Supplemental materials

Table of Contents

Supplement 1. Data Sources

The following national datasets in England, each accessible through National Health Service (NHS) Digital, were included in this study:

- **General Practice Extraction Service Data for Pandemic Planning and Research (GDPPR):** Central collection of primary care data for COVID-19-related purposes that includes patient characteristics, diagnoses, symptoms, signs, prescriptions, referrals, immunisations, behavioural factors, and tests. GDPPR data were extracted fortnightly.
- **COVID-19 Second Generation Surveillance System (SGSS) from Pillar 1 and Pillar 2:** Includes polymerase chain reaction (PCR) testing data from Pillar 1 (i.e., swab testing for those with a clinical need and healthcare workers, if analysed by Public Health England [PHE] laboratories or NHS hospitals), and Pillar 2 (i.e., swab testing for the broader community-dwelling population) in England. Information is included for all tested individuals regardless of outcome (i.e., positive or negative), as well as the reason for PCR testing and date of symptom onset (if symptomatic). Data were provided daily to NHS Digital.
- **COVID-19 Vaccination Status Data:** A database with records of individual vaccination events across England, including details on vaccinated individuals and vaccine batch information (e.g., date of vaccine, vaccine type)
- **COVID-19 Hospitalisation in England Surveillance System (CHESS)**: COVID-19 hospitalisation data, which include information on comorbidities, laboratory results, medications administered, and in-hospital use of mechanical ventilation. CHESS data are collected daily.
- **Hospital Episode Statistics (HES)**: Includes more than 1 billion records of patients attending accident and emergency (A&E) units, admitted to hospital for treatment, or attending outpatient clinics at NHS hospitals across England. HES data were available from 4 datasets: HES admitted patient care (APC), HES adult critical care (ACC), HES outpatient (OP), and HES A&E. There was a change in the provision of the A&E dataset; from 2019 to 2020 onward, the Emergency Care Data Set (ECDS) was requested instead of the A&E dataset. For hospital admissions, information on reason for admission using International Classification of Diseases, 10th Revision (ICD-10) codes are available, as are corresponding dates of admission/discharge and records of all interventions or surgical procedures (Office of Population Censuses and Surveys [OPCS]-4 codes) performed in hospitals. For appointments at outpatient clinics in NHS hospitals, information available includes, among other items, type of specialist visited, diagnoses recorded (ICD-10 codes) during the visit, source of referral, and waiting time between referral and visit. However, information on medications received or prescribed in secondary care settings was not available. HES data were updated monthly within NHS Digital.
- **NHS Business Service Authority (BSA)**: This dataset contains information on all medications dispensed by community pharmacies, including the actual cost paid for the dispensed medicine(s). Community dispensing data are updated monthly, with a lag of 7 to eleven weeks relative to receipt of information from the pharmacies.
- **Civil Registration (deaths)**: Death data are maintained by NHS Digital and are updated weekly, with relevant information obtained from the Office of National Statistics (ONS), including date, place, and certificated cause(s) of death.
- **Personal Demographics Service (PDS):** This is the master demographics database for the NHS in England, Wales, and the Isle of Man. It is the primary source of information for patients' NHS number, name, address, and date of birth. It does not hold any clinical information. The master database contains approximately 74 million patient records. Records are created for newborns or when a new patient makes contact with an NHS service, primarily by registering with a GP practice, but also through accessing A&E services or hospital visits. NHS Digital used this dataset to identify patients who were alive as of 1 January 2022 and prepare the data extract. The PDS dataset was used solely for patient selection by NHS Digital.

