female)	Male	0.49	0.34	0.71	<0.001
	Ethnicity (Ref = Caucasian)	Hispanic	2.96	1.18	7.40	0.021
	Health status (Ref = Excellent)	Good	2.85	1.55	5.26	0.001
		Fair	3.14	1.57	6.31	0.001
	Symptoms prior to vaccine (Ref = No)	Yes	1.49	1.01	2.18	0.043
IMID (All)	Intercept		11.46	4.04	32.49	<0.001
	Age		0.96	0.96	0.97	<0.001
	Gender (Ref = Female)	Male	0.50	0.42	0.58	<0.001
	Ethnicity (Ref = Caucasian)	Do not wish to disclose	2.17	1.45	3.24	<0.001
		Hispanic	1.94	1.36	2.75	<0.001
	Country economic status (Ref = Higher)	Lower	0.60	0.48	0.76	<0.001
	Health status (Ref = Excellent)	Very good	2.06	1.54	2.76	<0.001
		Good	2.32	1.75	3.09	<0.001
		Fair	2.87	2.10	3.93	<0.001
		Poor	2.18	1.47	3.23	<0.001
	Physical status (Ref = Completely)	A little	0.61	0.47	0.78	<0.001
		Moderately	0.70	0.57	0.86	0.001
		Not at all	0.63	0.44	0.91	0.013
	Steroids (Ref = No)	Yes	0.81	0.69	0.95	0.010
	Symptoms prior to vaccine (Ref = No)	Yes	1.42	1.22	1.65	0.000
Whole Cohort	Intercept		7.44	2.56	21.59	<0.001
	Age		0.96	0.96	0.97	<0.001
	Gender (Ref = Female)	Male	0.54	0.49	0.60	<0.001
	Ethnicity (Ref = Caucasian)	Asian	1.21	1.06	1.40	0.006
		Do not wish to disclose	1.35	1.08	1.69	0.010
		Hispanic	2.27	1.81	2.84	<0.001
	Country economic status (Ref = Higher)	Lower	0.62	0.53	0.72	<0.001
	Health status (Ref = Excellent)	Very good	1.73	1.48	2.02	<0.001
		Good	2.09	1.77	2.45	<0.001
		Fair	2.55	2.07	3.14	<0.001
		Poor	1.88	1.38	2.56	<0.001
	Physical status (Ref = Completely)	A little	0.72	0.58	0.90	0.004
		Moderately	0.79	0.67	0.93	0.005
	Steroids (Ref = No)	Yes	0.80	0.68	0.94	0.008
	Vaccine Type (Ref = Unsure)	Adenoviral	2.20	1.21	4.01	0.010
		Mix	6.04	1.20	30.38	0.029
		mRNA	3.20	1.75	5.84	<0.001

Model 3: incorporating age, sex, ethnicity, country economic status, health status, medication status, medication suspensions, vaccine dose, pre-vaccine symptoms and – where relevant – study category*

When examining both Table 4.13 and Appendix 19, intercept data were consistently statistically significant bar results from Model 3 amongst Single Organ IMID patients. This suggests a significant baseline likelihood of vaccine side effects being reported amongst this cohort independent of the predictors included in each model. Likewise,

instances of broad or even infinite confidence interval values indicate failures of the model due to low sample sizes.

Age and gender were universally statistically significant predictors of vaccine side effect reporting, however. The directionality of these relationships was also consistently negative, suggesting that younger and female respondents were more likely to report vaccine side effects than their older and male counterparts. Additional, but less consistently statistically significant, predictors of vaccine side effect reports were ethnicity, country economic status, health status, activity level, inflammatory symptoms prior to vaccination, steroidal medication and vaccine type. Almost any deviation from reference levels for health and activity status had a meaningful impact on the likelihood of reporting vaccine side effects amongst respondents. When statistically significant, poorer health ratings increased vaccine side effect reporting; physical restrictions were seen to reduce reporting by comparison. Being from a lower economic context and receiving steroidal medications produced statistically significant reductions in the likelihood of reporting vaccine side effects. Meanwhile, experiencing inflammatory symptoms prior to inoculation increased the likelihood of reporting vaccine side effects subsequently. Out of all vaccines included in this work, adenoviral, mRNA and mixed dosing amplified risks of reporting vaccine side effects most consistently. Vaccine dose number had no bearing on this outcome, however.

The relationship between ethnicity and the likelihood of reporting vaccine side effects was complex: both the direction and statistical significance of these relationships changed between study categories and models run. For example, Asian ethnicity

predicted increased reporting in select study categories; by comparison, reduced reporting was seen amongst Hispanic respondents and those that did not disclose their ethnic group.

A reduced number of statistically significant predictors were returned when COVID-19 hospitalisation data were modelled (Table 4.14, Appendix 19). As before, significant intercepts and broad and infinite confidence intervals were also observed – further suggestive of poor explanatory power amongst models run.

Table 4.14: Significant predictors of hospitalisation for COVID-19 according to Model 3*

Study Category	Variable Category	Variable	Odds Ratio	Lower 95% CI	Upper 95% CI	*p-value*
Control	Intercept		0.00	0.00	0.02	0.000
	Age		1.03	1.01	1.05	0.013
	Gender (Ref = Female)	Male	2.44	1.43	4.15	0.001
	Country economic status (Ref = Higher)	Lower	2.84	1.03	7.83	0.044
Systemic	Intercept		0.03	0.01	0.17	0.000
	Ethnicity (Ref = Caucasian)	Asian	2.43	1.07	5.53	0.034
		Other (please specify)	3.11	1.04	9.26	0.042
	Physical status (Ref = Completely)	A little	3.66	1.46	9.18	0.006
	Steroids (Ref = No)	Yes	2.19	1.28	3.72	0.004
Single Organ	Ethnicity (Ref = Caucasian)	Hispanic	0.03	0.00	0.64	0.024
	Health status (Ref = Excellent)	Good	0.01	0.00	0.33	0.008
	Steroids (Ref = No)	Yes	21.08	1.11	399.06	0.042
IMID (All)	Intercept		0.10	0.03	0.36	0.001
	Physical status (Ref = Excellent)	A little	2.99	1.40	6.39	0.005
	Steroids (Ref = No)	Yes	2.23	1.41	3.52	0.001
Whole Cohort	Age		1.02	1.01	1.03	0.007
	Gender (Ref = Female)	Male	1.75	1.22	2.51	0.002
	Physical status (Ref = Completely)	A little	2.96	1.56	5.60	0.001
		Moderately	1.92	1.15	3.22	0.013

Model 3: incorporating age, sex, ethnicity, country economic status, health status, medication status, vaccine dose, and – where relevant – study category*

Hospitalisation for COVID-19 amongst general population respondents was consistently predicted by increased age, male gender and living in a country of lower economic status. These variables were less influential over hospitalisations amongst

IMID patients, however; here, factors including ethnicity and declines in health status and physical activity level proved more significant – even if inconsistently so. No significant predictors for COVID-19 hospitalisation amongst Overlap IMID patients were returned by these models, however.

The influence of IMID subgroup over respondents' likelihood of being hospitalised for COVID-19 changed drastically between models: significant results in Model 1 were seen to attenuate once medications, specifically steroids, entered into Models 2 and 3. This indicates that steroid prescriptions may plan an oversized role in hospitalisation for COVID-19 amongst IMID respondents (Model 3 OR: 2.2, 95% CI: 1.4-3.5, p = 0.001), if concentrated within Systemic (Model 3 OR: 2.2, 95% CI: 1.3-3.7, p = 0.004) and Single Organ (Model 3 OR: 21.1, 95% CI: 1.1-399.1, p = 0.042) IMID patients.

iii. Discussion:

Principal findings and their implications:

This investigation applied two levels of the DESTINIES phenotype for COVID-19 risk in the adult immunosuppressed to test the hypothesis that the COVID-19 infection and vaccine experiences of patients with IMID would be more severe than general population controls with Overlap and Systemic categories faring worse than Single Organ counterparts. Key findings are summarised below.

In line with previous studies, our descriptive analysis identified that IMID patients were likelier to be older, female, Caucasian and from wealthier backgrounds than controls from the general population. This age disparity matches reports by Aletaha

et al (2019) [44], and the prevalence of women in our dataset is unsurprising given their well-documented susceptibility to inflammatory diseases [45;46]. As per geoepidemiological analysis by Shapira, Agmon-Levin & Shoenfeld (2010) [47], it is possible to attribute the underrepresentation of these conditions seen in lower economic countries to poorer medical resourcing: the diagnostic procedures, materials and records that necessitate a diagnosis of immunosuppression are scarcer in these contexts. These same socio-economic factors also underlie ethnicity-based disparities in IMID diagnostics: despite growing evidence for the excess vulnerability of ethnic minorities to certain forms of inflammatory disease [48], Caucasian patients are disproportionately represented in our IMID cohort.

COVID-19 vaccine uptake was seen to be similar between groups, however. This enabled fair comparisons between study categories' vaccine side effects – something that would have proven difficult at later stages of the pandemic as dose-on-dose disparities between clinical risk groups and general population controls increased over time [49]. Likewise, growing inequities in vaccine distribution would have impacted global comparisons of uptake and outcomes beyond the timepoints covered in this work [50].

Despite some increased risk of certain adverse events in IMID groups, COVID-19 vaccines were generally well-tolerated across all study categories. This replicates previous findings [49; 51]. However, when applying European Commission frequency categories [52], mild and major vaccine side effects would be classified as 'very common' and 'common' in this cohort; data that may be inflated by response bias. Mild vaccine side effects were not statistically dissimilar between groups and

statistically significant elevations in major vaccine side effects in IMID subgroups should be contextualised with their low event numbers overall. Disaggregated side effect data revealed specific patterns of side effect reporting amongst IMID patients, however, including underreporting of fever and disproportionate levels of rash, allergic reactions, nausea and vomiting, diarrhoea, dizziness, abdominal pain and high pulse rate and palpitations compared to controls. Overlaps between these symptoms and the pathology of underlying inflammatory illness make it unclear whether these events are novel-onset or flares, however – a limitation that has been declared elsewhere [53].

Vaccine side effects were most prevalent for recipients of mRNA and adenoviral products, though this is most likely an artefact of their dominance in our cohort [54]. Meanwhile, the tentative data this work supplies for increased asymptomatic responses to inactivated vaccines have been corroborated for Dadras and colleagues (2022) [55]. Vaccine side effects were less frequently reported by older survey respondents, men, certain ethnic minorities and those recruited from lower income countries; it cannot be discerned whether these observations are clinical in nature (attributable to sex-based hormonal differences [56] or immunosenscence amongst older participants [57], for example) or cultural (attributable to conflicts in masculine and feminine social norms [56] or disparities in medical literacy and international resourcing [47]). Divergent patterns in vaccine side effects were also observed by self-reported physical and health status: reports were significantly higher amongst those with active lifestyles and lower amongst those with worse baseline health. It is possible that the physical debilitation of vaccine side effects is more apparent to those accustomed to active living, engendering more reporting

amongst the fit; links between physical excretion and humoral responses to vaccination may also contribute to this relationship [58]. Meanwhile, those with worst baseline health, often necessitating medications, may be unable to distinguish side effects from prevailing illness or a stunted immune response.

The incidence of COVID-19 infection was significantly reduced amongst all IMID subgroups, likely attributable to the success of disease avoiding behaviours amongst these higher risk groups or their adherence to shielding guidelines [59]. However, COVID-19 infections clearly resulted in worse health outcomes for these patients than the general population reference. This is consistent with existing literature [60; 61]. In the first instance, case duration was substantially prolonged amongst IMID subgroups compared to general population controls. Reported elsewhere [62], such protracted recoveries can facilitate viral mutation and ongoing contagion, justifying policies that extended COVID-19 isolation periods amongst these patients [63].

Distinct patterns of COVID-19 symptoms were observable amongst IMID populations: skin rashes, breathlessness, oral ulcers and joint pains were significantly more prevalent. The inflammatory nature of these specific symptoms may again indicate a flaring of underlying IMID pathology as opposed to severe COVID-19 infection [62]. Finally, critical COVID-19 infection outcomes were significantly more prevalent in IMID patients than controls – a finding aligned with meta-analysis by Grainger and colleagues (2022) [64]. Replicating evidence presented by Gamboa-Cárdenas (2022) [65] for the influence of pre-existing multi-organ pathology over adverse COVID-19 outcomes, our data revealed that hospitalisation for COVID-19 with Oxygen support was concentrated amongst

Overlap and Systemic categories. That said, it cannot be ascertained whether this finding reflects true clinical risk or accelerated triage amongst patients considered more vulnerable to COVID-19. Likewise, reported inconsistencies in the COVID-19 hospitalisation data of IMID patients from lower economic contexts may reflect inconsistent access to hospital beds and not a true clinical difference to IMID cases from more affluent contexts.

When turning to regression data, the driving forces of COVID-19 hospitalisation amongst general population respondents, age and male gender, were less influential for predicting hospitalisation amongst IMID patients. Instead, steroidal medications were more consistently and robustly associated with hospitalised cases of COVID-19 in these groups – especially amongst Single Organ IMID users when both incidence data and regression outputs are cross referenced. These patterns are consistent with past research: outside of clinical risk groups, hospitalisation for COVID-19 is disproportionate amongst men [66] and vanishingly rare amongst the young [67]. Furthermore, the use of steroidal medications, particularly at higher doses at the earliest stage of COVID-19 infection, have been linked with delayed viral clearance [68], vulnerability to secondary infections [69] and, by virtue of both, elevated incidences of hospitalisation and death amongst those that take them [70]. While steroid medications can play a vital role in critical COVID-19 cases, including Randomised Evaluation of COVID-19 ThERapY (RECOVERY) Study reports of reduced overall 28-day mortality amongst recipients [71], the potentially negative impacts this work identifies for longitudinal use aligns with systematic review by Patel and colleagues [72]. Here, long-term corticosteroid therapy netted worse patient outcomes by their assessment. The tentative evidence this secondary analysis

supplies for especially poor COVID-19 outcomes amongst Single Organ IMID steroid recipients warrants further investigation. Although potentially attributable to varied IMID sample sizes and levels of steroid uptake therein (producing a selection bias for the sickest patients) it is conceivable that the generalised impacts of steroidal medication on a localised pathology such as Single Organ IMID could exacerbate infection risks in these patients. This may not be the case for those that have more to benefit from systems-wide immunosuppression.

Overall, this is the first research that has demarcated the COVID-19 infection and vaccination experiences of IMID patients between those with localised and distributed pathologies. It has leveraged the knowledge and data assets of both COVAD and DESTINIES Study groups and offers a higher resolution approach to pharmacovigilance than is achieved via conventional means. This work has provided detail on vaccine recipients' demographics, contemporary health status, medication history and subsequent adverse events that would be difficult to obtain from passive surveillance mechanisms or unsupervised patient reporting.

Disaggregating IMID data between Single Organ, Systemic and Overlap categories has been revealing and confirms the value of demarcation between local and diffuse IMID in the DESTINIES phenotype. The evidence supplied for disproportionate COVID-19 vaccine side effects and hospitalisations amongst patients with generalised inflammatory conditions is highly relevant for policymakers. Distinct patterns of vaccine side effects, COVID-19 symptoms and steroid-specific vulnerability between study categories and between side effect and symptom types have prospective value for clinical messaging, practice and patient triage. As a

collective, this evidence is a powerful illustration of both the danger of handling IMID patients, or the immunosuppressed more broadly, as a single entity and the potential of precision vaccine benefit-research for clinical risk groups.

Comparison to existing literature:

The findings just summarised have already provided key points of comparison to existing literature. In brief, however, this work corroborates existing evidence that the COVID-19 vaccine is, overall, well-tolerated by IMID patients [49; 51], with younger and female respondents most likely to report vaccine side effects overall [73]. Although reaching statistical significance, the excess major vaccine side effects we report amongst IMID patients compared to the general population still amount to vanishingly rare occurrences. This work also provides some tentative corroboration of Dadras et al (2022) [55] findings for increased asymptomatic responses to inactivated vaccines amongst immunosuppressed patients; this phenomenon should be further investigated to assess whether inactivated COVID-19 vaccines should be the first line option for this population.

In keeping with existing literature [60; 61; 64; 65] and our starting hypothesis, COVID-19 case rates were seen to be suppressed amongst IMID patients compared to the immunocompetent; however, critical COVID-19 outcomes were significantly elevated in IMID groups, with greatest prevalence amongst patients with multi-organ pathologies. IMID subgroups also reported significantly longer COVID-19 case durations than the general population, and their symptoms were more likely to be inflammatory in nature. However, as pointed out elsewhere [52], this is difficult to discriminate from patients' underlying aetiologies.

Steroidal medication was seen to selectively amplify COVID-19 risk in Single Organ IMID patients; this warrants further investigation and conflicts with RECOVERY Study findings for reduced overall 28-day mortality amongst those receiving these medications regularly [71]. It is possible such systemic medication may amount to overtreatment in those with pathologies located to single sites – producing irresponsible levels of immunocompromise, especially during periods of high COVID-19 circulation. This finding remains speculative, however.

Overall, this work was a welcome addition to the COVAD literature: its findings are of higher resolution than comparable investigations [74; 75] and underscore the clinical urgency of disaggregated pharmacovigilance and vaccine benefit-risk assessments for the IMID population – a case made most emphatically by Feretti and colleagues (2021) [76].

Limitations:

Limitations of this work have been partially acknowledged within its protocol [2]; issues associated with utilising self-reported (and not clinician-confirmed) data are well-catalogued, including the potential for demand characteristics and false recall. The delay between original data collection and the completion of this secondary analysis is also declared here. Additional criticisms are as follows, however:

Firstly, it was difficult for rheumatological experts to build consensus on the allocation of IMID conditions into the Single Organ and Systemic IMID subgroups. Strategies for doing so were idiosyncratic, considering whether a disorder required

multiple specialisms, had underlying causes, or targeted impact. Some noted demarcations of certain conditions felt arbitrary. As such, the 75% threshold of agreement utilised in the preceding eDelphi exercise could not be met for this purpose and a majoritarian approach had to be adopted for expediency. These ongoing disagreements affect our confidence in the generalisability of our findings. Moreover, once the IMID cohort or particularly rare events were differentiated, sample sizes were often too small to produce meaningful comparisons. Analysis of major vaccine side effects was especially affected. This, combined with stated demographic imbalances between study categories, also casts doubt on this work's external validity.

Furthermore, it was not possible to pinpoint whether reported symptoms, either from COVID-19 infection or following vaccination, were novel-onset or signified continuations or flares of preexisting conditions. Given that fearfulness of flares is an established barrier to vaccine uptake amongst the IMID population [77], future research must aim to rule out this confounder with more rigour than our approach of gathering data on pre-inoculation symptoms. The 7-day window for vaccine side effect reporting may also have precluded the documentation of delayed onset adverse events that are well-established within this clinical population [78]. Likewise, by not being able to confirm which vaccine dose was associated with the side effects reported, our differentiation of these data by vaccine type could be inaccurate for those that received heterologous doses. The absence of third COVID-19 vaccine dose from our analysis is also a limitation of this work. This is the requisite number of doses for a complete primary course against COVID-19 – our analysis therefore only pertains to incomplete inoculation – and has been seen to play a vital [36] role in

resolving disparities in vaccine effectiveness between the immunosuppressed and immunocompetent.

Meanwhile, the evidence this work supplies for the influence of steroidal medications on adverse COVID-19 infection outcomes is a further indictment of this thesis' exclusively diagnostic and procedural means of identifying and differentiating adult immunosuppressed cohorts. However, the clinical value of these medication-specific data was limited without being able to pinpoint the most influential prescriptions, dosages and time courses. We are aware of the sensitivity of all these variables: as alluded earlier, certain immunosuppressive drugs have produced diametric COVID-19 outcomes depending on these variables [79].

Finally, this work fails to operationalise all levels of the DESTINIES phenotype. While it has validated its demarcation between localised and generalised IMID conditions to an extent, it provides no information on the value or validity of wider DESTINIES phenotype levels. The next exercise was dedicated to this objective.

