Study Report

P4-C1-020

DARWIN EU® - Assessment of immunoglobulin use in clinical practice

01/06/2026

Version 5.0

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Public

CONTENTS

Study title	DARWIN EU® - Assessment of immunoglobulin use in clinical practice
Study report version	V5.0
Date	01/06/2026
EUPAS number	EUPAS1000000823
Active substance	Immunoglobulins: respiratory syncytial virus immune globulin intravenous, immunoglobulin G, freeze-dried pepsin-treated human normal immunoglobulin, ph4-treated acidic human normal immunoglobulin, ph4-treated acidic human normal immunoglobulin (for s.c. injection), polyethylene glycol-treated human normal immunoglobulin, freeze-dried ph4-treated human normal immunoglobulin, freeze-dried sulfonated human normal immunoglobulin, freeze-dried polyethylene glycol-treated human normal immunoglobulin, immunoglobulin M human, immunoglobulin A, Rho(D) immune globulin, tetanus immune globulin, varicella-zoster immune globulin, hepatitis B immune globulin, rabies immune globulin human, Immunoglobulin Anti-Rubella, human vaccinia immune globulin, staphylococcus epidermidis immunoserum rabbit, staphylococcus aureus immunoserum, cytomegalovirus immune globulin, diphtheria antitoxin, hepatitis A immunoglobulin (systemic), Immunoglobulin Anti-Tickborne Encephalitis, pertussis immunoglobulin; systemic, measles immunoglobulin; systemic mumps immunoglobulin; systemic, anthrax immune globulin, Bacillus anthracis immunoserum rabbit, Nebacumab, raxibacumab, bezlotoxumab, obiltoxaximab, palivizumab, MOTAVIZUMAB, tixagevimab, ansuvimab, sotrovimab, REGDANVIMAB, casirivimab, nirsevimab, Sipavibart
Medicinal product	Immunoglobulin brands: Flebogamma DIF, Kiovig, Privigen, Octagam, Yimmugo, Ig vena, Intratect, Iqymune, Panzyga/Globiga, Gamunex, Hizentra, Hyqvia, Cuvitru, Cutaquig, Xembify, Gammagard, Nanogam/Optiglobin, Clairyg, Tegeline, Pentaglobin, Keycute/Naxiglo, Gammaplex, Beriglobin, Rhesonativ, Rhophylac
Research question and objectives	Research question: What are the treatment and patient characteristics of individuals receiving immunoglobulins across European countries? Study objectives: 1. To estimate the overall and annual prevalence of immunoglobulin use in the general population, overall and stratified by i) type of immunoglobulin, and ii) route of administration. Estimates were stratified by age and sex. 2. To describe the distribution and quarterly trends of prespecified immunoglobulin brands among prevalent immunoglobulin users (if available). 3. To estimate the number of immunoglobulin prescriptions, treatment duration, and dose (initial, cumulative) of immunoglobulin use during the study period. 4. To characterise patients initiating treatment with prespecified immunoglobulins in terms of i) demographics at index date, ii) indication for use, iii) comorbidities, iv) common infections post-index, and v) antibiotics post-index.
Countries of study	France, Germany, the United Kingdom
Authors	Ellen Gerritsen, e.gerritsen@darwin-eu.org Dina Vojinovic, d.vojinovic@darwin-eu.org

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ATC	Anatomical Therapeutic Chemical
CC	Coordination centre
CDM	Common Data Model
CDW Bordeaux	Clinical Data Warehouse of Bordeaux University Hospital
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DDD	Defined daily doses
DOI	Declaration of Interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
DTZ	Data Transfer Zone
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
IG	Immunoglobulin
IP	Inpatient
IQVIA DA Germany	IQVIA Disease Analyzer Germany
IRB	Institutional Review Board
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
RxNorm	Medical prescription normalised
SNOMED	Systemised Nomenclature of Medicine
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Assessment of immunoglobulin use in clinical practice