Supplement 2. Comorbidities identified in the study population

Clinical characteristics	Codes or descriptions
Key immunocompromised groups	
Primary immunodeficiency	ICD-10 codes: D80.x, D81.x, D82.x, D83.x, D84.x, D89.x, D71; and SNOMED codes
Secondary immunodeficiency	OPCS codes: X89.1 – X89.5, X89.8, X89.9; and Dictionary of medicines and devices (dm+d) codes for immunosuppressive medications
High-dose, long-term moderate dose corticosteroids treatment	dm+d codes for corticosteroids
End-stage kidney disease or dialysis	ICD-10 codes: N18.5, Z99.2, Y84.1, Z49.1, Z49.2; OPCS codes: X40.x; and SNOMED codes
Organ transplants in the last five years	ICD-10 codes: Z94.0, Z94.1, Z94.2, Z94.3, Z94.4, Z94.5, Z94.6, Z94.9, T86.x and OPC and SNOMED codes
Stem cell transplants	ICD-10 code: T86.0; OPC codes:X33.6, W34.x, W99.x, X33.4, X33.5; and SNOMED codes
Solid tumours in the last five years	ICD-10 codes: C00 – C26, C30-C34, C37-C41, C43, C45-C80; SNOMED codes
Haematological malignancies in the last five years	ICD-10 codes: C81-C86; C88, C90-C97, D45; and SNOMED codes
HIV/AIDS	ICD-10 codes: B20.x, B21.x, B22.x, B23.x, B24.x; and SNOMED codes
Non-immunocompromised-related comorbidities	
Diabetes	ICD-10 codes: E10.x, E11.x; and SNOMED codes
Current or former smoker	SNOMED codes
Down's syndrome	ICD-10 codes: Q90.x, H19.8; and SNOMED codes
Sickle cell disease	ICD-10 codes: D57.x; and SNOMED codes
Thalassemia	ICD-10 codes: D56.x, D57.2; and SNOMED codes
Multiple sclerosis	ICD-10 codes: G35.x; and SNOMED codes
Motor neuron disease	ICD-10 codes: G12.2.; and SNOMED codes
Myasthenia gravis	ICD-10 codes: G70.0.; and SNOMED codes
Huntington's disease	ICD-10 codes: G710.x, F02.2; and SNOMED codes
Chronic heart disease	ICD-10 codes: I11.0, I13.0, I13.2, I21.x, I22.x, I23.x, I26.x, I42.x, I50.x, I63.x, I70.x, I71.x, I72.x, I73.x, I74.x, I77.x, I80.x, I81.x, I82.x ; and SNOMED codes
Cerebrovascular disease	ICD-10 codes: G45.x, G46.x, I60.x-I69.x; and SNOMED codes
Chronic liver disease	ICD-10 codes: B18.x, K70.1-K70.3, K71.0, K71.3, K71.4, K71.5, K71.7, K72.1, K73.x, K74.x, K76.0, K76.1, K76.6, K76.7, Q44.6; and SNOMED codes
Chronic lung disease	ICD-10 codes: J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3; and SNOMED codes
Pulmonary hypertension	ICD-10 codes:I27.0, I27.2; and SNOMED codes
Cystic fibrosis	ICD-10 codes: E84.x, P75; and SNOMED codes

Codes were identified in GDPPR and HES APC

Supplement 3. Immunosuppression or immunodeficiency definitions

Broadly defined immunocompromised individuals	Stringently defined immunocompromised individuals
Individuals with primary immunodeficiency	Individuals with moderate or severe primary immunodeficiency (i.e., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)
Individuals receiving immunosuppressive therapy[ies]	Individuals with active treatment with alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, TNF blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)
Individuals who have received a solid-organ or islet transplant, not including corneal transplants	Organ Transplant: Individuals who have received 1) a recent solid-organ transplant (not including corneal transplants) or islet transplant; or 2) a solid-organ transplant or islet transplant at any time and were also receiving immunosuppressive treatment; or 3) a solid-organ transplant or islet transplant at any time and with evidence of chronic graft versus host disease
Individuals who have received a stem cell transplant in the last 2 years	Individuals who have received a recent or haematopoietic stem cell transplant within the 2 years prior to 1 September 2020; or a haematopoietic stem cell transplant within 2 years and receiving immunosuppressive treatment; or 3) a haematopoietic stem cell transplant within 2 years with evidence of chronic graft versus host disease
Individuals with end-stage kidney disease	None
Individuals with evidence of solid tumour[s] in the 5-year baseline period classified into the following mutually exclusive groups based on the timing of cancer treatment: 0-6m; 6-12m; >12m	Individuals with evidence of solid tumour[s] in the 5-year baseline period with active treatment in the 6 months prior to 1 January 2022
Individuals with evidence of haematological malignancy[ies] in the 5-year baseline period classified into the following mutually exclusive groups based on the timing of cancer treatment: 0-6m; 6-12m; >12m	Individuals with evidence of haematological malignancy[ies] associated with poor responses to COVID-19 vaccines regardless of current treatment status (i.e., chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, multiple myeloma, acute leukaemia)
• Individuals who received high-dose corticosteroids (equivalent to ≥20 mg prednisolone per day) for more than 10 days in the month prior to 1 September 2020 • Individuals with chronic immune-mediated inflammatory disease and had received long-term moderate dose corticosteroids (equivalent to 10 mg prednisolone per day for more than 4 weeks) in the 3 months prior to 1 September 2020 • Individuals with high-dose steroids (equivalent to >40 mg prednisolone per day for more than a week) for any reason in the month prior to 1 September 2020.	Individuals on active treatment with high-dose corticosteroids steroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks)
	Individuals with advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)