4. Operationalising the DESTINIES phenotype to differentiate the COVID-19 infection outcomes of immunosuppressed patients compared to the immunocompetent within a double-pseudonymised, primary care dataset:

i. Method:

The ORCHID-Epidemiology database (ORCHID-E) is a UK repository of double-pseudonymised, routinely collected primary care data intended to facilitate

epidemiological research [80]. RSC membership contributes medical record data from over 1,900 general practices to this TRE, exceeding 19 million patients in all [3]. All intended research efforts must be reviewed and approved by the Primary Care Hosted Research Datasets Independent Scientific Committee (PrimDISC) at the University of Oxford. ORCHID-E extracts are performed and, subsequently, hosted on SQL (currently v15.0) with exact parameters of extraction and segmentation specified through queries.

The present study operationalised the entire DESTINIES phenotype within ORCHID-E via retrospective cohort design to assess whether its systematic literature review, meta-analysis and international panel-predicted hierarchy (DESTINIES hierarchy) for severe COVID-19 outcomes were borne out within historical primary care data. ORCHID-E patient data was eligible for extraction, phenotype level assignment and onward analysis if the patient in question was over 18 years by December 31st, 2019, and had not withdrawn consent for the use of their data in research via the national opt-out scheme [81]. Incidences and IRRs of specific COVID-19 infection outcomes were compared between phenotype-directed study groups in the follow-up period (2020-2023 inclusive): the immunosuppressed (experimental, or exposed, group), drug-managed HIV (internal reference group) and those not identified as immunosuppressed (control, or unexposed, group). A protocol to this effect was submitted to PRIMDISC and approved by its members (ref: PD-0033-2024) [82].

Data were collected on the following cohort-level outcomes over the follow-up period: confirmed COVID-19 infection in the study period, multiple confirmed COVID-19 infections in the study period, confirmed COVID-19 infection 0-3 months from latest

COVID-19 vaccine dose (breakthrough infection 1), confirmed COVID-19 infection between 4-6 months from latest COVID-19 vaccine dose (breakthrough infection 2) and chronic post-COVID-19 syndrome – a composite of new diagnoses of chronic post-viral sequelae (colloquially, 'Long COVID') and referrals to dedicated clinics. Data on the following case-level outcomes were also collected to compare COVID-19 severity between study groups: lower respiratory tract infection (LRTI), blood clots, cardiovascular event diagnosis (CVD) – a broad composite of myocardial ischaemia (myocardial infarction, angina, acute coronary syndromes and ischaemic cardiomyopathy), stroke and transient ischaemic attack – sepsis and mortality. Because ORCHID-E is not currently linked with secondary care data, these case-level outcomes could only be inferred as COVID-19 associated if they appeared in the primary care record within 28 days of a confirmed COVID-19 diagnosis. Those occurring outside of this window were omitted from analysis. These case-level outcomes were chosen due to their high fidelity within primary care records; alternative metrics for severe COVID-19 infection, including oxygen therapy, intubation and/or ICU-admission, are only reliably available within secondary care data.

Researchers produced episode variables to distinguish between multiple cases of a specific COVID-19 outcome and repeat codification of the same single case. This prevented multiple counting and allocations of events. In this, a 28-day window was constructed at the first point that a 28-day COVID-19 outcome of interest code was identified in the medical record (minimum episode onset date). When the same COVID-19 outcome was detected within 28 days of this minimum episode onset date, it would be absorbed into the same episode. Detection outside of this 28-day

period would indicate a repeat outcome had occurred and a new minimum episode onset date would be recorded.

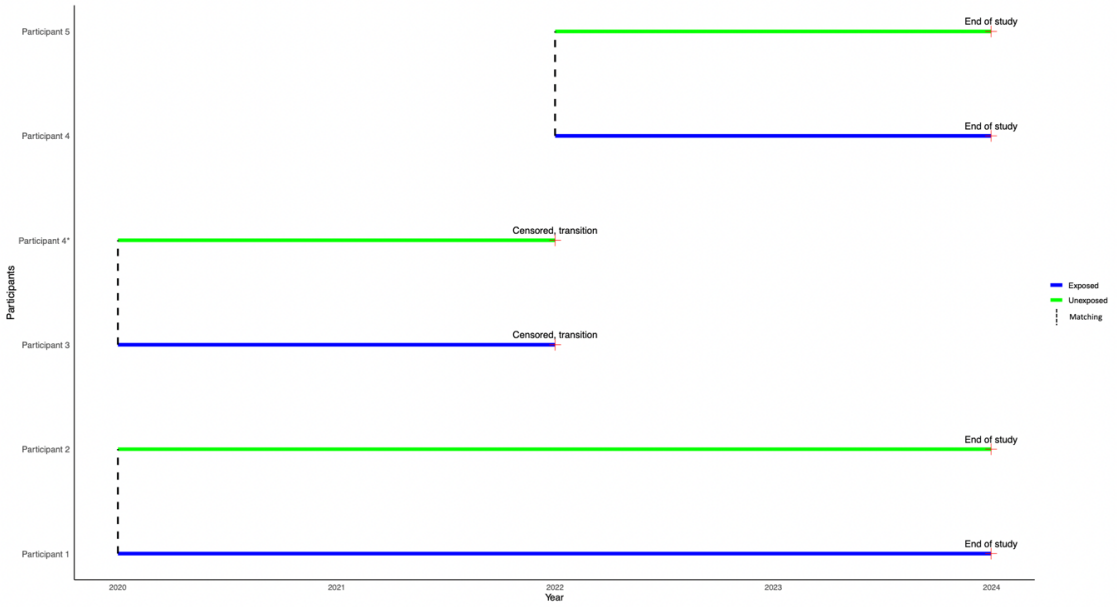
The doctoral candidate worked with departmental clinicians and data experts to convert the DESTINIES phenotype and all outcomes of interest into a digitally compatible format, allocating the ORCHID-E cohort into the experimental groups specified and time linking COVID-19 events as described. The in-house 'SNOMED helper tool' codified phenotype levels (Immunosuppressed, 1:10; Internal Reference Group, 11; Control, 0) and outcomes of interest in accordance with the SNOMED CT August 2024 release [83]. Once codified, SQL queries extracted our cohort sequentially, beginning with the highest risk group. This ensured mutual exclusivity between phenotype levels and that patients were allocated into the highest risk level they were eligible for. Patients not allocated to experimental or internal reference groups became our controls. Subsequent SQL queries extracted all descriptive data, outcomes of interest and patient vaccine history; unique Patient ID numbers allowed for easy linkage between extracts, populating cohort members' respective demographics, outcome events and vaccine doses correctly. Age was accurate as of follow up start date (Jan 1st, 2020), vaccine dose was cumulative over follow-up period and broader demographic variables (body mass index, ethnicity etc.), utilised the most recent data available for each unique Patient ID.

Experimental and internal reference group status was 'ever' coded, meaning – bar Pregnancy – all records identified as eligible for these groups between the ten-year period of Dec 31st 2009 and Dec 31st 2019 retained this Initial Assignment throughout the follow-up period. This cross-referencing of ten years of historical

primary care data aimed to address the inadequacies of the pilot phenotype's five-year determinations. However, in keeping with DESTINIES panel directives, this ten-year view did not apply in Pregnancy; only those identified as beyond their second trimester as of December 31st, 2019, were allocated into the experimental group.

Control group status was not 'ever' coded, however; individuals identified as immunocompetent by December 31st, 2019, could transition into experimental or internal reference groups during the follow-up period. This eventuality was closely monitored, with data collected on the date of transition and the phenotype level transitioned into to ensure the accurate assignment of all outcomes of interest. So-called transition patients had their records duplicated to assist this process – creating a unique record for the time the patient in question contributed to immunocompetent data (time-immunocompetent transition records) and their time contributing to immunosuppressed data (time-immunosuppressed transition records). This is illustrated in Figure 4.15 below. Data is censored at 1 day minus transition date for time-immunocompetent transition records.

Figure 4.15: Schema of follow-up timeline, including immunocompetent (unexposed) to immunosuppressed (exposed) transition



A new variable, Final Phenotype Level, was created to support accurate event assignment and age-sex matching between records over the course of follow up. Initial Assignment was updated for time-immunosuppressed transition records and retained for non-transition records or time-immunocompetent transition records. A flow chart was produced to quantify the impact of duplication on follow-up cohort size. Movement between Initial and Final Assignments were also tabulated.

Age-sex matching occurred between immunosuppressed and internal reference group records (Final Assignments 1:11) and those not identified as immunosuppressed (Final Assignment 0) on a 1:1 basis with random assortment to viable matches. There was insufficient internal reference group data to produce a separate age-sex matched cohort between Drug-managed HIV and the immunosuppressed cohort. DESTINIES panellists' discomfort with using Drug-

Managed HIV as an active control group justified its combining with the immunosuppressed cohort for matching with the immunocompetent.

Descriptive analysis summarised and compared the age, sex, ethnicity, body mass index (BMI), IMD deprivation quintile, rurality, smoking status, NHS region, COVID-19 vaccine status and dose-by-dose uptake of each study group, with disaggregated analysis between the DESTINIES phenotype levels of the experimental group specifically. Love plots were produced to illustrate pre- and post-matching standard mean differences (SMD) in these variables between experimental groups, aggregating and disaggregating immunosuppression. Variables that exceeded 0.1 SMDs even after matching were noted for onward adjustment; this denoted an important imbalance for a given covariate between groups of interest.

Study Entry, Study Exit, and Time in Level variables were constructed to report the exact number of days patients contributed to their study group, controlling for transitions where relevant. These variables cross-referenced Final Phenotype Level, Follow-up Start Date, Follow-up End Date, Practice Registration and Deregistration Date, Date of Transition and Date of Death. Study Entry utilised the latest date of follow-up start date, registration date, or – for transition records now contributing to immunosuppressed data – transition date. Study Exit utilised the earliest date of follow-up exit date, deregistration date, date of death or – for transition records contributing to immunocompetent data – transition date minus 1 day. Time in Level was then calculated as Study Exit minus Study Entry in days. Summing these values for each Final Phenotype Level created the necessary person-days denominator for standardising IRs of each outcome of interest in the 100-person-years format.

Using control group data as baseline, our main analysis used age-sex matched and fully adjusted data to produced IRs and IRRs estimates of our outcomes of interest via multivariable conditional Poisson regression. This was justified by the heterogeneity that persisted between groups' demographic variables even after age-sex matching. Full adjustment maximised the explanatory power of immunosuppression over our outcomes of interest. Multivariable conditional Poisson regression was selected to control for any potential overdispersion within our dataset, as per Armstrong et al (2014) [84]. IRR confidence intervals of this output were compared to those produced by a Quasipoisson model as a further check against overdispersion. Wider intervals than the Quasipoisson counterpoint would indicate that Poisson assumptions held, overdispersion was not present and that this conditional Poisson data could be carried forward as our primary output. The equivalence of raw outcome data's means and variances were also checked to ensure this core assumption of Poisson modelling was upheld. Finally, subgroup analysis by study year (2020, 2021, 2022, 2023) and vaccine uptake (unvaccinated, <5 doses and >5 doses) assessed whether our outcomes of interest were dynamic across the follow-up period or by influenced by vaccine dosage. The 'Time in Phenotype' variable was updated to facilitate this. Subgroup analysis for 2020 did not produce IRR estimates for Long COVID or breakthrough infections as neither event was documented consistently within medical records until 2021.

Unmatched and unadjusted IRRs and matched and unadjusted IRRs were produced as secondary points of comparison. These estimates were modelled via unconditional Poisson regression with the sandwich function in R Studio (Posit) [85] and via conditional Poisson, respectively. To address potential heteroskedasticity in

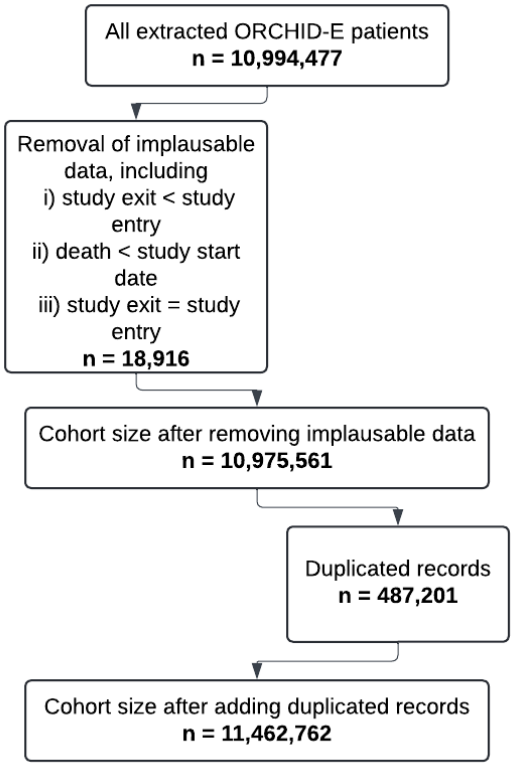
unmatched and unadjusted data, confidence intervals were produced via robust and non-robust standard errors with the most conservative (widest) estimates reported.

For transparency, any findings that failed to converge via Poisson models and returned implausible confidence intervals were tabulated in full (excluding when events <5 to prevent reidentification) but were manually suppressed for summary visualisations. In this, we instituted the convention of redacting IRRs data when confidence interval values were larger than 50. Areas of alignment and discrepancy between study outputs and those anticipated by the DESTINIES COVID-19 risk hierarchy were discussed.

ii. Results:

The full codification of the DESTINIES phenotype has been made publicly available on its dedicated study website [86]; here ORCHID specific TADDS variables are disaggregated into their constituent SNOMED CT codes. When embedded into SQL requests, this resource successfully extracted our study cohort, assigned their respective experimental groups (Immunosuppressed, Immunocompetent Controls and Internal Reference) and discerned Initial and Final Assignments. Cancer in remission was extremely poorly codified in the primary care record, however; our attempts to exclude these patients were unsuccessful as a result. Descriptive statistics of the study cohort prior to the follow up period are provided in Appendix 21 and are differentiated by Initial Phenotype Assignment. The flow diagram below (Figure 4.16) quantifies the impact of record duplication on this initial cohort.

Figure 4.16: Cohort inclusion and exclusion flow chart



Meanwhile, Table 4.15 summarises the shifts to phenotype assignments that occurred between Initial (December 31st, 2019) and Final Assignments (follow-up period). The impact of phenotype shift is quantified by absolute numbers of patients affected and the percentage of shifted data in each group at Final Assignment. Shifted data at Final Assignment is also summarised by group as a percentage of total shift.

Table 4.15: Shift in phenotype allocations over the course of follow-up

Initial Assignment*	Final Assignment* 0	1	2	3	4	5	6	7	8	9	10	11	Total Shifts
0	9069318	*1206*	*10512*	*20442*	*146172*	*10192*	*126223*	*4294*	*71228*	*666*	*149494*	*2986*	*543415*
1	0	8099	0	0	0	0	0	0	0	0	0	0	
2	0	0	29935	0	0	0	0	0	0	0	0	0	
3	0	0	0	69968	0	0	0	0	0	0	0	0	
4	0	0	0	0	344324	0	0	0	0	0	0	0	
5	0	0	0	0	0	30016	0	0	0	0	0	0	
6	0	0	0	0	0	0	527185	0	0	0	0	0	
7	0	0	0	0	0	0	0	20721	0	0	0	0	
8	0	0	0	0	0	0	0	0	312643	0	0	0	
9	0	0	0	0	0	0	0	0	0	1506	0	0	
10	0	0	0	0	0	0	0	0	0	0	494438	0	
11	0	0	0	0	0	0	0	0	0	0	0	11194	
% Shifted / Final Assignment	NA	*12.96*	*25.99*	*22.61*	*29.80*	*25.35*	*19.32*	*17.17*	*18.56*	*30.66*	*23.22*	*21.06*	
% Shifted / Total Shifts	NA	*0.22*	*1.93*	*3.76*	*26.90*	*1.88*	*23.23*	*0.79*	*13.11*	*0.12*	*27.51*	*0.55*	*100*

**0-11 denoting DESTINIES phenotype levels; transitions could only occur between the immunocompetent (0) to immunosuppression/ internal reference group (1-11)*

The disproportionate contribution of shift data to the Solid Tumour population (Final Assignment 4) is of note. Here, almost a third of patients were immunocompetent as of the 31st December, 2019. The dominance of Wider Determinants of Immunosuppression (Final Assignment 10) in overall shift data is unsurprising given the diverse and acute nature of constituent conditions (e.g. malnutrition, pregnancy etc.). Rarer transitions are aligned with the rarity of the conditions involved, including Transplantations (Final Assignment 1) and Asplenia & Severe Anaemia (Final Assignment 7).

Incorporating the follow-up period (2020-2023), Tables 4.16a, b and c provide the characteristics of our final cohort (age-sex unmatched), aggregating and disaggregating immunosuppression and internal reference groups.

Table 4.16a: Characteristics of age-sex unmatched final cohort, immunosuppression aggregated

	Immunocompetent	Immunosuppressed	HIV	*p-value*	SMD
n	9069318	2379264	14180		
Age (mean (SD))	42.89 (17.89)	58.82 (18.04)	43.38 (11.67)	<0.001	0.645
Ethnicity (%)				<0.001	0.625
A	1092033 (13.2)	232501 (10.2)	721 (5.3)		
B	413785 (5.0)	94233 (4.1)	4316 (31.9)		
M	166369 (2.0)	25837 (1.1)	723 (5.3)		
O	237953 (2.9)	31702 (1.4)	471 (3.5)		
W	6357905 (76.9)	1893620 (83.1)	7297 (53.9)		
Sex = M (%)	4515355 (49.8)	1198919 (50.4)	9854 (69.5)	<0.001	0.273
Urban/Rural = Urban (%)	8019742 (89.2)	2045279 (86.8)	13469 (95.8)	<0.001	0.216
IMD Quintile (%)				<0.001	0.351
1	1733717 (19.1)	452289 (19.0)	4534 (32.0)		
2	1973215 (21.8)	475128 (20.0)	4253 (30.0)		
3	1823110 (20.1)	474569 (19.9)	2481 (17.5)		
4	1769225 (19.5)	485822 (20.4)	1722 (12.1)		
5	1769437 (19.5)	491313 (20.7)	1190 (8.4)		
NHS Region (%)				<0.001	0.366
East of England	364288 (4.0)	100699 (4.2)	322 (2.3)		
London	2186552 (24.1)	438064 (18.4)	5935 (41.9)		
Midlands	1521927 (16.8)	437806 (18.4)	1686 (11.9)		
Northeast and Yorkshire	542997 (6.0)	173229 (7.3)	492 (3.5)		
Northwest	1592434 (17.6)	448586 (18.9)	2332 (16.4)		
Southeast	2072658 (22.9)	557517 (23.4)	2524 (17.8)		
Southwest	788462 (8.7)	223363 (9.4)	889 (6.3)		
BMI (mean (SD))	26.51 (6.10)	28.37 (6.63)	26.84 (6.11)	<0.001	0.196
Smoking Status (%)				<0.001	0.268
Active Smoker	1580333 (18.6)	351959 (14.9)	3681 (26.8)		
Ex-smoker	1627034 (19.2)	700070 (29.6)	2479 (18.1)		
Non-Smoker	5271570 (62.2)	1310680 (55.5)	7553 (55.1)		
COVID-19 Vaccinated over Follow Up = Yes (%)	6599919 (72.8)	2077782 (87.3)	10765 (75.9)	<0.001	0.247
Number of Doses (%)				<0.001	0.523
0	2469399 (27.2)	301482 (12.7)	3415 (24.1)		
1	311652 (3.4)	56023 (2.4)	632 (4.5)		
2	1298450 (14.3)	237548 (10.0)	1924 (13.6)		
3	2620863 (28.9)	491582 (20.7)	2909 (20.5)		
4	996160 (11.0)	330933 (13.9)	1556 (11.0)		
5	861570 (9.5)	477928 (20.1)	1309 (9.2)		
6	161470 (1.8)	162176 (6.8)	1267 (8.9)		
7	339287 (3.7)	296076 (12.4)	1003 (7.1)		
8	10173 (0.1)	24977 (1.0)	156 (1.1)		
≥ 9	294 (0.0)	539 (0.0)	9 (0.1)		