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigators	Ellen Gerritsen Dina Vojinovic	IQVIA
Data Scientists	Akram Mendez Gargi Jadhav	IQVIA
Study Manager	Natasha Yefimenko	Erasmus MC
Data source	**Names**	**Data Partner Organisation***
Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux)	Guillaume Verdy Loïc Ronflette	Centre Hospitalier Universite de Bordeaux
IQVIA Disease Analyzer Germany (IQVIA DA Germany)	James Brash	IQVIA
Clinical Practice Research Datalink GOLD (CPRD GOLD)	Antonella Delmestri Marta Pineda Moncusí Mandickel Kamtengeni Hezekiah Omulo	University of Oxford

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. ABSTRACT

Title

DARWIN EU® - Assessment of immunoglobulin use in clinical practice

Rationale and background

Immunoglobulins can be routinely administered as replacement therapy in immunodeficient patients or are used as immunomodulating doses to treat various immune-related and inflammatory diseases. Of note is that there is a significant off label use of immunoglobulins. The global demand of immunoglobulins increases every year, resulting in intermittent shortages that could affect individuals with conditions that have limited alternative treatments. Therefore, this study aimed to generate real-world evidence about use of immunoglobulins in clinical practice, including for which (off label) indications immunoglobulins are prescribed, treatment characteristics, and the clinical outcomes, such as infection rates and use of antibiotics.

Research question and objectives

What are the treatment and patient characteristics of individuals receiving immunoglobulins across European countries? The specific objectives of this study were:

1. To estimate the overall and annual prevalence of immunoglobulin use in the general population, overall and stratified by i) type of immunoglobulin and ii) route of administration. Estimates were stratified by age and sex.
2. To describe the distribution and quarterly trends of prespecified immunoglobulin brands among prevalent immunoglobulin users.
3. To estimate the number of immunoglobulin prescriptions, treatment duration, and dose (initial, cumulative) of immunoglobulin use during the study period.
4. To characterise patients initiating treatment of prespecified immunoglobulins in terms of i) demographics at index date, ii) indication for use, iii) comorbidities, iv) common infections post-index, and v) antibiotics post-index.

Methods

A descriptive retrospective cohort study was conducted to estimate the prevalence of 1) individuals with a recorded immunoglobulin prescription in the general population, and of 2) individuals with a record of a prespecified immunoglobulin brand among prevalent immunoglobulin users, and to characterise treatment and individuals receiving immunoglobulin treatment.

The study population included all individuals present in the data source (*objective 1*), those with a drug prescription or dispensing record of immunoglobulin (*objective 2*), or individuals with a first drug prescription or dispensing record of immunoglobulin (*objectives 3 and 4*) during the study period, between 01/01/2017 and 31/12/2024.

The following covariates were assessed: demographics, prespecified indication for use, comorbidities, prespecified common infections, and prespecified antibiotics. The prespecified indication of use was assessed by using conditions as proxies.

Data were used from three sources: a hospital data source (Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France), and two outpatient general practice care data sources (IQVIA Disease Analyzer Germany (IQVIA DA Germany) and the Clinical Practice Research Datalink GOLD (CPRD GOLD, The United Kingdom).

General prevalence of use was expressed as the proportion of individuals with any immunoglobulin prescription in the study population, while prevalence of individuals with a prespecified immunoglobulin brand was expressed as the proportion of individuals among immunoglobulin users. The number of immunoglobulin prescriptions, treatment duration, and initial and cumulative dose of the index drug was presented as minimum, q25, median, q75, and maximum. Patient demographics, comorbidities, common infections, and antibiotic treatments were described for each prespecified immunoglobulin.

Results

Prevalence of immunoglobulin use in the general population

The overall number of immunoglobulin users remained low across all three data sources during the study period. In the hospital data source CDW Bordeaux, annual prevalence was 0.2% (1,644 cases among 759,114 individuals) in 2017 and remained stable through 2019, decreased slightly in 2020, and then increased from 2023 onwards, reaching 0.4% (2,378 cases among 611,323 individuals) in 2024. In IQVIA DA Germany, annual prevalence was 0.03% (3,167 cases among 10,408,051 individuals) in 2017 and remained stable through 2023, with an increase to 0.1% (13,101 cases among 10,260,687 individuals) in 2024. In CPRD GOLD, annual prevalence was 0.02% (958 cases among 4,712,778 individuals) in 2017 and decreased to approximately 0 during the remainder of the study period due to limited use. Stratification by type of immunoglobulin revealed that annual prevalence was concentrated in a limited number of ingredients. One of the most prevalent immunoglobulin ingredients was immunoglobulin G, with annual prevalence estimates consistent in CDW Bordeaux (0.1%, representing 913 cases among 759,114 individuals, in 2017 and 773 cases among 611,323 individuals, in 2024, with a slightly decrease between 2020 and 2022) and IQVIA DA Germany (0.02%, representing 2,233 cases among 10,408,051 individuals in 2017 and 1,721 cases among 10,260,687 individuals in 2024), while the prevalence in CPRD GOLD was approximately 0. The annual prevalence of immunoglobulin Rho(D) use ranged from 0.09% (701 cases among 759,114 individuals) in 2017 to 0.1% (658 cases among 611,323 individuals) in 2024 in CDW Bordeaux, while it was censored or approximately 0 in IQVIA DA Germany and CPRD GOLD.