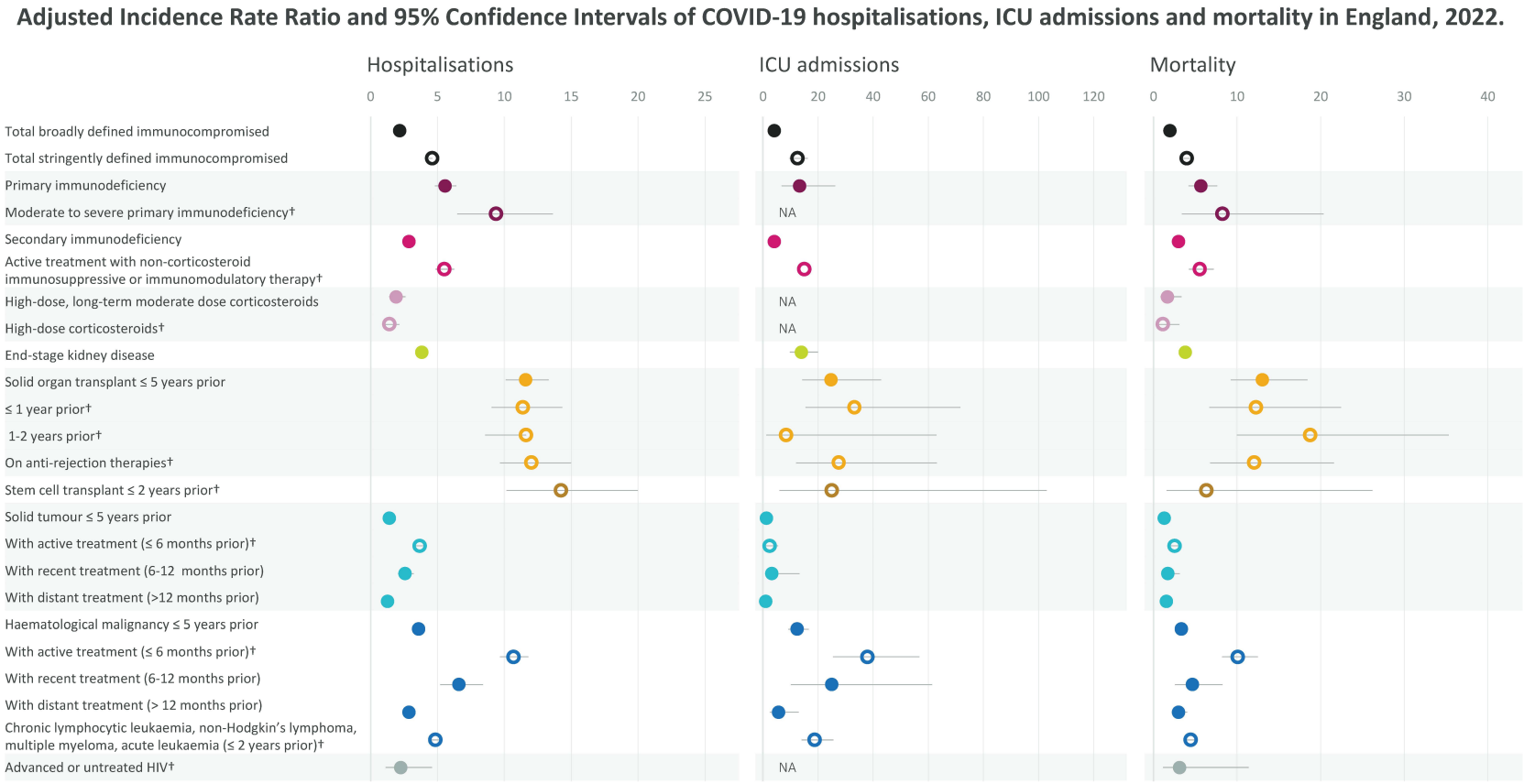
AIDS – Acquired immunodeficiency syndrome, HIV – human immunodeficiency virus, m – month(s), TNF – tumour necrosis factor