Table 4.16b: Characteristics of age-sex unmatched final cohort, immunosuppression (IS) aggregated and combined with internal reference group (IRG)

	IS + IRG	Control	*p-value*	SMD
n	2393444	9069318		
Age (mean (SD))	58.73 (18.05)	42.89 (17.89)	<0.001	0.882
Ethnicity (%)			<0.001	0.169
A	233222 (10.2)	1092033 (13.2)		
B	98549 (4.3)	413785 (5.0)		
M	26560 (1.2)	166369 (2.0)		
O	32173 (1.4)	237953 (2.9)		
W	1900917 (83.0)	6357905 (76.9)		
Sex = M (%)	1208773 (50.5)	4515355 (49.8)	<0.001	0.014
Urban/Rural = Urban (%)	2058748 (86.8)	8019742 (89.2)	<0.001	0.073
IMD Quintile (%)			<0.001	0.049
1	456823 (19.1)	1733717 (19.1)		
2	479381 (20.0)	1973215 (21.8)		
3	477050 (19.9)	1823110 (20.1)		
4	487544 (20.4)	1769225 (19.5)		
5	492503 (20.6)	1769437 (19.5)		
NHS Region (%)			<0.001	0.142
East of England	101021 (4.2)	364288 (4.0)		
London	443999 (18.6)	2186552 (24.1)		
Midlands	439492 (18.4)	1521927 (16.8)		
North East and Yorkshire	173721 (7.3)	542997 (6.0)		
North West	450918 (18.8)	1592434 (17.6)		
South East	560041 (23.4)	2072658 (22.9)		
South West	224252 (9.4)	788462 (8.7)		
BMI (mean (SD))	28.36 (6.63)	26.51 (6.10)	<0.001	0.291
COVID-19 Vaccinated over Follow Up = Yes (%)			<0.001	0.246
Active Smoker	355640 (15.0)	1580333 (18.6)		
Ex-smoker	702549 (29.6)	1627034 (19.2)		
Non-Smoker	1318233 (55.5)	5271570 (62.2)		
COVID-19 Vaccinated = Yes (%)	2088547 (87.3)	6599919 (72.8)	<0.001	0.368
Number of doses (%)			<0.001	0.668
0	304897 (12.7)	2469399 (27.2)		
1	56655 (2.4)	311652 (3.4)		
2	239472 (10.0)	1298450 (14.3)		
3	494491 (20.7)	2620863 (28.9)		
4	332489 (13.9)	996160 (11.0)		
5	479237 (20.0)	861570 (9.5)		
6	163443 (6.8)	161470 (1.8)		
7	297079 (12.4)	339287 (3.7)		
8	25133 (1.1)	10173 (0.1)		
≥ 9	548 (0.0)	294 (0.0)		
Final Assignment (%)			<0.001	5.248
0	0 (0.0)	9069318 (100.0)		
1	9305 (0.4)	0 (0.0)		
2	40447 (1.7)	0 (0.0)		
3	90410 (3.8)	0 (0.0)		
4	490496 (20.5)	0 (0.0)		
5	40208 (1.7)	0 (0.0)		
6	653408 (27.3)	0 (0.0)		
7	25015 (1.0)	0 (0.0)		
8	383871 (16.0)	0 (0.0)		
9	2172 (0.1)	0 (0.0)		
10	643932 (26.9)	0 (0.0)		
11	14180 (0.6)	0 (0.0)		

Table 4.16c: Characteristics of age-sex unmatched final cohort, immunosuppression disaggregated

	1	2	3	4	5	6	7	8	9	10	*p-value*	SMD
n	9305	40447	90410	490496	40208	653408	25015	383871	2172	643932		
Age (mean (SD))	52.01 (14.98)	63.92 (17.57)	51.35 (18.68)	67.82 (14.33)	70.00 (18.71)	57.98 (17.67)	58.28 (19.40)	46.47 (17.47)	49.66 (19.78)	60.37 (16.25)	<0.001	0.545
Ethnicity (%)											<0.001	0.302
A	1097 (12.4)	1936 (5.0)	13642 (15.7)	15887 (3.4)	3760 (9.9)	42885 (6.9)	1882 (7.8)	39439 (10.8)	116 (5.6)	111857 (17.9)		
B	565 (6.4)	891 (2.3)	11406 (13.2)	10775 (2.3)	2244 (5.9)	14414 (2.3)	2195 (9.1)	9827 (2.7)	52 (2.5)	41864 (6.7)		
M	133 (1.5)	296 (0.8)	1809 (2.1)	2941 (0.6)	409 (1.1)	5916 (0.9)	348 (1.4)	5659 (1.6)	33 (1.6)	8293 (1.3)		
O	161 (1.8)	454 (1.2)	1682 (1.9)	3842 (0.8)	427 (1.1)	6985 (1.1)	367 (1.5)	6883 (1.9)	32 (1.5)	10869 (1.7)		
W	6878 (77.9)	34764 (90.7)	58077 (67.1)	431855 (92.8)	31152 (82.0)	554950 (88.8)	19277 (80.1)	302409 (83.0)	1846 (88.8)	452412 (72.4)		
Sex = M (%)	5490 (59.0)	22422 (55.4)	36262 (40.1)	239161 (48.8)	19408 (48.3)	352342 (53.9)	9176 (36.7)	179125 (46.7)	930 (42.8)	334603 (52.0)	<0.001	0.171
Urban Rural = Urban (%)	8065 (87.3)	33901 (84.4)	80440 (89.8)	408740 (84.0)	35070 (88.1)	549368 (84.9)	21643 (87.2)	336195 (88.4)	1854 (85.8)	570003 (89.5)	<0.001	0.074
IMD Quintile (%)											<0.001	0.146
1	1809 (19.4)	5978 (14.8)	20774 (23.0)	70351 (14.3)	8841 (22.0)	108447 (16.6)	5461 (21.8)	76849 (20.0)	410 (18.9)	153369 (23.8)		
2	1928 (20.7)	7037 (17.4)	20084 (22.2)	83774 (17.1)	8614 (21.4)	121801 (18.6)	5305 (21.2)	79520 (20.7)	468 (21.5)	146597 (22.8)		
3	1839 (19.8)	8268 (20.4)	17353 (19.2)	98947 (20.2)	8009 (19.9)	132075 (20.2)	4884 (19.5)	75834 (19.8)	419 (19.3)	126941 (19.7)		
4	1874 (20.1)	9226 (22.8)	16426 (18.2)	112566 (23.0)	7681 (19.1)	142256 (21.8)	4775 (19.1)	76068 (19.8)	412 (19.0)	114538 (17.8)		
5	1854 (19.9)	9937 (24.6)	15766 (17.4)	124844 (25.5)	7061 (17.6)	148782 (22.8)	4590 (18.3)	75576 (19.7)	463 (21.3)	102440 (15.9)		
NHS Region (%)											<0.001	0.160
East of England	404 (4.3)	1885 (4.7)	2910 (3.2)	22684 (4.6)	1463 (3.6)	30191 (4.6)	777 (3.1)	16784 (4.4)	123 (5.7)	23478 (3.6)		
London	1990 (21.4)	6398 (15.8)	22613 (25.0)	68781 (14.0)	7504 (18.7)	97682 (14.9)	4964 (19.8)	78543 (20.5)	318 (14.6)	149271 (23.2)		
Midlands	1530 (16.4)	7512 (18.6)	15619 (17.3)	89147 (18.2)	7854 (19.5)	125846 (19.3)	4597 (18.4)	64435 (16.8)	394 (18.1)	120872 (18.8)		
Northeast and Yorkshire	641 (6.9)	2793 (6.9)	5553 (6.1)	35768 (7.3)	3141 (7.8)	51004 (7.8)	2180 (8.7)	27452 (7.2)	176 (8.1)	44521 (6.9)		
Northwest	1608 (17.3)	7295 (18.0)	17195 (19.0)	94060 (19.2)	8041 (20.0)	122908 (18.8)	5175 (20.7)	74919 (19.5)	355 (16.3)	117030 (18.2)		
Southeast	2227 (23.9)	10107 (25.0)	19100 (21.1)	127849 (26.1)	8323 (20.7)	160584 (24.6)	5072 (20.3)	87805 (22.9)	550 (25.3)	135900 (21.1)		
Southwest	905 (9.7)	4457 (11.0)	7420 (8.2)	52207 (10.6)	3882 (9.7)	65193 (10.0)	2250 (9.0)	33933 (8.8)	256 (11.8)	52860 (8.2)		
BMI (mean (SD))	26.93 (5.77)	26.90 (5.79)	26.29 (6.18)	27.05 (5.84)	27.85 (6.74)	28.46 (6.52)	27.27 (6.57)	27.62 (6.47)	27.62 (6.94)	30.18 (7.07)	<0.001	0.180
Smoking Status (%)											<0.001	0.166
Active Smoker	1069 (11.6)	4488 (11.2)	12424 (13.9)	58327 (12.0)	3960 (9.9)	89322 (13.8)	3685 (14.9)	82199 (21.7)	392 (18.5)	96093 (15.0)		
Ex-smoker	2431 (26.3)	12605 (31.5)	19668 (22.1)	164569 (33.7)	13080 (32.8)	197383 (30.4)	6296 (25.4)	96350 (25.4)	483 (22.8)	187205 (29.2)		
Non-Smoker	5733 (62.1)	22981 (57.3)	57066 (64.0)	264791 (54.3)	22893 (57.3)	362350 (55.8)	14814 (59.7)	200083 (52.8)	1245 (58.7)	358724 (55.9)		
COVID-19 Vaccinated over Follow Up = Yes (%)	8205 (88.2)	35305 (87.3)	74560 (82.5)	431066 (87.9)	32832 (81.7)	584897 (89.5)	21501 (86.0)	323365 (84.2)	1948 (89.7)	564103 (87.6)	<0.001	0.095
Number of Doses (%)											<0.001	0.456
0	1100 (11.8)	5142 (12.7)	15850 (17.5)	59430 (12.1)	7376 (18.3)	68511 (10.5)	3514 (14.0)	60506 (15.8)	224 (10.3)	79829 (12.4)		
1	222 (2.4)	851 (2.1)	2657 (2.9)	10535 (2.1)	1308 (3.3)	13094 (2.0)	661 (2.6)	10892 (2.8)	63 (2.9)	15740 (2.4)		
2	865 (9.3)	3072 (7.6)	12369 (13.7)	36193 (7.4)	4152 (10.3)	58288 (8.9)	2656 (10.6)	54213 (14.1)	261 (12.0)	65479 (10.2)		
3	1313 (14.1)	5031 (12.4)	21247 (23.5)	71236 (14.5)	6041 (15.0)	137886 (21.1)	5016 (20.1)	114946 (29.9)	569 (26.2)	128297 (19.9)		
4	997 (10.7)	3864 (9.6)	11479 (12.7)	66237 (13.5)	4614 (11.5)	98673 (15.1)	3365 (13.5)	52474 (13.7)	338 (15.6)	88892 (13.8)		
5	948 (10.2)	4367 (10.8)	12974 (14.4)	100953 (20.6)	6030 (15.0)	128838 (19.7)	4707 (18.8)	58167 (15.2)	417 (19.2)	160527 (24.9)		
6	1060 (11.4)	4949 (12.2)	5259 (5.8)	46860 (9.6)	3614 (9.0)	50121 (7.7)	1795 (7.2)	12344 (3.2)	106 (4.9)	36068 (5.6)		
7	1553 (16.7)	8891 (22.0)	7340 (8.1)	93777 (19.1)	6465 (16.1)	88485 (13.5)	3142 (12.6)	19167 (5.0)	194 (8.9)	67062 (10.4)		
8	1198 (12.9)	4156 (10.3)	1195 (1.3)	5177 (1.1)	602 (1.5)	9365 (1.4)	157 (0.6)	1138 (0.3)	0 (0.0)	1989 (0.3)		
≥ 9	49 (0.5)	124 (0.3)	40 (0.0)	98 (0.0)	6 (0.0)	147 (0.0)	2 (0.0)	24 (0.0)	0 (0.0)	49 (0.0)		

When age-sex unmatched, variation in study groups' demographics were statistically significant in all instances. At the aggregate level (Table 4.16a), immunosuppressed patients were likelier to be older, COVID-19 vaccinated, former smokers, and from higher socioeconomic settings than control and internal reference groups. Meanwhile, Drug-managed HIV patients were significantly more likely to be of Black ethnicity, from urban settings and lower socioeconomic quintiles than control and immunosuppressed counterparts. When disaggregating unmatched immunosuppression (Table 4.16b), age, gender ratio, ethnicity profile and vaccine uptake were also significantly heterogeneous. Although white patients predominated in our data, Transplantations saw disproportionate numbers of Asian patients compared to other immunosuppressed groups. Chronic kidney disease & Dialysis patients were, on average, significantly older than other populations and likelier to come from deprived backgrounds; this vulnerable profile contrasted starkly with their low COVID-19 vaccine uptake and dosing. Reports of less than universal COVID-19 vaccine uptake across immunosuppressed groups are of note; non-vaccination was disproportionate in Chronic kidney disease & Dialysis (18.3%) and Drug-managed HIV (24.1%) groups. However, it is unclear whether this is attributable to inaccuracies in the primary care record; our data did not benefit from linkage to vaccine registries. Reassuringly, however, those in highest DESTINIES risk groups were likeliest to have received eight or more doses by the end of 2023.

Table 4.17 provides the aggregated characteristics of our age-sex matched cohort (immunosuppression and internal reference group age-sex matched with control group data); Appendix 22 also tabulates matched and adjusted immunosuppressed and internal reference group data at the disaggregated level.

Table 4.17: Characteristics of age-sex matched final cohort, immunosuppression (IS) aggregated and combined with internal reference group (IRG)

	IS + IRG	Control	*p-value*	SMD
n	2359205	2359205		
Age (mean (SD))	58.38 (17.94)	58.38 (17.94)	1.000	<0.001
Ethnicity (%)			<0.001	0.086
A	231794 (10.3)	178910 (8.2)		
B	97680 (4.3)	80172 (3.7)		
M	26425 (1.2)	26489 (1.2)		
O	32024 (1.4)	39953 (1.8)		
W	1871241 (82.8)	1859319 (85.1)		
Sex = M (%)	1174534 (49.8)	1174534 (49.8)	1.000	<0.001
Urban/Rural = Urban (%)	2030344 (86.9)	2014307 (86.1)	<0.001	0.023
IMD Quintile (%)			<0.001	0.085
1	452068 (19.2)	390285 (16.5)		
2	473571 (20.1)	450956 (19.1)		
3	470085 (19.9)	476992 (20.2)		
4	479564 (20.3)	502863 (21.3)		
5	483775 (20.5)	537994 (22.8)		
NHS Region (%)			<0.001	0.034
East of England	99480 (4.2)	104951 (4.4)		
London	439451 (18.6)	442587 (18.8)		
Midlands	432660 (18.3)	426382 (18.1)		
Northeast and Yorkshire	171127 (7.3)	163439 (6.9)		
Northwest	444619 (18.8)	424975 (18.0)		
Southeast	551333 (23.4)	574973 (24.4)		
Southwest	220535 (9.3)	221898 (9.4)		
BMI (mean (SD))	28.39 (6.65)	26.93 (5.78)	<0.001	0.235
Smoking Status (%)			<0.001	0.092
Active Smoker	353592 (15.1)	346827 (15.2)		
Ex-smoker	686508 (29.3)	577349 (25.3)		
Non-Smoker	1302203 (55.6)	1356372 (59.5)		
COVID-19 Vaccinated = Yes (%)	2059393 (87.3)	1924785 (81.6)	<0.001	0.158
Number of Doses (%)			<0.001	0.204
0	299812 (12.7)	434420 (18.4)		
1	55757 (2.4)	57221 (2.4)		
2	236855 (10.0)	222326 (9.4)		
3	491579 (20.8)	496730 (21.1)		
4	329939 (14.0)	340825 (14.4)		
5	475995 (20.2)	410066 (17.4)		
6	159765 (6.8)	113167 (4.8)		
7	284341 (12.1)	277314 (11.8)		
8	24623 (1.0)	6981 (0.3)		
≥ 9	539 (0.0)	155 (0.0)		
Final Phenotype Assignment (%)			<0.001	5.227
0	0 (0.0)	2359205 (100.0)		
1	9280 (0.4)	0 (0.0)		
2	39496 (1.7)	0 (0.0)		
3	89779 (3.8)	0 (0.0)		
4	477311 (20.2)	0 (0.0)		
5	38938 (1.7)	0 (0.0)		
6	645448 (27.4)	0 (0.0)		
7	24705 (1.0)	0 (0.0)		
8	382477 (16.2)	0 (0.0)		
9	2159 (0.1)	0 (0.0)		
10	635437 (26.9)	0 (0.0)		
11	14175 (0.6)	0 (0.0)		

As seen when comparing Table 4.16a and 4.17 sample sizes, a subsection of immunosuppressed and internal reference group patients could not be age-sex matched with controls. Meanwhile, Solid tumour, Systemic and Single Organ IMID and Wider determinants of immunosuppression (Final Assignments 4, 6, 8 and 10,

respectively) dominated both matched and unmatched cohorts. The poor representation of Anatomical Barrier Defects, Transplantation, and Drug-Managed HIV (Final Assignments 9, 1 and 11) are of note. Poisson-based modelling of IRRs collapse when based on small sample sizes.

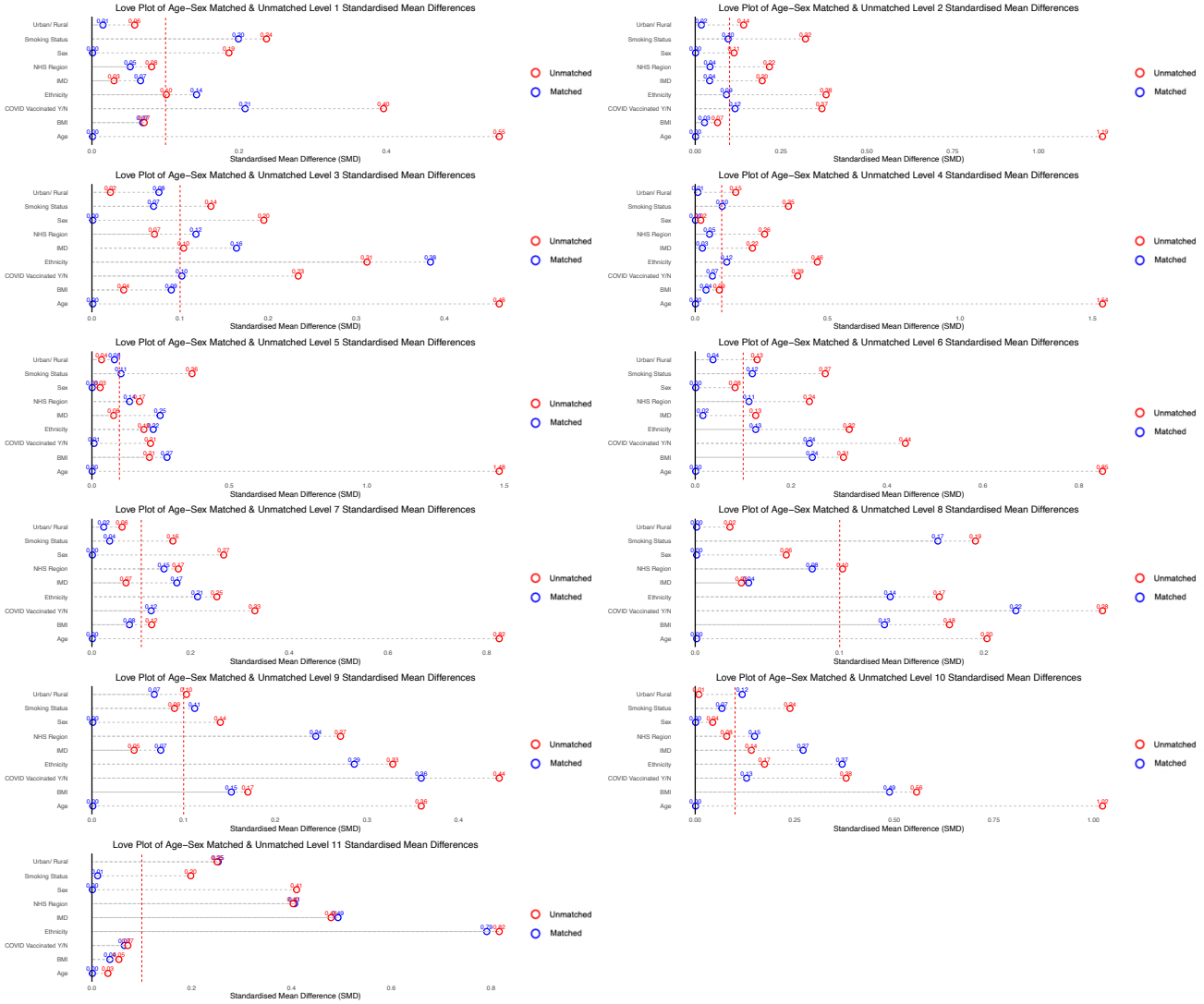
Although SMDs declined almost universally after age-sex matching, statistically significant heterogeneity persisted between study groups' ethnicity, urban/rural, IMD, NHS Region, BMI, Smoking Status, COVID-19 vaccination and dose profiles. The standard mean difference in BMI between controls and Final Assignments 1:11 was seen to inflate post age-sex matching, for example. Love plots (Figures 4.17a and b) captured these ongoing significant differences. When disaggregating age-sex matched and unmatched SMDs between phenotype final assignments (Figure 4.17b), it is possible to identify the subgroups that contributed most to ongoing heterogeneity in aggregated data. SMDs persisted most for Final Assignments 1, 3, 8, 9 and 11; age-sex matching supressed heterogeneity for Final Assignments 2, 4, 5, 6, 7 and 10, by comparison.