Sex-stratified prevalence analyses revealed a female predisposition for immunoglobulin G use in IQVIA DA Germany and for immunoglobulin Rho(D) in CDW Bordeaux. Age-stratified analyses revealed the highest prevalence estimates of immunoglobulin G among older adults (≥66 years) in CDW Bordeaux and among adults aged 19–65 years in IQVIA DA Germany. The highest prevalence of immunoglobulin Rho(D) was observed among adults aged 19–65 years in CDW Bordeaux. Sex- and age-related differences were negligible for the other types of immunoglobulins.

Quarterly trends of prespecified immunoglobulin brands among prevalent immunoglobulin users.

In general, the number of users was low across immunoglobulin brands and data sources. Among the prespecified brands, Beriglobin, Cutaquig, Cuvitru, Gamunex, Hizentra, Intratect, Kiovig, Octagam, Privigen, Rhesonativ, and Rhophylac were observed with at least five prevalent users in at least one calendar quarter during the study period. Privigen was the most frequently observed immunoglobulin brand overall, with the largest proportion of individuals with a Privigen record among prevalent immunoglobulin users ranging from 61.2% (406 cases among 663 prevalent users) in 2017 to 10.2% (70 cases among 688 users) and 6.4% (77 cases among 1,199 users) in the last two quarters of 2024 (CDW Bordeaux), and smallest proportion ranging from 1.0% (11 cases among 1,092 prevalent users) in 2017 to 2.7% (43 cases among 1,611 prevalent users) in the third quarter and 0.3% (32 cases among 10,557 prevalent users) in the final quarter of 2024 (IQVIA DA Germany). In CPRD GOLD, the number of Privigen users per quarter was 0 or censored. Other human normal immunoglobulin showed generally low use.

Number of immunoglobulin prescriptions, treatment duration, and dose of immunoglobulin use.

The indication of use could be approximated using proxies for five of the prespecified brands (Beriglobin, Kiovig, Privigen, Rhesonativ, and Rhophylac) by identifying conditions recorded within 30 days prior to 7 days following treatment initiation, with most prevalent conditions being oncology (Beriglobin in IQVIA DA Germany, and Kiovig, Privigen, and Rhophylac initiators in CDW Bordeaux) and neurology (Privigen initiators in IQVIA DA Germany).

Diagnosed comorbidities among immunoglobulin initiators varied substantially between brands and data sources. These included acute upper respiratory infection, immunodeficiency disorder, chronic obstructive pulmonary disease, illness (i.e. life expectancy limiting condition, terminal illness, or viral syndrome), essential hypertension, polyneuropathy, noninflammatory disorder of the vagina, first degree perineal laceration, and pregnancy.

The most common infections among immunoglobulin initiators, within 30 days after treatment initiation, were bacterial infections and respiratory, ear, nose, throat, and ocular infections, affecting up to 22.1% (Privigen, CDW Bordeaux) and 21.8% (Privigen, CDW Bordeaux) individuals, respectively.

The most frequently recorded antibiotics were 'Beta-lactam antibacterials, penicillins' and 'Sulphonamides and trimethoprim', recorded among up to 12.7% (Privigen, CDW Bordeaux) and 13.1% (Privigen, CDW Bordeaux) individuals.