Supplement 4. Estimated number of COVID-19 events by immunocompromised condition, England, 2022.

	Overall population				Vaccinated population			
	Total population	**COVID-19 hospitalisations**	**COVID-19 ICU admissions**	**COVID-19-related deaths**	**Total population**	**COVID-19 hospitalisations**	**COVID-19 ICU admissions**	**COVID-19-related deaths**
Overall study population (aged 12+ years)	47962920	83640	1760	19240	24242540	58400	1020	13700
Total broadly defined immunocompromised	1883640	18340	500	4580	1591340	14500	360	3420
Total stringently defined immunocompromised	332740	6700	300	1420	278240	5340	220	1180
Primary immunodeficiency	37280	780	<40	180	26420	620	<40	140
Moderate to severe primary immunodeficiency†	5080	120	0	<40	3480	80	0	<40
Secondary immunodeficiency	359540	3380	100	780	301860	2740	80	520
Active treatment with non-corticosteroid immunosuppressive or immunomodulatory therapy†	45460	1020	60	240	37480	800	40	180
High-dose, long-term moderate dose corticosteroids	16520	160	0	<40	14040	140	0	<40
High-dose corticosteroids†	13460	80	0	<40	11080	80	0	<40
End-stage kidney disease	93260	2360	140	580	72220	1720	100	400
Solid organ transplant in last five years	29500	860	60	140	23060	680	40	120
≤ 1 year prior†	10820	300	<40	40	8260	220	<40	40
>1 year and ≤ 2 years prior†	6160	180	<40	40	4800	140	0	<40
On anti-rejection therapies†	10560	340	<40	40	8300	240	<40	40
Stem cell transplant in last two years†	5740	140	<40	<40	3980	80	100	<40
Solid tumours in last five years	1237580	9660	140	2500	1063840	7660	<40	1860
With active treatment (≤6 months prior)†	110800	1720	<40	240	93900	1340	<40	200
With recent treatment (>6-12 months prior)	27940	300	<40	40	23840	200	<40	<40
With distant treatment (>12 months prior)	145920	820	<40	240	125220	680	160	160
Haematological malignancy in last five years	241080	4580	220	1200	202660	3700	80	1000
With active treatment (≤6 months prior)†	33680	1680	100	360	27840	1300	<40	300
With recent treatment (>6-12 months prior)	9000	280	<40	40	7500	200	<40	40
With distant treatment (>12 months prior)	47960	660	<40	180	40660	560	160	160
Chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, multiple myeloma, acute leukaemia (≤ 2 years prior)†	142880	3700	200	940	121180	3020	0	800
Advanced or untreated HIV†	2320	<40	0	<40	1820	<40	100	<40