Figure 4.17a: Love Plot of age-sex matched and unmatched cohorts standardised mean differences, immunosuppression (IS) aggregated and combined with internal reference group (IRG)



To minimise the attributability of these broader demographic variables to any differences observed in our outcomes of interest, urban/rural, smoking status, NHS region, IMD, ethnicity, COVID-19 vaccination status and BMI were either all adjusted for in our primary analysis or incorporated into subgroup analyses.

Figure 4.17b: Love plot of age-sex matched and unmatched cohorts standardised mean differences, immunosuppression (IS) and internal reference group (IRG) disaggregated

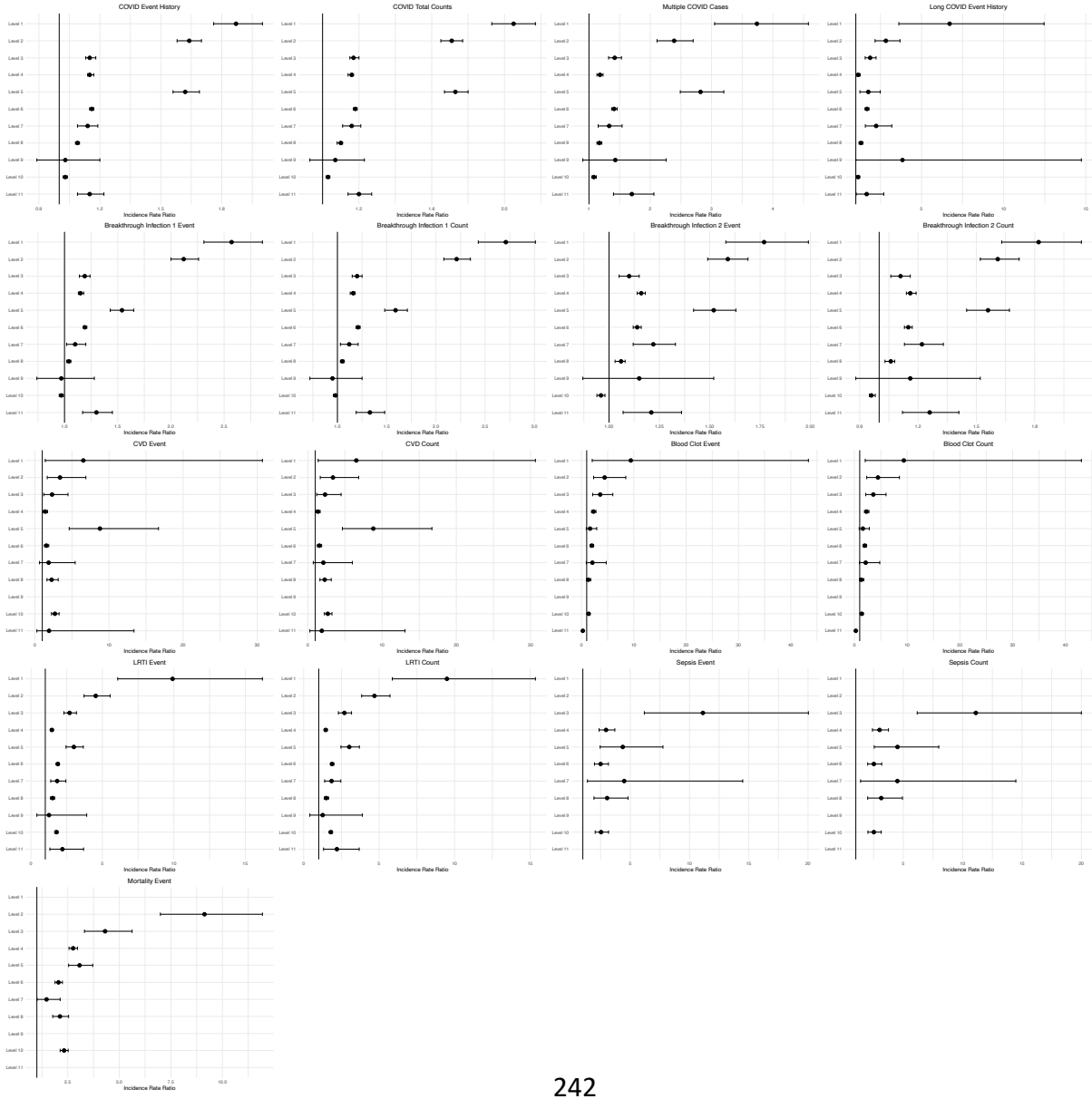


Age-sex matched and fully adjusted IRs and IRRs of our outcomes of interest are tabulated by Final Assignment level in Appendix 23; sample sizes, event counts and person years are supplied, and a demarcation is made between the incidences of outcomes ever occurring in patients (binary) and incidences that utilise total count data (total count) for each outcome of interest. Confirmation of the equivalence of outcomes' means and variance as well as outputs from Quasipoisson modelling are also provided in Appendix 23. Quasipoisson data was not taken forward for our primary reporting, however; with conditional Poisson modelling returning more conservative confidence intervals for all outcome IRRs, overdispersion was ruled out and Quasipoisson estimates made redundant. Appendix 24 tabulates our secondary analysis: unmatched and unadjusted IR and IRR data and matched and unadjusted IR and IRR data. Non-robust standard errors were used when reporting unmatched and unadjusted IRRs 95% confidence intervals after establishing that only 18% of these exponentiated values were smaller than robust alternates.

DESTINIES phenotype predictions of COVID-19 risk were, broadly speaking, borne out in these data and were reasonably robust to matching and full adjustment of wider explanatory variables. In all circumstances and permutations of analysis, immunocompetent and immunosuppressed incidence rates, and the disparities between them, for COVID-19 infection rates (single, multiple or breakthrough) were significantly smaller than those of severe 28-day outcomes. Event history and total count incidences and IRRs of these severe outcomes and their associated confidence intervals were also typically identical given the exceedingly low likelihood of a repeat occurrence per patient.

As per Figure 4.18 and Appendix 23, after age-sex matching and full adjustment, hierarchical results were most observable within COVID-19 case (event history, count, multiple and breakthrough), 28-day LRTI and Long COVID conversion data.

Figure 4.18: Age-sex matched and fully adjusted incidence rate ratios of 2020-2023 outcomes of interest, differentiated by phenotype level (1:10, immunosuppression; 11, internal reference group). Data suppressed when 95% CI >50.



The decision to demarcate solid tumour from haematological malignancies and systemic IMID from single organ counterparts in the DESTINIES phenotype was validated by these outputs; DESTINIES risk predictions (Final Assignment Levels 2 > 4; Final Assignments 6 > 8) were replicated for almost every outcome assessed, bar 28-day CVD, sepsis and mortality for IMID pairwise comparisons.

IRR gradients were not always linear, however, with runaway risk often concentrated amongst Transplantation and Haematological & Distributed Malignancy patients (Final Assignments 1 and 2) compared to clustering amongst lower risk patient populations. This was markedly different to the more consistent intervals reported between Final Assignments in unmatched and unadjusted outcome data (Appendix 24), indicating that differential risk observed between immunosuppressed subgroups are not just clinical in nature, but highly attributable to demographic differences. This was especially pronounced in rarer outcomes: after age-sex matching and full adjustment, Transplantation (Mortality IRR: 37.21, 95% CI: 14.21-97.48; Sepsis, Binary IRR: 51.9, 95% CI: 6.68-403.3; Blood Clot, Binary IRR: 9.43, 2.05-43.36) and Haematological & distributed malignancy (Mortality IRR: 9.13, 95% CI: 6.99-11.94; Sepsis, Binary IRR: 46.63, 95% CI: 20.58-105.62; Blood Clot, Binary IRR: 4.43, 95% CI: 2.32-8.47) data outstripped remaining DESTINIES subgroups.

This contrasts with evidence that demographic variation in raw data may suppress excess clinical vulnerability in the immunosuppressed compared to non-immunosuppressed controls: when contrasting Appendices 23, 24 and the data tabulated in Figure 4.18, IRRs of outcomes of interest typically inflated after matching and demographic adjustment. This was not the case for outcomes that

were affected by small sample sizes and subsequent failures of convergence, however; here, IRRs from raw data superseded their matched counterparts (28-day CVD, blood clots, sepsis, mortality). This conflicting relationship is visualised in Figure 4.19 below.

Figure 4.19: Summary forest plot of the influence of matching and adjustment on outcome IRRs; evidence provided in most populated data for IRRs with increased matching and adjustment



The elevated vulnerability of Chronic kidney disease & Dialysis patients (Final Assignment 5) was not predicted by the DESTINIES phenotype, however; their vulnerability to 28-day cardiovascular outcomes exceeded that of all other immunosuppressed populations assessed irrespective of data matching and adjustment (IRR: CVD, Binary: 8.78, 95% CI: 4.63-16.68). COVID-19 case load (COVID-19 infection, Binary: 1.62: 95% CI: 1.56-1.69; Multiple infection, Binary IRR: 2.82, 95% CI: 2.49-3.2) and breakthrough infections (Breakthrough infection 1, Binary IRR: 1.54, 95% CI: 1.43-1.65; Breakthrough infection 2, Binary IRR: 1.52, 95% CI: 1.42-1.63) in this group also exceeded DESTINIES' expectations. These matched and adjusted outcomes were suppressed compared to unadjusted and unmatched counterparts, however - underscoring the influence of demographic differences on COVID-19 outcomes even within existing risk groups.

Furthermore, despite their small sample size, the internal reference group returned elevated incidences of key 28-day severe COVID-19 outcomes compared to the immunocompetent. Confirming DESTINIES Panellists' hesitations, this suggests Drug-managed HIV would be an inappropriate control group for the broader immunosuppressed category and that the immunocompetent should be retained for this purpose.

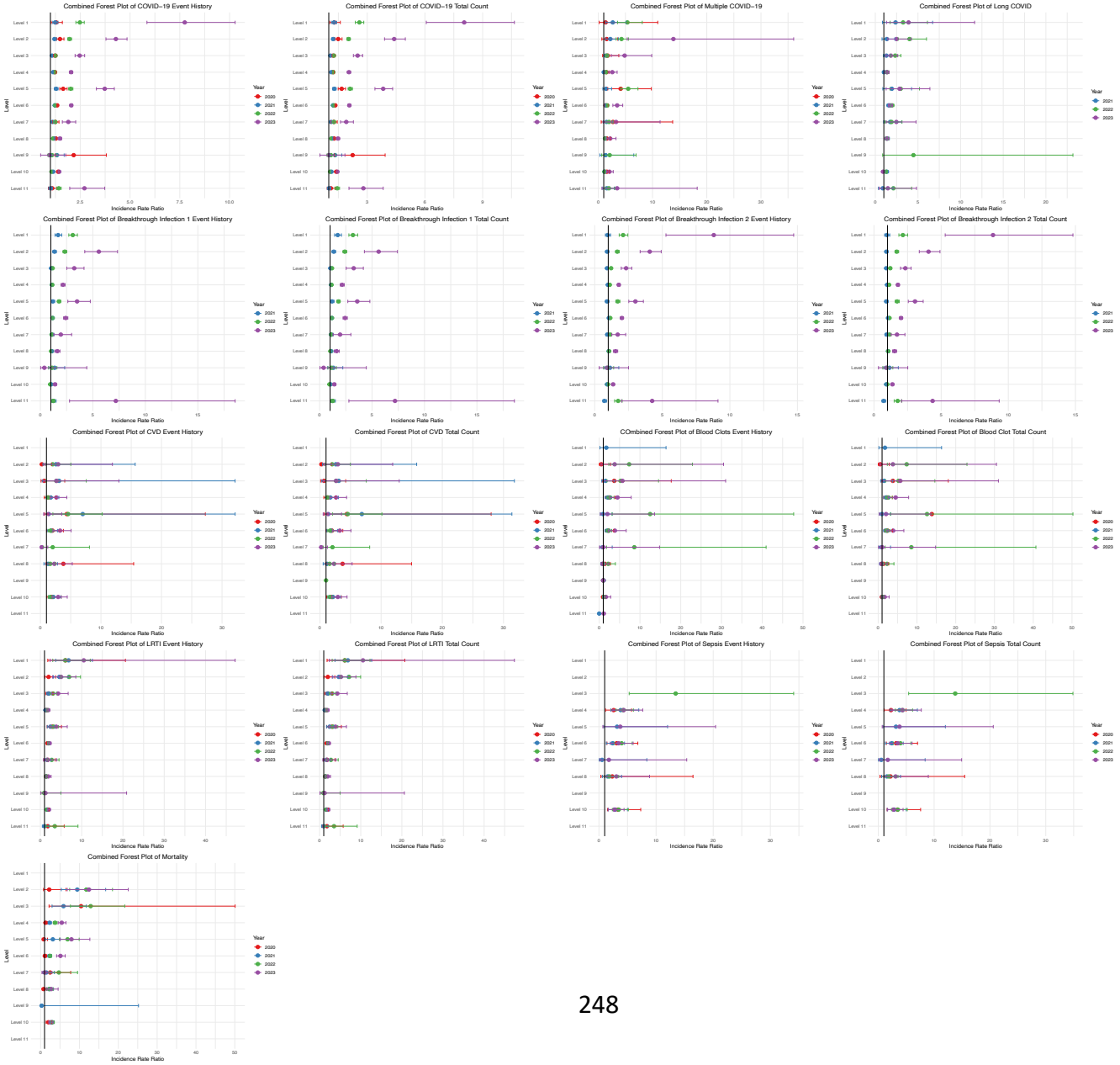
The small sample sizes of specific immunosuppressed subgroups hampered our differential analysis; outcomes are reported with extremely wide confidence intervals in several instances. As expected, Poisson modelling of Anatomical Barrier Defect, Drug-Managed HIV and Transplantation patients was especially degraded, often returning infinite or otherwise implausible confidence intervals. These were manually

suppressed from certain summary plots for clarity but are tabulated in full within Appendix 23. Rarer 28-day COVID-19 outcomes were especially affected by these issues of convergence.

Subgroup analysis of age-sex matched and fully adjusted data also proved challenging. Once our data was segmented by year or vaccine uptake, small sample sizes for certain immunosuppressed subgroups in parallel with small numbers of outcomes of interest created widespread convergence issues for multivariable conditional Poisson modelling. Estimates of IRRs and associated 95% confidence intervals were often either unreliable or completely implausible as a result.

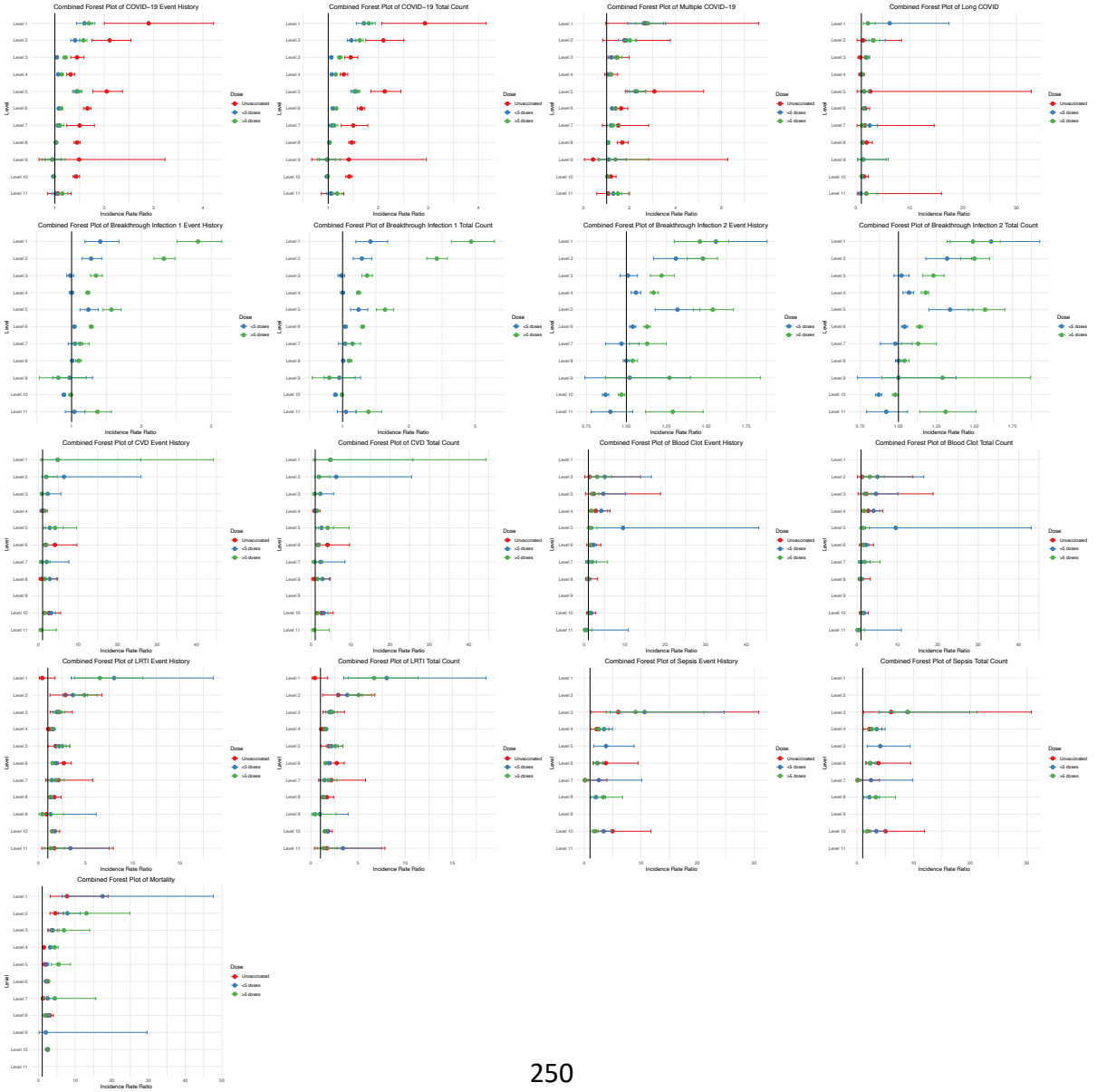
For year-by-year subgroup analysis (Appendix 25), these issues were especially pronounced in 2020 data where almost no clinical inferences could be made. Analyses in later years fared better by comparison. Overall, incidence rate data per 100 person-years indicated a sharp drop-off in COVID-19 cases and associated severe outcomes in 2023; all outcomes were seen to increase incrementally prior to this timepoint. Meanwhile, in subgroups and outcomes where data was substantial enough to converge via conditional Poisson regression, year-on-year increases in IRRs were reported and the DESTINIES COVID-19 risk hierarchy persisted (Figure 4.20) most visibly in COVID-19 infection IRR data. The influence of study year on rare outcome data was less directional, however, and the DESTINIES risk hierarchy was seen to flatten as Final Assignments 1, 2 and 3 were manually suppressed.