Discussion

This multi-country study provides real-world evidence on immunoglobulin use across three European healthcare systems. The overall prevalence of immunoglobulins was low during the complete study period (CDW Bordeaux: 10,551 cases among 1,723,887 individuals; IQVIA DA Germany: 29,369 cases among 29,757,040 individuals; CPRD GOLD: 1,725 cases among 6,305,333 individuals) and use was concentrated in a limited number of ingredients and brands. Nevertheless, temporal variations were observed across products and data sources. The number of nirsevimab cases rose from 0 in 2022 to 854 (CDW Bordeaux) and to 10,748 (IQVIA DA Germany) in 2024, which caused an increase in the overall prevalence of immunoglobulin use. The quarterly proportion of Privigen initiators decreased by more than half within a year (CDW Bordeaux). Such increases may have resulted from market authorisation or expansion of approved indication of use, whereas decreases may have been influenced by shortages, availability issues, or differences in prescribing practices. While some immunoglobulin brands were administered only once (e.g. Rhesonativ and Rhophylac) others were routinely administered (e.g. Hyqvia and Kiovig). These varying treatment characteristics potentially result from different indications of use and accompanying treatment regimens or from differences in prescribing practices and data capture methods. For example, among Kiovig initiators, 41.7% had a recorded oncology-related diagnostic code, and 16.7% had a record of primary immunodeficiency syndrome around the index date in CDW Bordeaux. Although the observed indications of use for the prespecified brand were consistent with clinical practice, indications were not captured in a large proportion of individuals who initiated treatment with the prespecified brands, even after widening the time window.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	22 January 2026	19 January 2026
Creation of Analytical code	December 2025/January 2026	January 2026
Execution of Analytical Code on the data	January 2026	January/February 2026
Draft Study Report	30 January 2026	27 February 2026
Final Study Report	05 June 2026	01 June 2026

6. RATIONALE AND BACKGROUND

Immunoglobulins are purified products from plasma of human donors. They can be routinely administered as replacement therapy in immunodeficient patients or are used as immunomodulating doses to treat various immune-related and inflammatory diseases.[1, 2] It is known that there is a significant off label use of immunoglobulins.[3] Therefore, following interactions with internal EMA Working Parties and European patient organisations, and as a feasibility pilot for engaging patient's associations in DARWIN EU® studies, the European Medicines Agency (EMA) would like to learn more about use of immunoglobulins in clinical practice, including for which (off label) indications immunoglobulins are prescribed, the route of administration, dose and frequency of these immunoglobulins, and the clinical outcomes, such as infection rates and use of antibiotics.

The global demand of immunoglobulins increases every year, resulting in intermittent shortages that could affect individuals with conditions that have limited alternative treatments.[1, 3] This study aimed to generate real-world evidence on the treatment and characteristics of individuals receiving immunoglobulins and the clinical outcomes.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What are the treatment and patient characteristics of individuals receiving immunoglobulins across European countries?

Objectives

The specific objectives of this study were:

1. To estimate the overall and annual prevalence of immunoglobulin use in the general population, overall and stratified by i) type of immunoglobulin and ii) route of administration. Estimates were stratified by age and sex.
2. To describe the distribution and quarterly trends of prespecified immunoglobulin brands among prevalent immunoglobulin users (if available).
3. To estimate the number of immunoglobulin prescriptions, treatment duration, and dose (initial, cumulative) of immunoglobulin use during the study period.
4. To characterise patients initiating treatment with prespecified immunoglobulins in terms of i) demographics at index date, ii) indication for use, iii) comorbidities, iv) common infections post-index, and v) antibiotics post-index.

8. RESEARCH METHODS

8.1. Study design

A cohort study was conducted using routinely collected health data from 3 data sources from 3 European Union (EU) member states.

The study comprised of:

- A population-level drug utilisation study to address *objectives 1* and *2*, assessing the prevalence of individuals with a recorded immunoglobulin prescription, stratified by type of immunoglobulin and route of administration, among the general population (**Figure 1a**) and the prevalence of prespecified immunoglobulin brands among individuals with an immunoglobulin prescription (**Figure 1b**).
- A patient-level drug utilisation study to address *objectives 3* and *4*, assessing treatment characteristics and clinical characteristics of individuals initiating treatment with prespecified immunoglobulin brands, including dose, treatment duration, number of prescriptions, and indication for use, comorbidities, and common infections and antibiotics prescribed (**Figure 2**).