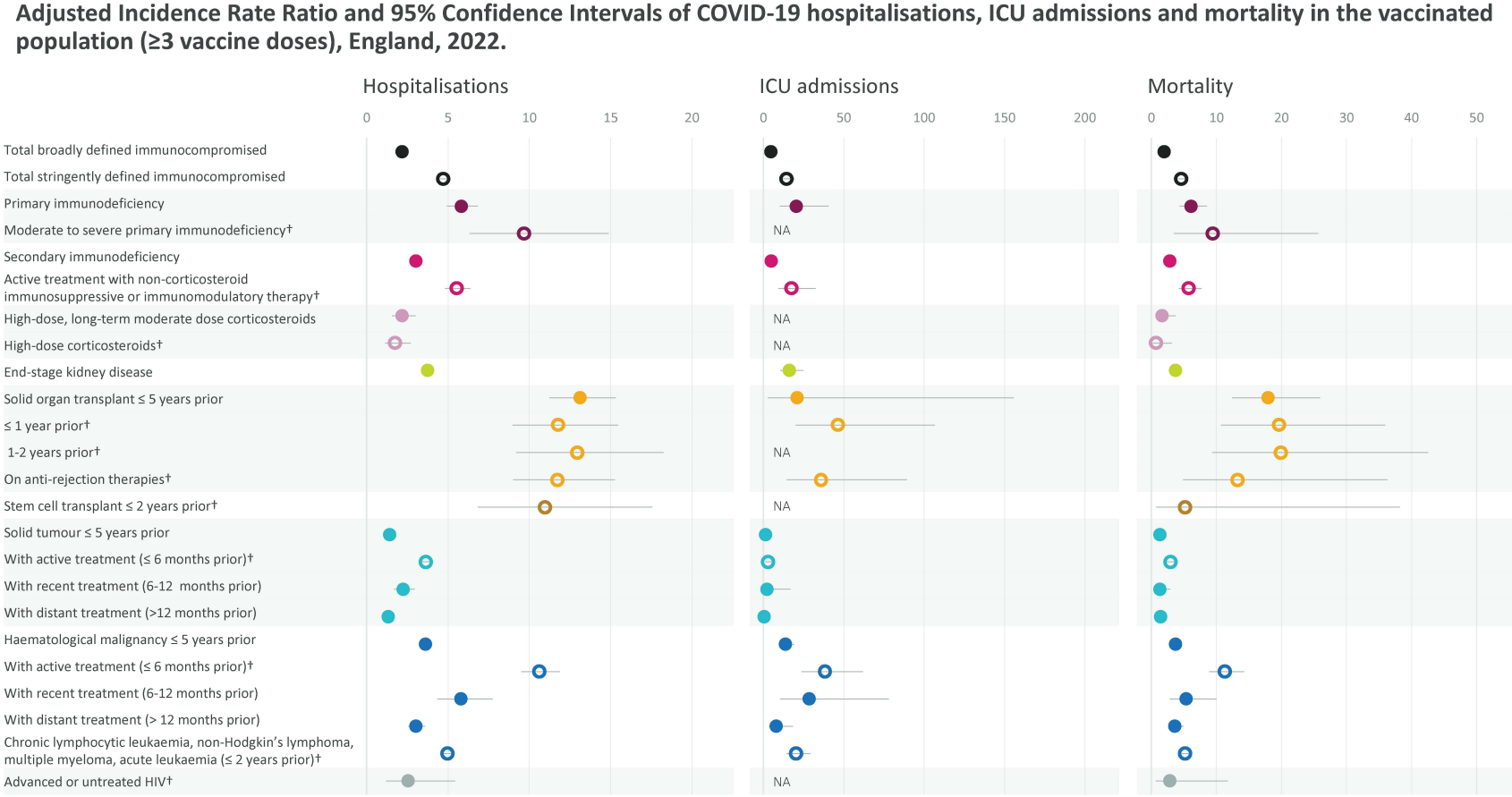
†Stringent immunocompromised subgroups, HIV – human immunodeficiency virus.
Since the study sample consists of a random sample of 25% of patients in NHS, approximate numbers for the total England population were obtained by multiplying the numbers in the study sample by 4.

Supplement 5. The incidence rate ratio of COVID-19 hospitalisation, ICU admission and mortality in immunocompromised groups compared to the total study population.