Figure 4.20: Summary forest plot of subgroup analysis of age-sex matched & fully adjusted cohort by study year; evidence provided in most populated data for increased IRRs with study year



Subgroup analysis by vaccine uptake (unvaccinated, <5 doses and >5 doses) proved similarly challenging, though informative in parts (Appendix 26). Firstly, incidence rates of both COVID-19 cases and severe outcomes were seen to increase marginally with vaccine uptake. This is unlikely to reflect poor vaccine effectiveness in these patients, however. Increased vaccine dosage selects for more vulnerable patients and, by virtue of the dose number accrued, longer participation in our follow-up period - both of which lead to disproportionate case rates and severe outcomes. Moreover, ratio data was less consistent than incidence rate data. As per Figure 4.21, disparities between immunosuppressed and immunocompetent COVID-19 case rates were usually most substantial in the unvaccinated. By comparison, vaccine uptake did not appear to have any consistent effect on Long COVID IRRs or severe 28-day COVID-19 outcomes - though small sample sizes and inaccurate Poisson modelling may have been disrupting these relationships. Interestingly, mortality IRRs were smaller in unvaccinated patients than in their highly vaccinated counterparts. Overall, the DESTINIES hierarchy was consistently degraded by this subgroup analysis, especially for the IRRs of rare outcomes. Previously reported gradients collapsed, though non-convergence amongst highest risk groups also made this difficult to assess in full.

Figure 4.21: Summary forest plot of subgroup analysis of age-sex matched & fully adjusted cohort by vaccine uptake; evidence provided for lowest mortality IRR and highest COVID-19 case IRR amongst the unvaccinated.



iii. Discussion:

Principal findings and their implications:

This exercise successfully codified and operationalised the DESTINIES phenotype in primary care data to differentiate key outcomes of interest by immunosuppressed status and subgroup. Attempts to exclude cancer in remission as per DESTINIES panellists' instruction proved unsuccessful, however; these codes were not used reliably enough in primary care data to make these exclusions either meaningful or accurate.

Immunosuppression was seen to be a highly dynamic and highly heterogenous risk group. Monitoring and controlling for transitions from immunocompetent to immunocompromised over the follow up period proved challenging, but possible when duplicating single records into two study entries. Reverse transitions could not be easily assessed and controlled for, however. Persistent heterogeneity in immunosuppressed subgroups' demographics and COVID-19 vaccine status even after age-sex matching justified lengthy adjustment terms in our conditional Poisson-based modelling of IRRs. The majority of our cohort, immunosuppressed or otherwise, had received their primary course of COVID-19 vaccination, however, Chronic kidney disease & dialysis and Drug-managed HIV patients both higher levels of non-vaccination than the wider immunosuppressed population. This was concerning and is unlikely to be an artifact of EHR inaccuracy for these patients specifically. Beyond this, almost universal patterns of dose-by-dose uptake in the immunosuppressed conflicted with differential COVID-19 outcomes.

Low sample sizes in certain DESTINIES phenotype subgroups affected the accuracy of IRR estimation. This was especially pronounced after age-sex matching, full adjustment and subgroup analysis. Implausible or infinite outcomes were manually suppressed in summary visualisations. However, the DESTINIES hierarchy was broadly borne out when data successfully converged with conditional and unconditional Poisson modelling. In almost all circumstances and subgroups, the immunosuppressed reported significantly elevated incidences of COVID-19 infections and serious consequences thereafter compared to the immunocompetent. Transplantation and Haematological and distributed malignancy subgroups consistently returned the most severe COVID-19 outcomes (elevated incidences of 28-day secondary lower respiratory tract infections, blood clots, cardiovascular outcomes, sepsis and mortality). However, some important divergences from the DESTINIES hierarchy were reported.

Firstly, DESTINIES phenotype 'goodness of fit' was deeply affected by cohort age-sex matching and full adjustment. The consistent and hierarchical intervals seen in raw outcome IRRs between Final Assignments flattened into a single demarcation of extreme versus elevated COVID-19 risk after matching and adjusting. This suggests that within-immunosuppressed heterogeneity in COVID-19 risk may be attributable to demographic differences between subgroups in some cases. Such observations conflict with overall increases seen to IRRs after age-sex matching and full adjustment, however – increases that indicate true clinical disparities between immunosuppressed and immunocompetent COVID-19 outcomes may be suppressed by demographic variation between these experimental groups. These nuances are poorly represented by the inflexibility of the DESTINIES phenotype.

Meanwhile, Chronic kidney disease & dialysis patients returned unexpected levels of COVID-19 caseloads and severe outcomes – reporting the highest IRRs for 28-day cardiovascular outcomes, for example. Likewise, DESTINIES predictions for within immunosuppressed subgroup differences in COVID-19 risk were not borne out in all instances: Single Organ IMID patients returned greater IRRs for 28-day CVD, sepsis and mortality than their Systemic counterparts. Finally, unexpected statistically significant differences between immunocompetent and internal reference group COVID-19 data confirmed that Drug-managed HIV should not be utilised as an isolated active control moving forwards.

Our subgroup analyses of DESTINIES phenotype performance were hampered by low sample size, however; segmenting data by study year and key vaccine milestones caused widespread issues of non-convergence. That said, some top-level inferences could still be made. Although conflicting with 2023 declines in IR data, outcome IRRs were seen to increase year on year for immunosuppressed subgroups. This can be attributed to improved COVID-19 case management over the study time course – including the introduction of vaccines and therapeutics – and resultant impacts on outcome disparities between the immunosuppressed and immunocompetent; over time, COVID-19 mortality or severe outcomes became vanishingly rare in the latter group [87]. The cadence of the DESTINIES risk hierarchy fell apart in these year-by-year subgroup analyses, however; it is unclear whether this observation has a clinical basis or is a purely statistical failing. 2020 study data was almost completely unusable, for example, though later years fared slightly better. Our 28-day outcome data was contingent on the joint presence of a

confirmed COVID-19 diagnosis code and secondary outcome; this was less tenable in 2020 when community testing was at its lowest [88].

Likewise, vaccine uptake was seen to have an inconsistent effect on COVID-19 IRs and IRRs between immunosuppressed subgroups. In certain instances, both metrics were seen to increase with vaccine dosing, though this is not necessarily an indicator of vaccine failure: high vaccine uptake can indicate underlying patient vulnerability and/ or increased time spent in our cohort, making COVID-19 reporting more likely. Indeed, deviations from the overall trend of reduced mortality incidence with vaccine uptake only occurred in highest risk categories receiving less than 5 doses of vaccine. Meanwhile, reports of inflated COVID-19 mortality IRRs in high-vaccine dose immunosuppressed patients reflect the extremely low likelihood of a matched highly vaccinated non-immunosuppressed individual succumbing from COVID-19. Between-group differences in unvaccinated mortality would be smaller by comparison. However, it is of interest that increased vaccine uptake was not seen to reduce Long COVID incidences or rate ratios, though increases in this condition's codification over time (coextensive with vaccine uptake) may have cancelled out any observable reductions brought about by repeat vaccination. As an overarching observation, the DESTINIES hierarchy was also eroded when IRR outputs were differentiated by vaccine uptake.

Many of the issues described in these data – notably small sample sizes and unreliable performance during more precise analyses - are inherent to working with primary care data. Even despite these challenges, the DESTINIES phenotype still proved itself to be a viable and valuable means of segmenting immunosuppressed

COVID-19 data. Its findings make it evident that a universal vaccine offering for the immunosuppressed is insufficient for preventing severe COVID-19 outcomes for all patient subgroups. Its risk hierarchy was also, mostly, borne out in this exercise. That said, Chronic kidney disease warrants inclusion in its top tier risk band moving forwards. Likewise, aiming to exclude cancer in remission from immunosuppressed cohorts is unlikely to be tenable and Drug-managed HIV should not, according to this output, be positioned as its active control group.

Comparison to existing literature:

There is strong concordance between the key findings of this study and the outcomes of INFORM [7; 87], including inflated COVID-19 infections and severe outcomes amongst Chronic kidney disease and dialysis patients. Indeed, from the outset, this investigation considered Chronic kidney disease patients as at highest risk – something that the DESTINIES phenotype would do well to adopt. This work also made similar demographic observations about the immunosuppressed: they were significantly likelier to be older, report higher BMIs and reside in more affluent areas. Statistically significant disparities between immunosuppressed and immunocompetent mortality levels also persisted after multiple vaccine doses in INFORM analysis. Like our own work, these critical risks were concentrated within transplantation and haematological malignancy patients. Their conclusion that immunosuppressed patients require additional preventative measures beyond current COVID-19 vaccine provisions is one aligned with our own. Less differentiated work by Turtle and colleagues (2023) [89] pushes this recommendation further, however: here, the targeted delivery of additional vaccine doses, monoclonal antibodies and non-pharmaceutical preventative interventions to highest risk patients

are positioned as essential for closing gaps in COVID-19 disparities between immunosuppressed and immunocompetent patients. Indeed, work by Lahouati et al (2023) [90] have established how effective such an approach can be: 95% of immunosuppressed patients provided with targeted access to COVID-19 prophylactics and booster vaccine doses did not progress beyond mild disease.

The persistent and disproportionate incidences of breakthrough infections that this work identified in the immunosuppressed have been replicated elsewhere [91]. The excess vulnerability of Transplantation patients to this particular outcome are also well documented [92]. The value of vaccination for the immunosuppressed should not be called into question by this work, however. Decreases in mortality incidence rates with vaccine uptake were almost universal: deviations from this trend only occurred in highest risk groups and resolved once uptake exceeded five doses. This dose-dependent resolution in vaccine effectiveness has been reported in OCTAVE DUO: consistent with our own preliminary serosurveillance, here seronegativity began to resolve after the third COVID-19 dose had been received but that further boosting was needed for rare, but persistent, non-responders [36]. These findings must be communicated to the immunosuppressed who have only received a primary schedule of COVID-19 vaccination.

Our work did not corroborate the range of investigations that have associated increased COVID-19 vaccine uptake with reduced incidences of Long COVID [93; 94] even amongst the already immunosuppressed [95]. However, this discrepancy is more likely to reflect inconsistent codification of Long COVID in the primary care record than a unique clinical outcome of this cohort. By comparison, the

disproportionate incidences of severe COVID-19 outcomes amongst Dialysis, Chronic kidney disease and Single Organ IMID patients to severe COVID-19 outcomes (most notably for 28-day CVD events) we were surprised to report are well-established elsewhere. For example, the end-stage renal disease population sees a near twentyfold increase in the likelihood of mortality related to cardiovascular disease compared to the general population [96] – a pre-existing susceptibility that Zhu, Zhang and Peng have successfully linked with excess COVID-19 mortality in this group [97]. Known associations between Type 1 Diabetes and cardiovascular risk [98] may, in the same vein, account for the unanticipated levels of 28-day CVD, sepsis and mortality outcomes we report amongst Single Organ IMID patients.

Finally, statistically significant disparities in adverse COVID-19 outcomes between controls and our internal reference group conflict with DESTINIES panellists' predictions and the wider literature. It may have been wrong to assume that ORCHID-E HIV patients who were not allocated to our Primary immunodeficiencies, unmanaged acquired immunodeficiencies & underlying aberrant immunity subgroup were drug-managed. Alternatively, the disproportionate levels of deprivation seen in our cohort's internal reference group may be accountable for these inflated risks.

Limitations:

Although this piece of work was successful in its primary objective of implementing the full DESTINIES phenotype in primary care data, its outputs and clinical relevance are limited in several ways.

Firstly, low sample sizes in key subgroups and low event numbers for key outcomes significantly affected the accuracy of our Poisson modelling and, thereby, our confidence in any inferences made with resultant data. Our decision to manually suppress implausible data (using an arbitrary cut-off of 50 to do so) could also be criticised: future iterations of this work should perform sensitivity analyses to statistically assess and suppress the influence of smaller subgroups and low event numbers on IRR data.

This work would also have benefited greatly from data linkages with secondary care, death registry and vaccine records. Failing this, lower-resolution analysis could have been conducted: the validity of risk bands was not assessed by this work, and it is likely that this cruder level of analysis would have fared better than our eleven demarcations.

By only using primary care data, it was also difficult to establish whether observed changes in COVID-19 outcomes are clinically or socially determined. For example, abrupt declines in COVID-19 infection and severe outcomes seen in 2023 could be attributable to novel therapeutics, increased vaccine uptake or – more likely – declines in community testing and case reporting. As discussed elsewhere, data segmentation by immunosuppressive prescriptions were precluded by using this data source in isolation.

Finally, despite considerable effort to control for patient transitions from immunocompetent to immunosuppressed within the follow-up period, this work failed to adjust its analysis for any reversals in immunosuppressed status. Our ‘ever’ based

coding for immunosuppression made this impossible and did not reflect the clinical realities and COVID-19 risks of extremely acute forms of immunosuppression such as malnutrition and pregnancy. Any future replications of this work should attempt to address this issue.

5. A patient engagement exercise to refine and ratify the DESTINIES phenotype for ongoing use in national disease surveillance:

i. Method:

The DESTINIES Patient Panel webinar (*Improving how we monitor COVID-19 spread and outcomes in the immunosuppressed)* was conducted to give a representative group of immunosuppressed patients the opportunity to quality assure, refine and ratify the DESTINIES phenotype. Assessing patients' comfort with and confidence in the phenotype was essential before recommending its wider implementation in disease surveillance pathways on their behalf.

Prior to recruitment, the doctoral candidate confirmed with the University of Oxford Research Governance Ethics and Assurance Team that, like the eDelphi study that preceded it, this study would be categorised as 'pre research, priority setting or survey' and therefore would not require formal ethical review.

Recruitment for this webinar was global and purposive, remaining active until expressions of interest had been received from patient representatives of every DESTINIES phenotype level. The doctoral candidate and DESTINIES patient champion managed this process, advertising the opportunity on the National Institute

of Health Research (NIHR)'s *People in Research* portal [99] and within the EULAR People with Arthritis/Rheumatism in Europe (PARE) community [100] and relevant immunosuppressed affinity and advocacy groups. Prospective patient panellists were told that this one-hour webinar would be an opportunity for them to learn more about immunosuppressed disease surveillance, its current limitations and the efforts taken by the doctoral candidate to resolve these issues. Those still interested in participating were invited to register.

A Google Form (Alphabet) was distributed to all who registered to identify the most popular presentation date for the webinar. When completing their availability, patients also had to confirm they were aware that their participation would be anonymised, recorded and utilised in academic work and that a final vote would be taken on the phenotype's retention after the session. This understanding was also checked for via consent forms sent to all those who confirmed their availability on the most popular date. A copy of this consent form can be accessed in Appendix 27.

The doctoral candidate worked with the DESTINIES patient champion to ensure that her presentation materials and messaging were completely accessible for patients. Here, the doctoral candidate converted thesis outputs, including the DESTINIES phenotype, into a patient-oriented presentation. Panellists were given foundational knowledge about disease surveillance, digital phenotyping and prevailing means of monitoring immunosuppressed outcomes before key findings from the doctoral programme of work were shared. This included the candidate's systematic literature review and meta-analysis, the international consensus building study and preliminary findings from the full implementation of the DESTINIES phenotype. Drawing upon

Alley's 'The Craft of Scientific Writing' (1996), due consideration was given to presentation audience, purpose and mode to optimise communication and understanding [101]. The careful use of personal disclosure [102] and analogy [103] aimed to eliminate power dynamics between researcher and subject, build rapport and improve the accessibility of all findings shared.

The DESTINIES patient panel webinar was hosted on Zoom (Zoom Video Communications, Inc). To maintain their anonymity, patient panellists were assigned unique ID numbers and were instructed to turn off their cameras throughout the presentation and discussion. The presentation itself took up half an hour with several breaks to facilitate questions and clarifications in real-time; the remaining 30 minutes were used to field final panel questions and criticisms with the help of the DESTINIES patient champion.

To maximise patient engagement, this presentation was recorded and emailed to all those who had expressed an interest in joining the DESTINIES Patient Panel. A Google forms-based questionnaire was distributed alongside the recorded presentation; a copy of the presentation slides and follow-up questions is provided in Appendix 27. This collected Patient Panellists' final feedback on the DESTINIES phenotype and their vote as to whether it should be implemented as standard within UK disease surveillance flows. To create coherence between the two exercises, this form incorporated the non-specialist questions that ratified the DESTINIES phenotype amongst DESTINIES Consortium members.

Patient responses to the following items are summarised: i) '*Please write down any questions you have about the research we presented, the DESTINIES phenotype or our future plans'*, ii) *'Please write down any feedback you have on the research we presented and our DESTINIES phenotype'.* Patient votes on the following items were evaluated by Likert scale (Strongly disagree, somewhat disagree, unsure, somewhat agree, strongly agree): i) '*I think this phenotype should be used in COVID-19 disease surveillance moving forwards'*, ii) '*I think this phenotype represents a step forward for immunosuppressed COVID-19 disease surveillance'* and iii) '*I would like to see this phenotype trialled in the surveillance of other diseases (e.g. seasonal flu, pneumonia etc.)'.* As per the DESTINIES Study and Diamond et al (2014) [104] precedent, consensus was said to have been reached when 75% or more of respondents aligned with the poles of Likert-based agreement (e.g. Strongly or somewhat disagree and strongly or somewhat agree).

ii. Results:

A total of 25 patients attended the DESTINIES Patient Panel webinar in real-time; however, after distributing the presentation file and recording, a total of 33 submitted their final feedback and vote via Google Forms. Cohort characteristics are tabulated in Table 4.18. Patient panellists could select multiple conditions for when declaring their form of immunosuppression.

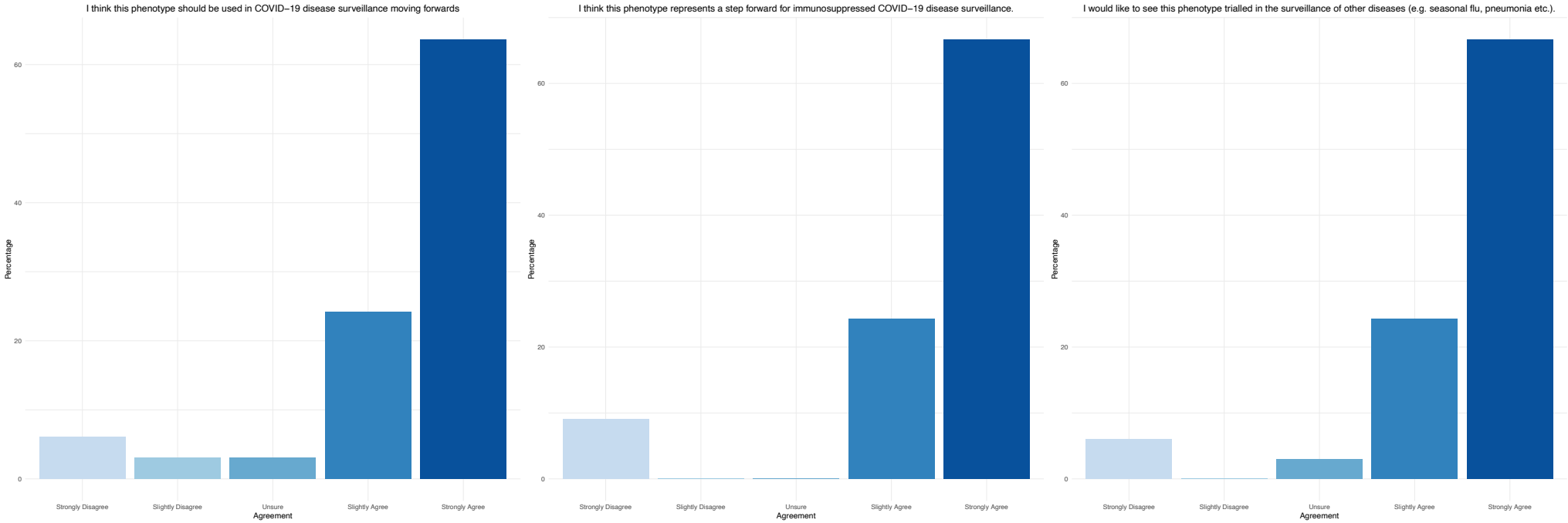
Table 4.18: Characteristics of the DESTINIES patient voting cohort

	Variable	n = 33
Sex	Male	6
	Female	26
	Other	1
Country	India	1
	United Kingdom	27
	USA	2
	Czech Republic	1
	Netherlands	1
	Switzerland	1
Immunosuppression	Autoimmune disease	16
	Cancer	11
	Nutritional deficiency/ malnutrition	2
	Transplantation	5
	Primary immunodeficiency	4
	Renal disease	1
	Rheumatological disease	7
	Other	2

Despite obtaining expressions of interest from all immunosuppressed subgroups incorporated in the DESTINIES phenotype, representatives from the HIV patient community did not return their completed feedback forms by the study deadline and did not participate in this work. Likewise, male patients were poorly represented in this exercise. Participants were primarily from the UK.