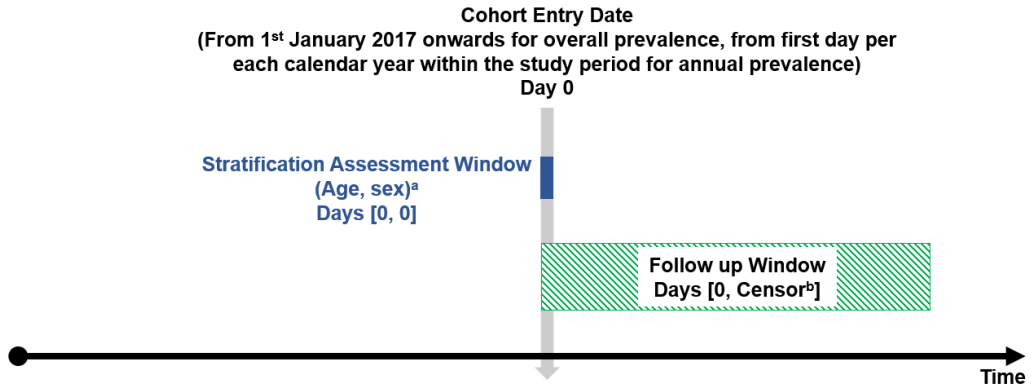


Figure 1a. Graphical depiction of the study design *objective 1*.

a. Stratification by sex or age group (i) 1 to 18 years, ii) 19 to 65 years, and iii) >65 years and older) was done at cohort entry date.
b. Earliest of: 1) loss to follow-up, 2) death, 3) end of observation period (the latest available data), or 4) study end date 31/12/2024.

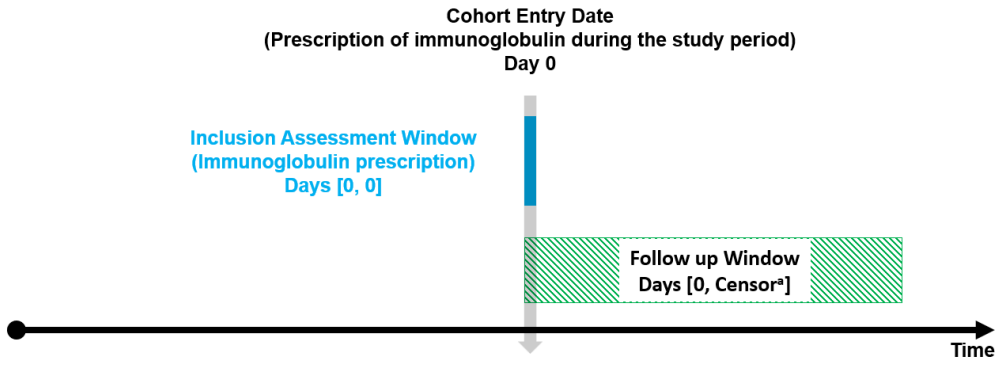


Figure 1b. Graphical depiction of the study design *objective 2*.

a. Earliest of: 1) loss to follow-up, 2) death, 3) end of observation period (the latest available data), or 4) study end date 31/12/2024.