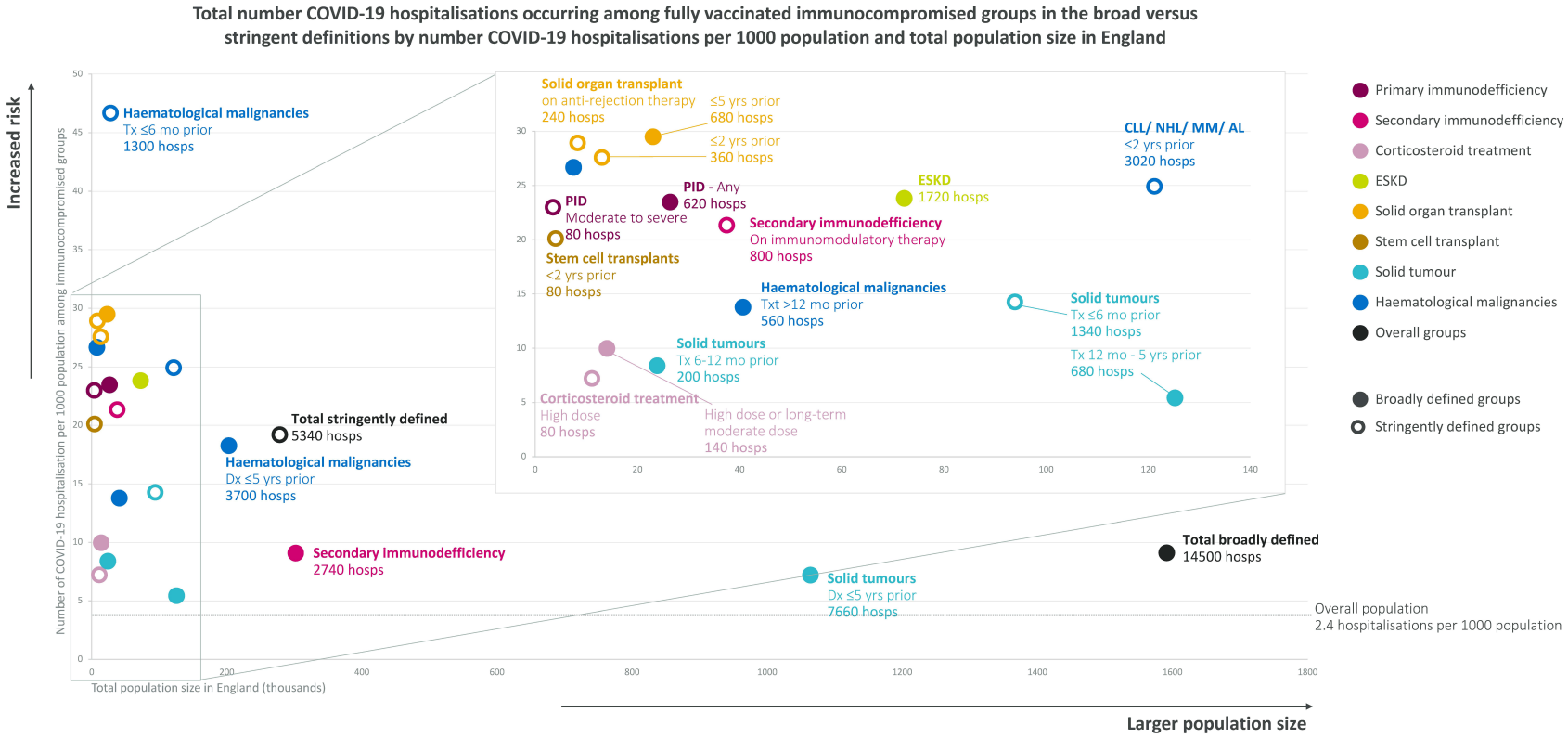
† Stringently-defined immunocompromised groups, HIV – human immunodeficiency virus, ICU – intensive care unit

Supplement 6. The incidence risk ratio of COVID-19 hospitalisation, ICU admission and mortality in fully vaccinated immunocompromised groups compared to the total study population.



† Stringently-defined immunocompromised groups, HIV – human immunodeficiency virus, ICU – intensive care unit

Supplement 7. Total number COVID-19 hospitalisations occurring among fully vaccinated immunocompromised groups in 2022 by number of COVID-19 hospitalisations per 1000 population and total population size in England.



AL – acute leukaemia, CLL – chronic lymphocytic leukaemia, Dx – diagnosis, ESKD – end-stage kidney disease, hosps – hospitalisations, MM – multiple myeloma, mo – months, NHL – non-Hodgkin's lymphoma, PID – primary immunodeficiency, Tx – treatment, yrs – years