A bulleted summary of patient feedback and questions is provided in Appendix 27. Visualisations of their votes are provided in Figure 4.22 below with full tabulations also available in Appendix 27.

Figure 4.22: DESTINIES patient panel voting data



iii. Discussion:

Principal findings and their implications:

The DESTINIES Patient Panel webinar, '*Improving how we monitor COVID-19 spread and outcomes in the immunosuppressed',* successfully ratified the DESTINIES phenotype for ongoing use in national disease surveillance from the perspective of a relevant patient cohort. Overall, patients commended this research and expressed excitement that the interests of the immunosuppressed would be better centred in disease surveillance pathways. They expressed deep frustration with the scaling back of protections, centralised support and enhanced medical care for those shielding from COVID-19. Many were disturbed by the aggregated approaches to surveillance that preceded the DESTINIES phenotype and encouraged the doctoral candidate to continue dismantling the 'one size fits all' approaches to immunosuppressed care and disease prevention that such an evidence base engenders. Over 90% of patient panellists considered the DESTINIES phenotype an improvement to its predecessors. Over 90% agreed that it should be tested within other disease remits, including seasonal flu and pneumonia.

That said, approval was not unanimous: 88% of patients gave their assent to seeing this phenotype instituted as default. Certain patients expressed concerns that the evidence base produced by this tool might risk increasing barriers to key therapeutics rather than facilitating access. They also emphasised the need for careful and clear communication if making this work publicly available: without proper contextualisation, it would be easy to misinterpret the DESTINIES phenotype as a clinical decision-making tool and not a means of enhanced surveillance. This would risk causing undue alarm in patients. The absence of any mechanism to

prioritise the risks of patients with multiple conditions was criticised; so too was the absence of Mast Cell Activation Syndrome (MCAS) patients and cancers in remission. The accessibility of the presentation itself could also have been improved; patients recommended visuals be enlarged and a glossary of key terms and an accompanying fact sheet be produced.

Comparison to existing literature:

To the best of the doctoral candidate's knowledge, this work is the first to centre patient feedback when refining and ratifying a new method for disease surveillance. Previous work has successfully embedded patient reported outcomes [105] and direct self-report [106] into trial protocols, clinical care and, by extension, disease surveillance pathways [107; 108], but have never fielded their perspectives on the performance of surveillance itself. This is to its detriment. Patient self-report is a highly valuable source of information: indeed, in multiple instances, it has proven itself to be more accurate and sensitive than disease surveillance in isolation [109; 110]. Failing to give patients any influence over their own disease surveillance pathways is an oversight.

Patient panellists' concerns that others might misinterpret this research without ample contextualisation is also consistent with the literature. Disease surveillance is a specialist subject that is difficult to communicate to the public; the use of R0, a metric of viral reproduction, produced more confusion than coordination in the acute phase of the pandemic, for example [111]. The term surveillance is also highly loaded, and disease surveillance is not immune to politicisation [112] – recently revoked plans for an autism registry being a salient example [113]. With public health

discourse currently so susceptible to misinformation [114], this research must be brought into the public domain with extreme sensitivity, emphasising its pseudonymised nature and public service motive.

Finally, our panellists' welcoming of a more needs-based disease surveillance system is also consistent with existing literature: patient advocates have long-since championed this issue [115] and its prospective value for circumventing sparse trial data and improving equitable care [116].

Limitations:

This work was limited in the following ways. Firstly, it was unable to field the perspectives of all patients included in the DESTINIES phenotype. Despite registering for this work, HIV patient representatives did not attend the webinar or submit their perspectives and final vote via Google Form. This is a considerable loss to the ratification of the DESTINIES phenotype given that its positioning of Drug-managed HIV patients as a reference group to immunosuppressed cohorts. This exclusion is unique to the DESTINIES phenotype and would have benefitted from patient oversight.

Furthermore, patient panellists ratified the DESTINIES phenotype with preliminary outputs of its implementation in ORCHID-E. They did not have access to the full reporting outlined above. Worse still, the summary forest plots of raw and unadjusted data that were presented contained errors in their confidence intervals. Although this was not considered a fatal flaw of this work – IRR estimates remained stable – these

communicated greater accuracy in our unconditional Poisson modelling than was the eventual reality.

Moreover, our patient panellists' engagement with both the NIHR *People in Research* [98] portal and a range of advocacy or affinity groups indicates they possessed higher levels of scientific literacy than layman patients. This self-selection bias is inherent to patient engagement exercises, however, and is difficult to control for in practice.

Finally, the poor representation of male patients and the UK-centricity of this work were both detrimental to the external validity of results.

6. Chapter commentary:

Overall, this chapter has successfully demonstrated the value of better differentiating immunosuppressed COVID-19 outcomes in real-world data assets. Both our pilot and DESTINIES phenotype returned nuanced findings on the COVID-19 infection and vaccination experiences of specific immunosuppressed subgroups and agreed on a clear demarcation between extremely vulnerable immunosuppressed patients and, by contrast, those with only slightly elevated risk for severe outcomes. Higher resolution surveillance has proven to offer significantly greater value to policymakers and clinicians than aggregated counterparts. Moreover, our final output – the DESTINIES phenotype – is the first the doctoral candidate is aware of to have secured both expert and patient approval for ongoing use in disease surveillance.

However, the only thing worse than no surveillance is inaccurate surveillance. Although the diversity and scale of the exercises presented in this chapter are to be applauded, their limitations and resulting lapses in confidence must also be considered in turn.

Firstly, this chapter does not amount to clinical advice. Its conflicting evidence base and only partially validated nature makes this inappropriate. Patients, clinicians and policymakers must therefore not interpret these findings as predictive for ongoing COVID-19 risk or instructive for targeting scarce medical resources or enhanced care at this moment intime. This work is surveillance-specific and must always be communicated as such.

Secondly, this chapter does not use a consistent data source to audit candidate phenotypes for adult immunosuppression. The pilot phenotype was implemented in secondary-linked data (secondary care and serosurveillance) whereas the DESTINIES phenotype was trialled in survey data and operationalised in full within a primary care trusted research environment. This deeply affected the comparability of this chapter's outputs: at present, it is not possible to quantify the added value of the DESTINIES phenotype compared to its pilot predecessor, for example. However, it is likely that this phenotype will be trialled in these same secondary-linked UKHSA data assets soon.

Meanwhile, the absence of immunosuppressive medication variables from most experimental outputs is an established limitation of this work. Although this choice has been justified throughout this thesis, it has been detrimental to producing the

robust, needs-based surveillance this chapter aspired to. Our success in identifying the subgroups that appear to confer most COVID-19 risk for a patient (transplantation, haematological malignancy, primary immunodeficiency, chronic kidney disease and dialysis) provides no detail on how these risks are attenuated by medication regimens. Indeed, evidence from this chapter cannot be used to assess whether COVID-19 risk is diagnosis or medication-driven.

Finally, the historical nature and COVID-19 specificity of these implementation studies can be criticised. Although the DESTINIES phenotype is based on contemporary expert risk assessments, it has only been trialled in 2020-2023 inclusive data. It therefore cannot be certain the DESTINIES risk hierarchy remains relevant in 2025, the time of thesis submission. Likewise, this chapter does not assess the value of the DESTINIES phenotype for differentiating infections outcomes outside of COVID-19. These limitations cast doubt on both the internal and external validity of this work and must be immediately addressed. The concluding chapter outlines the incoming works that will aim to accomplish this.

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5

Discussion

1. Introduction:

Utilising a combination of literature review, international consensus building and real-world study, this thesis aimed to establish the immunosuppressed subgroups at greatest risk for severe COVID-19 infection outcomes. Additional considerations – notably vaccine effectiveness and adverse events of interest - were incorporated as part of this overall risk assessment over the course of this doctoral programme.

This chapter will summarise key thesis findings and the extent to which they address the central thesis objective. Echoing the narrative structure of its opening chapter, the implications of this thesis' evidence base for COVID-19 clinical management, vaccination and non-pharmaceutical intervention will be outlined in detail. Suggested improvements to current COVID-19 clinical workflows and public policies will be outlined and their relevance for broader disease remits considered. This thesis will close once strengths, weaknesses and prospective future directions for research have been catalogued in full.

2. Key findings:

The introduction of this thesis outlined ongoing uncertainties surrounding differential COVID-19 risk in the immunosuppressed and demonstrated how prevailing methods of collecting, analysing, interpreting and actioning immunosuppressed COVID-19 disease surveillance were inconsistent and overly one size fits all – underserving the

most vulnerable and over-restricting the lives of patients seen to present minimal excess risk for severe infection outcomes than the immunocompetent. Laying the foundation for the work to follow, this introduction signposted the prospective value of an internationally harmonised, digitally compatible and clinically meaningful method for segmenting this patient population in disease surveillance flows.

Chapter 2 successfully reviewed and meta-analysed all contemporary literature directly comparing the COVID-19 mortality of specific immunosuppressed subgroups with an immunocompetent control. The rapid scoping review that preceded this systematic exercise informed study design and provided early signals for COVID-19 risk gradients both between and within subgroups – gradients that were reproduced at higher resolution during meta-analysis. This intra-subgroup variance suggested that segmenting immunosuppressed surveillance exclusively by common clinical denominator would continue to erase clinically meaningful sub-trends in outcomes; more nuanced approaches had to be explored, with risk stratification offered as a potential solution. Likewise, failure to cleanly identify, extract and compare medication-specific COVID-19 mortality from available literature was our first indication that diagnostic and procedure-based extraction and differentiation of immunosuppressed data would prove more successful. Finally, the observed vulnerability of primary or genetic immunodeficiencies to COVID-19 at systematic review overruled rapid review risk profiling. The otherwise broad agreement between these two exercises was encouraging, however.

In its entirety, this chapter confirmed that COVID-19 mortality literature is substantive, detailed and heterogeneous enough to support COVID-19 risk

stratification across the entire immunosuppressed population. When only using medical literature to answer the central question posed by this thesis, transplantation and malignancy patients would be singled out as at critical risk for severe COVID-19 outcomes, with special emphasis placed on haemapoietic and haematological or metastasising patients, respectively. However, the absence of very rare or complex forms of immunosuppression from both literature reviews and discrepancies in international definitions for immunosuppression (and, thereby, non-immunosuppressed controls), affected the comprehensiveness of this work and our overall confidence in its reporting. International consensus building was required to address these limitations.

Chapter 3 was dedicated to this exercise. Bringing together 64 eminent figures in immunology, vaccinology and infectious disease, this eDelphi exercise surfaced and ratified an internationally aligned, digitally compatible and COVID-19 stratified means of identifying and segmenting the immunosuppressed in disease surveillance. Creating continuity with the exercises that preceded it, panellists were supplied with systematic review and meta-analysis data in their pre-read packs.

The DESTINIES phenotype offers two levels of resolution for segmentation: tripart risk banding and a ten-level hierarchy. This tool was approved for trial in real-world surveillance with 94% remaining panel consensus. This exercise also addressed longstanding disputes within the immunosuppressed medical literature, including certain variables that would reverse immunosuppressed status. Drug-managed HIV and cancer in remission were agreed as inappropriate for inclusion in an adult immunosuppressed phenotype for the express purpose of disease surveillance,

though with important caveats. Uncomfortable with it being designated an active control group, panellists agreed to see Drug-managed HIV positioned as an internal reference group: closer in demographic composition and vaccine uptake to the immunosuppressed than those not identified as immunosuppressed (essential for fair vaccine effectiveness comparisons), but not without clinical vulnerability.

There was near universal panel agreement that immunosuppression is poorly defined with COVID-19 care – including vaccination and the distribution of therapeutics - remaining overly one size fits all. There was near universal panel disagreement, however, that COVID-19 no longer poses a threat to this patient population and that this vulnerability is equally dispersed across the patient spectrum. Agreement was also more tenuous on the time conditionalities of immunosuppressive status, including treatment regimens (discontinued for more than 1 year or on medication for less than 6 months) – once again, important caveats were defined. Likewise, disagreement persisted for determining immunosuppression based on cancer stage or medication dose.

Panellists were also reticent to see the DESTINIES phenotype immediately applied to other disease domains or considered applicable in lower economic contexts; they agreed doing so would be an interesting intellectual exercise, but that the idiosyncrasies of COVID-19 infection and global health inequities prohibited this tool from being considered appropriate for general use. External validity must first be established in both these remits. Likewise, panellists were emphatic that this phenotype should not be used to inspire clinical decision-making or resource prioritisation until the cadence of its COVID-19 risk hierarchy had been replicated in

real-world data. Panellists especially regretted the absence of medications from this exercise, though understood the doctoral candidate's rationale for their omission.

Importantly, clinical consensus echoed the higher versus lower COVID-19 risk demarcation that was identified in rapid and systematic reviews – though with 'the messy middle' of immune mediated inflammatory disorders, chronic kidney and liver disorders and certain wider determinants of immunosuppression remaining difficult to risk categorise due to medication and comorbidity dependencies. When only using the eDelphi exercise to answer the central question posed by this thesis (inclusive of meta-analysis data, however), transplantation, haematological and distributed malignancy and primary immunodeficiencies, unmanaged acquired immunodeficiencies and underlying aberrant immunity would be singled out as at critical risk for severe COVID-19 outcomes. Solid tumours, Chronic kidney disease & dialysis, Systemic IMID conditions and asplenia and severe anaemia would be proposed as at moderate risk for severe COVID-19 outcomes. Meanwhile, Single site (or organ) IMID, Anatomical barrier defects and Wider determinants of immunosuppression would be considered as at lowest risk for severe COVID-19 outcomes within the patient spectrum. Drug-managed HIV results would tentatively be proposed as comparable to the general population and appropriate for use as baseline risk assessment. It remained to be seen whether these appraisals were replicated in real-world data, however, and whether this approach to segmenting immunosuppressed disease surveillance had the full endorsement of patients themselves. Chapter 4 hosted these concluding research activities, assessing pilot and DESTINIES phenotype validity and the patient acceptability of the latter.

Despite its notable limitations, rapid scoping review findings were successfully converted into a pilot phenotype for adult immunosuppression stratified by COVID-19 risk. When implemented into secondary-linked RSC dataflows, universal patterns of vaccine uptake across all immunosuppressed subgroups conflicted starkly with heterogeneity in severe COVID-19 outcomes. Vaccine waning was also universal. However, this phenotype's use of prescription variables significantly affected implementation and the accuracy of segmentation. Recently treated cancer and Immunosuppressives unrelated to cancer levels returned unreliable estimates of vaccine effectiveness, seroconversion and COVID-19 infection outcomes. The mutually exclusive and hierarchical nature of this pilot phenotype - as well as five-year determinations of immunosuppressed status - likely created cannibalisation between these two levels, with cancer patients diagnosed even a day before its dedicated window misallocated into Immunosuppressives unrelated to cancer.

Unconditional phenotype levels, those based on either standalone procedural or diagnostic codes, fared far better by comparison. Separate antibody-, TNCC- and cohort-based estimates of vaccine effectiveness were reported for Bone Marrow Compromised, Solid Organ Transplant and Immunodeficiency subgroups. Between group differences in TNCC and retrospective cohort estimates of vaccine effectiveness were erased when the immunosuppressed were handled as a risk binary; these results approached the non-immunosuppressed standard, providing an inappropriately reassuring and universalised view of immunosuppressed vaccine benefit.

Disaggregated analysis of immunosuppressed sera revealed higher concordance between patient record of COVID-19 infection and N antibody confirmation of previous infection than that of non-immunosuppressed counterparts. This is attributed to higher levels of asymptomatic infections amongst non-immunosuppressed patients and restricted access to testing. Although hampered by low sample sizes, differential analysis of s-antibody concentrations indicated especially poor seroconversion amongst solid organ transplant recipients – mapping onto elevated levels of critical infection outcomes in this group. Disparities in seroconversion between immunosuppressed subgroups and those without any record of immunosuppression were seen to resolve by the third dose, with no indication of non-seroconversion in any group by the fifth dose.

The operationalisation of the DESTINIES phenotype occurred in two stages: a pilot of IMID-related levels within COVID-19 infection and vaccination survey data (Systemic IMID, Single Organ IMID and a novel Overlap category for patients reporting diagnoses that spanned both categories) and its full operationalisation within ORCHID-E. The first exercise validated the DESTINIES Panel directive to distinguish between Systemic and Single-Organ forms of IMID: distinct patterns of COVID-19 symptoms, outcomes and vaccine side effects were observed between these categories, with greatest severity in Systemic and Overlap categories in both instances. Disaggregating symptom and adverse event data to individual reports also proved fruitful: Systemic and Overlap conditions returned increased incidences and wider ranging symptoms in both instances, though all IMID groups shared the same tendency towards inflammatory and autoimmune presentations (rash, muscle aches etc.). These were difficult to distinguish from underlying aetiologies; as a

result, the potential influence of condition flares could not be ruled out from these data. The unique influence of steroid medication over risk of COVID-19 hospitalisation in Single Organ IMID patients was also notable. Likewise, tentative evidence for reduced adverse events amongst IMID recipients of inactivated viral vaccines warrants further investigation. Beyond these idiosyncrasies, COVID-19 cases were consistently and significantly lower for IMID groups than general population controls – likely reflecting the increased preventative measures taken by, and on behalf of, these patients.

When operationalised in full, broadly speaking, the DESTINIES phenotype was borne out in real-world data. Observed gradients in COVID-19 infections (single, multiple, breakthrough) and severe 28-day outcomes mostly matched that anticipated by the phenotype's cadence, though with some notable discrepancies. For example, this linear relationship degraded when cohort data was matched and fully adjusted: incidence rates once again demarcated between extreme excess risk and elevated risk. Furthermore, 28-day cardiovascular outcomes were most concentrated amongst Chronic kidney disease & Dialysis patients with incidences amongst Single Organ IMID patients also seen to supersede their Systemic IMID counterparts – both findings that had not been anticipated by the DESTINIES exercise. Meanwhile the statistical significance of Drug-managed HIV patients' IRRs for certain severe COVID-19 outcomes compared to those without immunosuppression confirmed that this subgroup should not be positioned as an active control group.

The limitations of primary care data greatly affected this exercise and its ability to fully interrogate the DESTINIES phenotype. Low sample sizes for certain phenotype levels and severe 28-day COVID-19 outcomes proved difficult to model; IRR and associated 95% confidence interval estimates were either inaccurate or implausible as a result. This was especially the case after age-sex matching, full adjustment and during subgroup analyses. Extremely small sample sizes for Anatomical barrier defects and Transplantation subgroups indicates that these groups may need assimilating into adjacent risk categories for future replications of this work. Furthermore, time-linked health complications served as unreliable proxies for severe COVID-19 outcomes and, without access to death registries, IRs and IRRs reported for 28-day COVID-19 mortality were likely underestimates. Even still, some credible evidence was provided for year-on-year increases to COVID-19 infection and outcome IRRs and reversals with vaccine uptake. Disparities between immunosuppressed and immunocompetent COVID-19 mortality were at their highest amongst the most vaccinated, however.