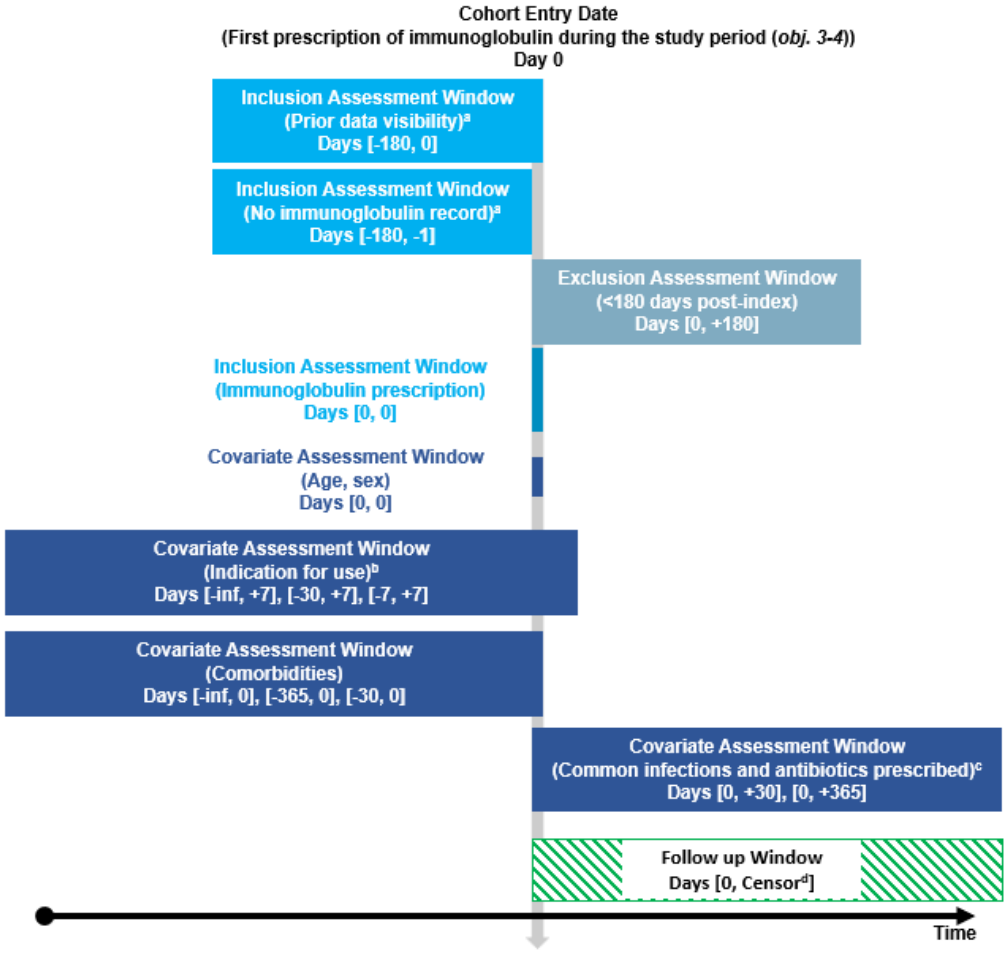


Figure 2. Graphical depiction of the study design *objectives 3–4*.

a. Criterion only applied for primary care data sources (IQVIA DA Germany and CPRD GOLD).
b. Indication for use included the following prespecified indication groups 1) primary immunodeficiency syndrome, 2) secondary immunodeficiencies, 3) neurology, 4) haematology, 5) infectious diseases, 6) solid organ transplantation, 7) internal medicine, 8) hepatology, and 9) other indications. Detailed information can be found in **Section 8.6.3.**
c. Overview of prespecified infections and antibiotics can be found in **Section 8.6.3.**
d. Earliest of: 1) loss to follow-up, 2) death, 3) end of observation period (the latest available data), or 4) study end date 31/12/2024.

8.2. Follow-up

For prevalence estimations of individuals with recorded immunoglobulin prescriptions among the general study population (*objective 1*), individuals present in the data source between 1st of January 2017 and 31st of December 2024 were included. For prevalence estimations among immunoglobulin users (*objective 2*), follow up started on the date of immunoglobulin prescription during the study period.

For patient-level drug utilisation (*objective 3*) and characterisation of individuals who initiated immunoglobulin treatment (*objective 4*), follow-up of incident immunoglobulin users started on the date of the first immunoglobulin prescription record of prespecified immunoglobulin brands during the study period. For primary care data sources, individuals were required to have 180 days data visibility prior to study inclusion and were not allowed to have record of immunoglobulin prescription in the 180 days prior to study inclusion. For hospital care data settings, individuals were not required to have prior data availability, and no washout period was applied prior to study inclusion. To ensure sufficient follow-up (*objectives 3–4*), only individuals with a first record of immunoglobulin prescription at least 180 days before the end of data availability in each data source were included.

Follow-up (*objectives 1–4*) ended on the earliest of i) loss to follow-up, ii) death, iii) end of observation period (the latest available data), iv) or study end date 31/12/2024, whichever occurred first.

The code lists used to identify the start and end of follow-up determining events are presented in **ANNEX IV**.

8.3. Study population with inclusion and exclusion criteria

Objective 1

Inclusion criteria

- Present in the data source during the period of 01/01/2017 to 31/12/2024.