Despite its limitations, the DESTINIES phenotype was well-received by our representative patient panel: 88% of respondents felt it should be instituted in COVID-19 disease surveillance going forwards, 91% agreed the phenotype represented a step forward for immunosuppressed COVID-19 disease surveillance and 91% voted to see it used to segment the surveillance of wider disease remits, including seasonal influenza, RSV and pneumonia.

When only using the outputs of the implementation studies summarised to answer the central question posed by this thesis, Transplantation, Haematological and

distributed malignancy and Primary immunodeficiencies, unmanaged acquired immunodeficiencies and underlying aberrant immunity and Chronic kidney disease & dialysis would be singled out as at greatest risk for severe COVID-19 outcomes. Remaining subgroups proved vulnerable to COVID-19, but this risk was greatly attenuated after controlling for demographic differences and vaccine uptake.

As a result of all the activities and results described, this thesis has produced a clinician and patient approved means of identifying and segmenting immunosuppressed patient data based on historical COVID-19 risk. The excess vulnerability of Risk Band 1 groups has been identified consistently and is of urgent clinical importance. The relative resilience of Risk Band 3 groups to COVID-19, especially Drug-managed HIV, should also be better recognised in disease surveillance and, subject to further validation, clinical guidelines.

3. Comparison to existing literature:

The findings just summarised have already been compared to existing literature on a chapter-by-chapter basis. However, additional considerations, corroborations and deviations are discussed below for completeness.

A wide variety of publications, related and unrelated to COVID-19 management, have expressed frustration at the absence of a universal definition of clinical immunosuppression [1] and its confusability with related terms [2]; this thesis now offers a clinician and patient approved candidate, confirming immunosuppression's non-synonymity with immunocompromised.

A justifiable criticism of this work, however, is its historical nature; all research activities bar the international clinical consensus building exercise curtailed their assessments of differential COVID-19 risk in the immunosuppressed to 2023. This omits outcomes of later variants and opens this work up to accusations of redundancy given the fast-paced and ongoing mutation of SARS-CoV-2; the weeks prior to thesis submission has seen the global spread of variant NB.1.8.1 pose new uncertainties, for example [3]. However, it has been gratifying to see key outputs of this thesis act as the foundation for go-forward exploration of COVID-19 and broader infections in the immunosuppressed. For example, beyond the immediate commentary and welcome critique of Moreno-Torres and colleagues (2024) [4], our systematic literature review and meta-analysis has informed more recent investigations by Iwu (2024) [5], Alsoubani & Chow (2025) [6] and Loubet et al (2025)[7]. Likewise, colleagues within the London School of Hygiene and Tropical Medicine (LSHTM) have successfully converted our pilot code list into a Clinical Practice Research Datalink (CPRD) format to assess whether immunosuppressed Shingrix uptake (prevention of herpes zoster) was universal and, if not, at least aligned with our initial risk hierarchy. This work will be published imminently.

Prescription variables are a notable absence from our phenotype. That said, studies that have successfully appraised COVID-19 outcomes by immunosuppressive medication status [8] have still struggled to consistently differentiate outcomes by the condition being treated and found no significant association between all drugs assessed (glucocorticoid, interleukin inhibitor, Janus kinase inhibitor, rituximab, tumour necrosis factor inhibitor, antimetabolites, Azathioprine, Calcineurin inhibitor, mycophenolic acid, cancer medications, checkpoint inhibitors, anthracycline, protein

kinase inhibitors) and in-hospital deaths bar rituximab usage in rheumatological and cancer patients (the only conditions reported). Moreover, long-term immunosuppression was associated with a reduced risk of invasive ventilation in propensity matched immunosuppressed and non-immunosuppressed cohorts. This suggests segmentation on a medication-specific basis might have proven less fruitful. Furthermore, it is reassuring that our difficulty segmenting immunosuppressed COVID-19 risk by medication history is shared by other groups attempting similar observational research; misclassification persisted even in US settings, where access to insurance claims data enables a higher degree of accuracy when assessing medication status, dose and time course [9]. Non-adherence to medications also cannot be confirmed by these data alone. Although the omission of medication variables is a major limitation of this work, these difficulties in even ideal circumstances further justifies our decision to produce a diagnosis and procedure-based phenotype for adult immunosuppression. The Mass Evaluation of Lateral flow immunOasseys for the Detection of SARS-CoV-2 antibodY responses in immunosuppressed people (MELODY) Study took this same tact, targeting those with solid organ transplants, blood cancers and autoimmune disease [10].

Encouragingly, the procedures and diagnoses identified as at greatest risk for severe COVID-19 by this work are aligned with the largest efforts in this remit: INvestigation oF cOvid-19 Risk among iMmunocompromised populations (INFORM) [11] and Emerging Populations and Outcomes associated with COVID-19-Health Conditions in the United States (EPOCH) [12]. Transplantation, haematological malignancy, primary immunodeficiency and renal disease patients were consistently flagged as at

greatest risk for hospitalisation and, in the US context, highest medical expenditure for their stay. The tentative evidence this thesis provides for especially impaired vaccine seroconversion in Solid Organ Transplantation patients was recently reiterated in a systematic review by Olivieri et al (2025)[13] but runs contrary to risk assessments made by Werbel et al (2023) [14].

Meanwhile this thesis' shifted COVID-19 risk appraisal for primary immunodeficiencies reflects the breadth of this population and diversity of associated infection outcomes; systematic review by Drzymalla and colleagues (2022)[15]. quantified this internal heterogeneity, identifying the immunodeficiencies with outcomes more comparable to the general population (complement deficiencies, MyD88 deficiency) versus those with idiosyncratic profiles, including prolonged infection (X-linked agammaglobulinemia, B-cell pathway defects). However, this work and its less detailed analogue by Bucciol and colleagues (2021) [16] confirmed an overall elevated risk profile that our DESTINIES phenotype is now right to acknowledge. Likewise, our initial failure to appropriately COVID-19 risk categorise patients with late-stage renal disease or receiving dialysis is not without precedent. These patients are commonly positioned as only at moderate risk for severe COVID-19 [17] - to their detriment. As recently argued by an INFORM Study spokesman, this is a view that needs urgent correction [18].

The diagnoses and procedures that failed to achieve consensus as either at higher or lower risk for severe COVID-19 risk– colloquially classed as 'the messy middle' – are frequently cited as hard to classify or context-dependent immunosuppressed [19]. Meanwhile, those identified as at lowest risk for severe COVID-19 are also

consistent with findings from wider research groups. For example, only advanced or untreated HIV were included in INFORM cohorts; treated HIV was excluded from even broadly defined criteria, presumably viewed as insufficiently immunosuppressed. That said, the choice to exclude cancer in remission from our COVID-19 risk hierarchy could be considered more controversial. The wider literature does not consistently discount cancer survivors from COVID-19 risk; indeed, work by Mangone et al (2021) early in the pandemic reported five times the incidence of COVID-19 related deaths in cancer survivors than those with no history of cancer, even after age-sex adjustment [20]. Given that the exclusion of cancer in remission from immunosuppressed COVID-19 disease surveillance was only ratified with marginal consensus from expert panellists (77%), was met with some resistance from patients themselves and was impossible to institute in primary care data, the DESTINIES phenotype should continue to extract patient records with any evidence of cancer, historical or otherwise, provided that it falls within the ten year window of assessment. This decision aligns with DESTINIES Panellists' refusal to rule out immunosuppression solely by cancer stage or medication dosage; such rules are too simplistic to do so accurately in all cases.

The expansiveness of the DESTINIES phenotype, especially its Wider determinants of immunosuppression category, is unique, but justified by the increasing prominence of social determinants of health (SDoH) in clinical research and associated policymaking [21]. Appraisals of COVID-19 risk by these SDoH factors have also spotlighted the role of inadequate nutritional intake as a key predictor for poor outcomes [22]. Our consideration of anatomical barrier defect patients'

immunological disadvantage for COVID-19 is also echoed in work by Walters et al (2023) [23].

To the best of the doctoral candidates' knowledge, this thesis is the only academic exercise that has sought out patient approval for changing a prevailing approach to disease surveillance. Given that such systems are generally taxpayer funded [24], this seems a major oversight.

4. Implications of research:

i. Implications for COVID-19 clinical management:

The present thesis offers considerable insight into the ways in which the clinical management of the immunosuppressed might be enhanced to promote better patient outcomes – in the COVID-19 remit and beyond. This section will present clinical workflow-based recommendations for infection prevention and response.

As specified in the introduction, in almost all cases, previous measures to prevent nosocomial COVID-19 infections have since been discontinued [25]. The evidence this thesis provides for the extreme vulnerability of certain tranches of the immunosuppressed to COVID-19 should inform their selective retention, however. For example, solid or haemopoietic transplant recipients, haematological malignancy patients and those managing late stage, renal disease, regular dialysis or primary immunodeficiencies may still benefit from segregated care. Practitioners coming into contact with these patients may be advised to continue to don PPE during consultations and follow enhanced disinfection protocols prior. Medical settings

should also closely monitor their own incidences of hospital-acquired illness, communicating significant changes to either invite or dissuade vulnerable patients from in-person attendance. At-home care should be explored during periods of especially high community or clinical transmission. To this end, announcements of increased government investment in telemedicine, virtual wards and remote monitoring technologies are welcome [26], though additional support must be provided for non-digital native patients or those without English as a first language.

While such enhanced precautionary measures are not tenable, or indeed advisable, for all those specified within the DESTINIES phenotype, all immunosuppressed patients should be empowered to request their clinicians mask or maintain social distance during consultations if it makes them feel safer. Recent work by Linsenmeyer and colleagues (2023) should affirm patients in this: almost half of the healthcare workers they surveyed admitted to some form of ‘sickness presenteeism’ – going to work when feeling unwell [27]. Likewise, the wider public should be made aware of the value of masking, practicing good hand hygiene and socially distancing for protecting these patients when utilising waiting rooms in clinical settings.

Meanwhile, public health awareness campaigns must ensure the immunosuppressed are up to date with COVID-19 vaccine schedules and familiar with the pre-exposure and post-exposure prophylactic treatment options they are entitled to, including key antiviral, monoclonal antibody and convalescent plasma therapies [28]. As the fast-waning efficacy of Evusheld [29] proved, purchasing decisions for prophylactics and therapeutics must also be made as quickly as possible to protect patients; INFORM analysis suggests over 14,500 hospitalisations

in England could have been prevented through the targeted release of prophylactic medications in conjunction with vaccination [30]. The real-time and segmented surveillance the DESTINIES phenotype affords could be used to better target these resources and persuade patients of their ongoing relevance. Growing evidence for contraindications in certain immunosuppressed patients must also be considered and communicated, however [31].

The combined evidence this thesis provides for reduced COVID-19 vaccine uptake, elevated COVID-19 caseloads and serious infection outcomes amongst Chronic kidney disease & Dialysis patients suggests that these patients may have been insufficiently prioritised during the pandemic. Clinical pathways may need to adapt to ensure this patient group are not omitted from the enhanced protections and accelerated triage that more conventional forms of immunosuppression are afforded. These patients' regular attendance in hospital or primary care settings make this especially important. Clinicians would be advised to ensure their patients are aware of their potential ongoing vulnerability to COVID-19 and to take additional precautions during consultations or care to reduce patient risk of hospital-acquired infection.

Accelerated triage into primary and secondary care should be retained for confirmed COVID-19 cases in the immunosuppressed. The highly variable symptomology of these patients [32] could see them underserved by triage tools designed for the general population; out of an abundance of caution, medical contact should therefore always be recommended. Instating point of care tests in primary care settings to discriminate between the overlapping symptomologies of COVID-19 and other

seasonal illnesses could support this process with added benefits for antimicrobial stewardship more generally [33].

These recommendations are equally applicable to protecting the immunosuppressed from seasonal or emerging illness [34]. The risk of novel threats to these patients, including recent re-emergences of vaccine preventable illnesses in certain contexts [35], could also be mitigated by these same enhanced clinical workflows.

ii. Implications for COVID-19 vaccination:

Overall, the evidence produced by this thesis provides clear proof of concept for the value of more targeted vaccination for clinical risk groups: despite universal roll-out of COVID-19 vaccine offerings for the immunosuppressed, subsequent vaccine effectiveness (measured through TNCC, seroconversion or breakthrough infection incidences) and adverse events of interest varied significantly within this patient population. Moving forward, a needs-based or more prescriptive approach to vaccination and boosting for the immunosuppressed is recommended – both in the COVID-19 remit and more broadly [36; 37]. This recommendation must be contextualised by what is actually feasible within nationalised healthcare, however. While the naissance of mRNA vaccination holds promise for more personalised forms of vaccination [38], the crudeness of prevailing approaches suggests this remains aspirational at present. Expanded needle sizes for patients with larger BMIs only came into common usage during the pandemic, for example [39]. However, differentiated dataflows – DESTINIES phenotype-directed or otherwise - can inform more needs-based approaches to COVID-19 vaccine scheduling, dosing, pacing or withholding when passive inoculation would be more suitable [37].

To facilitate this, it is essential that future vaccine development trials recruit immunosuppressed patients [40]. Government intervention and subsidy [41] may be necessary for establishing this as standard practice given the lack of immediate commercial incentive amongst pharmaceutical firms to target studies to rare or complex patient groups [42]. However, recent calls for a decentralised network of clinical trials for the immunosuppressed made by a consensus group convened by the Fred Hutchinson Cancer Center demonstrates the public and professional appetite for this work [43].

Immunosuppressed vaccine pharmacovigilance must also be enhanced to offer clinicians the real-time and high-resolution vaccine benefit-risk data needed for tailoring schedules to patient need. In line with our findings for the differential impacts of steroidal medications on COVID-19 infection and vaccination outcomes in these patients, collecting detailed data on the interactions between patient diagnoses, medications and vaccine effectiveness and safety is recommended. Investing in this surveillance, ideally incorporating direct patient feedback as per the COVAD study, is especially important in a broader context of vaccine politicisation and disinformation; as expanded upon elsewhere, vaccine hesitancy in high-risk patients will persist without targeted performance and safety reporting as well as radical patient involvement and transparency [44]. The growing popularity of value-based agreements between pharmaceutical firms and government purchasers also selects for products that offer more differentiated safety profiles – further justifying the costs associated with enhanced pharmacovigilance for industry [45]. However, concerted policy pressure is still needed to address the commercial disincentives of pharmaceutical companies to identify and report adverse effects of products,

especially within specific clinical subgroups [46; 47], and to encourage government agencies to act on this evidence.

Thesis reports of increased COVID-19 vaccine waning within the immunosuppressed and the resolution of non-seroconversion after multiple doses both suggest that booster campaigns hold value for these patients. Given dose-by-dose declines seen in immunosuppressed COVID-19 vaccine uptake [50], however, such data must be made widely known amongst the immunosuppressed, their clinicians and caregivers. Offering inoculation against COVID-19 alongside the seasonal influenza vaccine is one strategy to bolster adherence [51], however, this may be insufficient for year-round protection against infection amongst the immunosuppressed [52]. Further data is needed. This thesis has also highlighted the very real risk of vaccine failure within the immunosuppressed and, as mentioned, the need to better specify those who might benefit from passive immunisation products. Current clinical guidelines are extremely vague on this point at this moment in time [53]. If instituted as standard practice, the differentiated serosurveillance piloted by this thesis may inform this decision-making moving forwards.

At present, it is only possible to speculate how closely the COVID-19 risk hierarchy produced by this doctorate maps onto immunosuppressed infection and vaccine outcomes for other illnesses. That said, its layering of literature review, international consensus building, and real-world study could be replicated to better understand how immunosuppressed patients fare against additional infections and whether current vaccine products and policies are proportionate to need. This evidence-based enhancement of immunosuppressed disease surveillance and

pharmacovigilance is especially crucial in the current context of disease re-emergence. Mumps, measles and rubella (MMR) vaccine performance in the immunosuppressed must be carefully monitored if measles outbreaks become more commonplace, for example – booster doses may have to be recommended subject to this intelligence [54].

iii. Implications for COVID-19 non-pharmaceutical interventions:

The evidence this thesis presents for extreme historic vulnerability to COVID-19 amongst certain segments of the immunosuppressed population has direct implications for the mitigating behaviours these patients may wish to enact during periods of high disease transmission. However, the ability to invest in personal protection is a privilege; the recommendations that follow will require central subsidisation for those who would find them financially prohibitive. These recommendations also hold prospective value for mitigating infections beyond COVID-19 and can be considered domain-general.

It is essential that the clinically vulnerable and their caregivers are updated on the risk that COVID-19 presents to them. The discontinuation of accessible government reporting on disease transmission, hospitalisation and fatality rates jeopardises patients' ability to adjust their behaviours – reducing or increasing social contact with proportionality to risks posed [55]. Central dashboards are beneficial for those with this vested interest in monitoring COVID-19 transmission and should be reinstated; recent divestment from publicly available dataflows in the US is deeply concerning in this light [56; 57]. Failing this, clinical networks and relevant non-profit groups should be made aware of changing patterns in COVID-19 transmission to support their

respective patient populations to make the safest possible decisions for themselves. Now-defunct guides for friends and family members on the safe visitation of vulnerable loved ones should also be updated.

This is especially important for patients with chronic kidney disease. The evidence this thesis presents for surprisingly low vaccine uptake and disproportionate adverse infection outcomes amongst those with chronic kidney disease casts doubt on whether past awareness campaigns were sufficient for their protection. Indeed, work by Joslin and colleagues (2021) [58] established a sizable segment of this population who were unaware of their personal risk for COVID-19 or their need to shield during periods of high disease transmission and seek out vaccination when offered. The omission of chronic kidney disease from the WHO's updated target to reduce non-communicable disease by one-third by 2030 (citing only heart disease, stroke, cancer, diabetes and chronic lung disease) suggests this example of poor communication may not be an isolated incident [59]. Moving forwards, it is essential that resources be allocated to ensuring these patients, their caretakers and their clinicians are aware of their vulnerability to infection, COVID-19 or otherwise, and the prophylactic and therapeutic products they are eligible for.

The poor targeting of shielding notices in the acute phase of the pandemic may have been unnecessarily disruptive to the routine care and financial wellbeing of less at-risk patients [60] and had significant ramifications for public confidence in government mandates more broadly [61; 62]. As such, future shielding recommendations must be provably evidence-based where possible - reserved only for the patient groups at highest risk of severe disease outcomes. Those known to be at comparatively lower risk for disease, COVID-19 or otherwise, should be

encouraged and supported to re-engage with social and economic life. That said, the public health convention of overestimating risk in the face of a novel infection still holds: all patients identified as immunosuppressed via the DESTINIES phenotype would benefit from NPI advisories, including guidance on shielding or restricting social contact, in this specific circumstance.

The value of point of care testing (POCT) has not diminished since the end of the acute phase of the COVID-19 pandemic; these products facilitate safe visitation of the clinically vulnerable as well as effective clinical triage [63]. Subsidised access has since been discontinued, however, and the pricing of these products is subject to free market forces [64]. This discriminates against those without the disposable income needed for repeat purchasing. Moreover, the sensitivity and specificity of these products for newer variants of COVID-19 are no longer being regularly evaluated – public confidence in their results have been impacted as a result [65]. As such, it is recommended that government actors consider re-investing in needs-based POCT distribution – especially during periods of high disease transmission - and centralised research efforts to monitor their ongoing effectiveness [63]. Maintaining COVID-19 detection as a public health priority has the added benefit of incentivising device manufacturers to reformulate reagents for products' ongoing accuracy.

Instructions given to work from home during the acute phase of the pandemic were especially suited to the immunosuppressed [66]; indeed, the ease and speed by which such arrangements were made were received with some frustration amongst those that had long-since advocated for hybrid working models to better

accommodate the clinically vulnerable [67]. Although imperfect for all sectors, the paradigm shift from office-based productivity provided vital proof of concept for more flexible working arrangements moving forwards. This inclusivity has value for those managing childcare, dependents and long-term conditions and should not be scaled back now the acute phase of the pandemic is over. Subject to the requirements of the role, employment law and workers protections should aim to codify against discrimination on the basis of remote working requests – especially amongst those whose medical status demands it. Increasing pressures upon employees to return to the office must also be justified by a job description which necessitates on-site work.

Public confidence in the value of mask wearing must also be restored. Inconsistent messaging during the pandemic, most notably in the USA where the public purchasing of masks was actively discouraged during initial personal protective equipment (PPE) shortages, has sowed widespread confusion as to how, when and where mask wearing is advisable or efficacious [68]. Encouraging mask wearing in clinical settings – especially amongst those symptomatic for respiratory infections – and within crowded public spaces during peak periods of disease circulation are valuable means of curbing nosocomial and community transmission respectively. Socially normalising these behaviours, incorporating them into general personal hygiene, will be key for their depoliticisation and retention. That said, PPE must still be stockpiled centrally for distribution to healthcare workers and the clinically vulnerable in future public health emergencies. The shortages that characterised the early phases of the COVID-19 pandemic came at the expense of the taxpayer with emergency orders vulnerable to price gouging and fulfilment with products that later proved faulty [69].

Overall, the confluence of NPIs that were stood up to curb COVID-19 transmission still hold significant value for protecting the clinically at risk [70]. Their divestment is concerning. Selective reinstatement is recommended to offset the 'Quademic' winter pressures of COVID-19, seasonal influenza, RSV and norovirus that are at risk of becoming a new normal otherwise [71]. However, not all NPIs are made equal and a packaged approach to implementation – where multiple interventions are stood up in unison – is not financially sustainable for the long term. Instead, historical investment and infection data must be interrogated to identify the individual interventions that conferred the most protection over the clinically vulnerable and the timepoints at which they provided most value for patients and the public purse alike. For example, evidence from the Royal Society suggests investments in NPIs are most successful at the first phases of disease emergence or resurgence [72]. Establishing international protocols for harmonising NPI investments and collecting data on their individual effectiveness within specific communities will be key for optimising the population health and economic returns of NPIs in future public health emergencies.

5. Strengths and weaknesses of research:

This work constitutes an original and valuable contribution to the field of primary care. To the best of the doctoral candidate's knowledge, it is the first to pursue a comprehensive, internationally harmonised and digitally compatible approach to immunosuppressed disease surveillance. This surpasses previous efforts that have subdivided and surveilled immunosuppression without considering machine-readability or securing international consensus - including the common clinical denominator and net score of immunosuppression approaches outlined in the opening chapter.

As per Comparison to existing literature sections, the congruence of thesis findings with largescale and longitudinal investigations of a similar nature is reassuring. However, by assessing COVID-19 risk from such a diverse range of perspectives and data sources (primary care records, secondary care records, vaccine registries, serosurveillance, patient surveys and clinical consensus), this work sets itself apart from contemporaries. The consistency of highest and lowest risk subgroups across all these exercises, with some notable adjustments for primary immunodeficiencies, renal disease and cancer in remission, is a major strength of this work.

As a collective, the systematic literature review and meta-analysis, eDelphi study and original, real-world research just presented address prevailing uncertainties in the COVID-19 infection and the vaccine experiences of the immunosuppressed and resolve long-standing disputes in the immunosuppressed literature. Its wider policy potential has also just been catalogued and its scale - attracting international support and interrogating nationally representative datasets – as well as the range and calibre of expertise it has benefited from lends weight to the final recommendations specified. Likewise, the number of prestigious publications this work has accumulated only further underscores its originality, scientific rigour and real-world applicability.

Indeed, the UK Joint Committee of Vaccination and Immunisation (JCVI) has already utilised thesis outputs to inform COVID-19 care for the immunosuppressed, most notably the DESTINIES manuscript and pilot phenotype outputs. Likewise, collaborators at the London School of Hygiene and Tropical Medicine (LSHTM) have successfully implemented the pilot phenotype within their own dataflows (Clinical

Practice Research Database; CPRD) and multiple Consortium members have expressed an interest in implementing the full DESTINIES phenotype within their respective institutions' surveillance systems. To facilitate this, the valueset that codified the DESTINIES phenotype for SNOMED-CT compliant surveillance systems has been made freely available on the DESTINIES study website [73]. Finally, following a successful patient engagement seminar, this work is now being championed by Forgotten Lives UK [74] and will support key stakeholders within the WHO and the UK All Party Parliamentary Group on Groups Vulnerable to Pandemics (GVP) [75] to centre the immunosuppressed within the pandemic preparedness agenda.

Although still in its preliminary stages, partial and full operationalisation of the DESTINIES phenotype have already returned actionable intelligence about distinct trends in COVID-19 infection and vaccine outcomes between immunosuppressed subgroups. While it remains to be seen whether these COVID-19 specific learnings are continually borne out in real-world data or applicable to other disease domains, this evidence base creates a clear proof of concept for risk stratifying immunosuppressed surveillance as standard. This work's spotlight on the elevated cardiovascular risks of renal or dialysis patients infected with COVID-19 as well as the differential predictive value of steroidal medication for hospitalisation from COVID-19 in single organ versus systemic IMID conditions are both demonstrative of the nuance such segmented surveillance can provide. Likewise, maintaining highest resolution surveillance on those historically at greatest risk for severe COVID-19 outcomes promotes vigilance against disease mutation or waning, ongoing clinical benefit-risk assessment and, by extension of both, needs-based prioritisation of

scarce medical resources (monoclonal antibodies, convalescent plasma, booster vaccine doses, next-generation therapeutics etc.). Aggregated surveillance or that selecting for dominant or common clinical categories, is not fit for service in any of these regards. Most importantly, targeted intelligence can bolster patient confidence in their disease prevention and response plans.

The value of this cannot be understated: without clarity on their vulnerability to COVID-19, many immunosuppressed patients still decide to remain socially isolated. Recent surveying by the Association of Clinical Psychologists (ACP) UK [76] found 95% of a sample of 471 immunosuppressed patients were continuing to lead restricted (63%) or fully shielded (32%) lives; these individuals experience disproportionate levels of anxiety, depression, work restriction and financial hardship. But these outcomes are not restricted to patients themselves: 93% of a corresponding sample of 129 family members were also living highly restricted or fully shielded lives to protect the health of their relative. While the work presented in this thesis is not meant to direct clinical care or medical prioritisation, the high-resolution surveillance it offers could help ensure that, in future, patients can make more informed choices about the decision to shield and are more confident in planning their return to normal social activity.

Finally, as a body of work that aims to promote the interests of the immunosuppressed, it was integral to the doctoral candidate that patients themselves be aware of thesis activities, their results and give their full endorsement to its future intentions. Closing this doctoral programme with a patient engagement seminar gave patients the final word on DESTINIES phenotype structure and

adoption and, to the best of our knowledge, made this resource the first of its kind to secure both expert and patient approval. This is of credit to this thesis.

Throughout this thesis, the doctoral candidate has gone to great effort to declare the limitations of this work and key areas for improvement. However, these appraisals have not been made of the thesis as a body of work; for completeness, this will be provided below.

It could be argued that attempting to assess the variability of COVID-19 risk across the immunosuppressed patient spectrum without incorporating medication variables amounts to a job half finished. Indeed, entire definitions of immunosuppression are given over to the medication classes that would temporarily suppress normal immune functioning [77]. Despite best efforts, the early exercises of this doctorate established how problematic phenotyping with prescription codes and conditionalities would prove. Out of an abundance of caution, the decision was made to exclude these variables from our hierarchical sort rather than risk inaccuracies at implementation. This is detrimental to the clinical rigour of this work and limits our ability to answer the central question set: we cannot answer which medication classes confer the most COVID-19 risk on immunosuppressed subgroups, whether this risk is evenly distributed across the patient spectrum and whether it can be offset by dose reductions or discontinuation. Moreover, we cannot assess how much of the COVID-19 risk or resilience we have identified in the immunosuppressed is attributable to difference in diagnosis or its associated medication class. Other research groups exploring these questions have proven more successful: observational study by the INFORM group delineates severe COVID-19 outcomes

between corticosteroids (high-dose vs long-dose), B-cell therapy (occurring less than 12 months ago), anti-rejection therapies, systemic anti-cancer therapy (occurring less than 6 months ago, between 6 and 12 months ago, and greater than 12 months ago), alkylating agents, antimetabolites and TNF blockers [11]. Here, medications were seen to have their own gradients of impact - consistent with our own attempt at literature reviewing mortality risk across medication classes. Recency of treatment was also seen to be especially influential on patient vulnerability. It is of note that INFORM study members did not attempt run sensitivity or subgroup analysis between treated and untreated study populations to establish medication-specific risks. The interpretability of their medication data was also limited due to low sample sizes for certain medication groups.

Although this thesis represents a considerable step forward from the aggregated approach to immunosuppressed disease surveillance that preceded it [78], segmentation by subgroup remains crude and divorced from clinical reality. Risk is not as clean cut as the DESTINIES phenotype would infer. Beyond its omission of medication variables, phenotype levels' mutual exclusivity completely erases comorbidity or demographic information – most notably age - that would, in practice, create additional mobility between risk levels. Likewise, although DESTINIES rankings were contemporaneous (late 2024), they were informed by the previous clinical encounters of panellists and may correspond to the go-forward risks of an immunosuppressed population that is no longer COVID-19 naïve. Furthermore, static phenotype assignments conflict with the dynamic nature of immunosuppression; while our implementation studies went to great lengths to capture and censor patient transitions from immunocompetence to immunosuppression, we were unable to

attempt the reverse. As borne out in the overlapping confidence intervals of our incidence rate ratio reporting, there is still more to do to see the DESTINIES phenotype offer a more precise, adaptable and sophisticated means of COVID-19 risk assessing the immunosuppressed population.

Writing from the vantage of early 2025, some may criticise this thesis for its focus on COVID-19, a disease considered by many as a historical concern. While the doctoral candidate has gone to great lengths to emphasise the ongoing vulnerability of the immunosuppressed to COVID-19 (a statement that also secured consensus agreement from our international expert panel), the policy potential of this work could be undermined by its singular focus on a disease and vaccine course that are both highly politically charged and increasingly deprioritised and divested from. As made plainest by a US Health and Human Services (HHS) spokesman: *"The COVID-19 pandemic is over, and HHS will no longer waste billions of taxpayer dollars responding to a non-existent pandemic that America moved on from years ago"* [79]. Failing to establish the performance of the DESTINIES phenotype for other infectious diseases or vaccine types fell out of the scope of this doctoral course but should be attempted as soon as possible to demonstrate its broader value. Likewise, the ongoing accuracy of the DESTINIES COVID-19 risk hierarchy should be continually assessed; our final implementation could only evaluate its performance in 2020-2023 inclusive data and novel therapeutics, booster doses or even disease variants may shift current rankings substantially. How DESTINIES fares in a no longer COVID-19 naïve immunosuppressed population remains uncertain.

This thesis also only assesses the varied impact of immunosuppression on COVID-19 outcomes; it does not investigate the converse relationship despite increasing evidence for novel-onset autoimmunity post-infection [80; 81; 82]. Indeed, conversion to Long COVID – a syndrome characterised by immune dysregulation – is handled in this thesis as a COVID-19 outcome to be differentiated by pre-existing immunosuppressed diagnoses and not as an immunosuppressed diagnosis in its own right. Although post-viral sequalae and syndromes are far from unique to COVID-19 [83], the hyperinflammatory nature of its severe manifestations (characterised by 'cytokine storms' and other maladaptive immune responses [84]) combined with the infection's global burden makes failing to control for this bidirectional relationship between infection and immunosuppression especially confounding. This may further undermine the generalisability of the DESTINIES phenotype to infections without these second order immunosuppressive effects.

The Euro- or western-centricity of this work is also to its detriment. Research was primarily conducted in a UK environment, allowing for inferences about drug-management – especially in the context of HIV – that are impossible in other parts of the world. Although the DESTINIES Consortium initially contained representation from the African continent, these panellists withdrew before final ratification of the DESTINIES phenotype. This is a great loss to external validity. Furthermore, this work demands a high degree of digital maturity to be replicated; the accuracy of the DESTINIES phenotype would no doubt be severely hampered if applied in contexts with only inaccurate or partial medical records. The inflated disparities our systematic review identified between immunosuppressed and immunocompetent COVID-19

mortality in lower economic contexts is testament to the importance of testing our phenotype's rigour internationally.

The DESTINIES phenotype's holistic interpretation of immunosuppression is valuable for emphasising the scale of community vulnerability and the importance of prioritising immunosuppressed interests in policymaking; however, it is not economically tenable to enhance medical care for all those identified as immunosuppressed through this means. As such, this phenotype may produce an evidence base that is only partially actionable. This thesis also, at present, offers no advice on how this evidence base should inform clinical decision-making; specifically, the thresholds for severe COVID-19 events or adverse vaccine side effects within each subgroup that would warrant intervention. This is in-part due to the preliminary nature of this work and the ongoing inaccuracies or limitations of its implementation in real-world data. Our inability to test the validity of the DESTINIES phenotype within secondary-linked data greatly affected our confidence in final reporting, for example. These issues must be addressed, and our final phenotype updated and refined, before any translational strategy can be produced.

Finally, despite best efforts to reiterate the surveillance-specific nature of this work, the patients it aims to support easily, and understandably, confused its COVID-19 risk hierarchy with a clinical decision-making tool. Without careful explanation, this created some distress amongst those identified as at relatively lower risk for severe COVID-19 outcomes; these patients had already experienced considerable difficulty in obtaining booster vaccines or prophylactic treatments and expressed concern that this work would increase, not reduce, barriers to care. More patient engagement

efforts are needed before this work should be taken up and promoted by the international public health agencies that were involved with its development; researchers must work with patients themselves to find the best language to discuss this work's intentions, limitations and disease surveillance-specificity.

6. Future directions:

To move forward successfully, the limitations just specified must be fully addressed. This is the doctoral candidate's priority, and the following actions have been taken to see this accomplished in a timely manner. Firstly, Forgotten Lives UK [74] have agreed to champion the DESTINIES phenotype and has connected the doctoral candidate to their patient membership to ensure all messaging about this tool is patient centred. Secondly, several members of the DESTINIES Consortium have agreed to test the international validity of the refined phenotype in their own dataflows; some have also committed to promoting this tool within the vaccine decision-making groups they are part of to assess its value for segmenting immunosuppressed benefit-risk for other vaccine candidates and vaccine-preventable illnesses (RSV, seasonal influenza, measles etc.). Collectively, these activities will go some distance to addressing criticisms of this work's external validity (internationally and across disease and vaccine domains).

Countering criticisms of this work's omission of medication variables will likely prove more difficult, however. It is recommended that the entire scope of this thesis – spanning systematic literature review, international consensus building and real-world observational study – be replicated to establish the COVID-19 risks of different immunosuppressive medication classes. Once completed, these data, and resultant

medication-specific COVID-19 risk hierarchy, could interface with the DESTINIES phenotype – possibly acting as a second axis for overall COVID-19 risk segmentation. Secondary-linked disease surveillance data should also be differentiated by treated and untreated immunosuppressed subgroups – ideally with subgroup analysis by treatment class - to assess if medications confer any additional risk or, alternatively, play a protective role over COVID-19 outcomes. The doctoral candidate has been brokering collaborations with other major UK immunosuppressed initiatives (OCTAVE [85], INFORM [11] and, most recently, the Stratification of Clinically Vulnerable People for COVID-19 Risk Using Antibody Testing [STRAVINSKY] Study [86]) to attempt this work in the near future.

Likewise, this work's failure to incorporate post-COVID immunosuppression - including Long COVID, Type 1 Diabetes and other forms of autoimmunity – requires redress. At present, such eventualities - specifically Long COVID - are handled as an outcome of interest and not a constituent of our population of interest. Given that this subgroup shows substantial evidence of immune dysregulation [87], are underrepresented in clinical research (initial COVID-19 vaccine trials often excluded all those with a history of infection, for example [88]) and continue to experience significant uncertainties as to their specific risks of COVID-19 reinfection [89] and vaccine benefit-risk [90], any replications of future iterations of this work would do well to build clinical consensus on the inclusion of post-COVID syndromes in immunosuppressed surveillance. This was advocated for strongly by several members of the DESTINIES Consortium, though will likely present challenges in practice due to the extreme heterogeneity of Long COVID clinical presentations.

Beyond these more immediate concerns, the doctoral candidate is exploring more expansive programmes of work within the same immunosuppressed disease surveillance and precision vaccine benefit-risk remits of this thesis. For example, a collaboration with the aforementioned ImmunOptimize initiative [43] has been explored to assess whether the research presented here provides sufficient evidence to justify more targeted and decentralised clinical trials for this population – or at least those identified as most susceptible to poor vaccine response and/or disproportionate adverse events. The doctoral candidate is using DESTINIES Consortium connections to this initiative and her wider network within pharmaceutical leadership to develop the feasibility tests and patient engagement exercises needed to confirm the profitability and popularity of such a targeted research and development pathway. The doctoral candidate has also been exploring whether DESTINIES-segmented disease surveillance and pharmacovigilance dataflows be converted into an open access platform. Now called 'VaxSEEN' [91], such an initiative hopes to provide an open access platform for pharmaceutical stakeholders to assess the post-marketing performance of key prophylactics and offer health agencies the real-time information needed to adjust public policy and clinical recommendations to changes reported in the vaccine benefit-risk profiles of these patients.

Finally, the doctoral candidate is excited to explore the prospective value of artificial intelligence (AI) for enhancing the disease surveillance and clinical care of the immunosuppressed. The proliferation of AI technologies, especially large language models and sophisticated natural language processing, coincided with this doctoral

programme [92]. However, there was insufficient time to apply for the necessary ethical permissions to conduct AI-enabled extraction or manipulation of our patient data, though this would have produced valuable opportunities for a more inductive approach to immunosuppressed COVID-19 risk assessment than the deductive, pre-categorised approach of operationalising risk-stratified phenotypes that was attempted. The accuracy of the latter is dependent on the manual identification and application of pre-specified diagnostic, procedural and (in our pilot phenotype) prescription codes – an approach that could be criticised for confirmation bias and remains highly prone to inaccuracy, inefficiency and incompleteness. In future, similar work will be expedited as medical codification is automated, cohorts or risk-assessments are defined and updated in real-time, and complex extraction queries are executed through simple prompting. Nevertheless, the inherently retrospective nature of artificial intelligence may see the services, products and clinical pathways it claims to enhance underperform for complex or rare patients in the immunosuppressed spectrum [93]. This would perpetuate, not mitigate, the inverse care law [94]. As such, the doctoral candidate intends to dedicate the next phase of her career to advocating for greater immunosuppressed representation in the development of clinical AI as well as auditing its value for these patients during deployment.

7. Conclusion:

Based on the systematic review, meta-analysis, international clinical and patient consensus building, and real-world observational studies enclosed, this doctoral thesis has identified the following immunosuppressed subgroups as at historically greatest risk for severe COVID-19 outcomes: Transplantation, Haematological or

metastasising cancer, Primary immunodeficiency, Advanced chronic kidney disease and Dialysis patients. Conversely, the following subgroups were identified as at historically lowest risk for severe COVID-19 outcomes: Single organ IMID, Anatomical barrier defects, Wider determinants of immunosuppression and Drug-managed HIV.

Global efforts to prioritise the wellbeing of the immunosuppressed during the COVID-19 pandemic were commendable, but the homogenised approaches to clinical care, vaccination and non-pharmaceutical intervention this thesis outlined inadvertently underserved the needs of the most at-risk and over-constrained the lives of the comparatively more resilient. As a body of work, this thesis therefore makes a resounding case for monitoring, managing and vaccinating the immunosuppressed in a more targeted and needs-based manner and offers a new system for disease surveillance that can evidence these ambitions going forward - the DESTINIES phenotype. While its findings are not yet clinically instructive or generalisable to other disease domains, they are testament to the potential of more personalised forms of care for the immunosuppressed and serve as important first steps towards addressing their hitherto poor representation in clinical trials and disease surveillance.

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