Exclusion criteria

- Not applicable for this objective.

Objective 2

Inclusion criteria

- Present in the data source during the period of 01/01/2017 to 31/12/2024.
- Drug prescription or dispensing record of prespecified immunoglobulin brands during the study period.

Exclusion criteria

- Not applicable for this objective.

The final code list for immunoglobulins is provided in **ANNEX IV**.

Objectives 3–4

Inclusion criteria

- Present in the data source during the period of 01/01/2017 to 31/12/2024.
- Minimum 180 days of available history before index data. This criterion did not apply for hospital data source CDW Bordeaux.
- First drug prescription or dispensing record of prespecified immunoglobulin brand during the study period.

- No prior immunoglobulin exposure in the 180 days prior to the index date. This criterion did not apply for hospital data source CDW Bordeaux.

Exclusion criteria

- Individuals with a first immunoglobulin record <180 days prior to the end of data availability in the respective data source (to ensure sufficient follow-up).

The final code list for immunoglobulin brands is provided in **ANNEX IV**.

8.4. Study setting and data sources

This study was conducted using routinely collected data from primary and secondary care data sources in the DARWIN EU® network of data partners from 3 European countries, of 3 EU member states. All data were a priori mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM).

Table 1. Data sources.

Country	Name of data source	Health care setting	Type of data	Number of active individuals*	Calendar period covered by each data source	Contributing to
France	CDW Bordeaux	Hospital care	EHR	247,200	2005 – 09/2025	All objectives
Germany	IQVIA DA Germany	Outpatient General Practitioner and Specialist Care	EHR	4,484,200	1989 – 06/2025	All objectives
The United Kingdom	CPRD GOLD	Outpatient General Practitioner Care	EHR	2,632,700	1987 – 05/2025	All objectives

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; EHR = electronic health records; IQVIA DA Germany = IQVIA Disease Analyzer Germany. * = Number of active individuals is defined as the number of individuals present in the last six months of the respective data source.

1. France: Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux)
2. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
3. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Data sources selection

These data sources fulfilled the criteria required in terms of data quality, completeness, timeliness, and representativeness for a drug utilisation and characterisation studies while covering different regions of Europe (**ANNEX II**).

8.5. Study period

The study period was from 01/01/2017 to 31/12/2024. The data availability of the included data sources aligned with the study period.

8.6. Variables

8.6.1. Exposure

For *objective 1,* the primary exposure was defined as a prescription or dispensing record of a prespecified immunoglobulin drug (ingredient level). For *objective 2,* prescriptions of all prespecified immunoglobulin brands of an individual during the study period were included. For *objectives 3* and *4,* the prescription or dispensing record of prespecified immunoglobulin brands represented the first recorded prescription in the study period, and individuals from primary care data sources were required to have no prior immunoglobulin use in the 180 days prior the index date.

To define treatment episodes, sequential prescriptions were grouped into drug eras, allowing a maximum gap of 30 days between the end of one prescription and the start of the next. More details about the definition of a treatment episode are provided in **Section 8.9.1**.

The final concept sets used for the identification of exposures are described in **ANNEX IV**. These codes were refined during the study execution following the DARWIN EU® phenotyping standard processes, which involved the review of code lists and the review of phenotypes after their execution in the participating data sources. Final concept sets were defined following input from the EMA.

8.6.2. Outcome

The outcomes of interest were as follows:

- Prevalence of individuals with a recorded immunoglobulin prescription among the general population, including type of immunoglobulin, route of administration (*objective 1*).
- Proportion of individuals with a prespecified immunoglobulin brands prescription among prevalent immunoglobulin users (*objective 2*).
- Initial and cumulative dose, number of prescriptions, and treatment duration of prespecified immunoglobulin brands among treatment initiators (*objective 3*).
- Characterisation of individuals initiating treatment with prespecified immunoglobulin brands (*objective 4*).

8.6.3. Covariates, including confounders, effect modifiers, intercurrent events, and other variables

The variables for *objective 1* were as follows:

- Calendar period
    - Year
- Route of administration:
    - Intravenous
    - Subcutaneous
    - Intramuscular
    - Other
    - Missing
- Age groups, defined at cohort entry date:
    - Overall population
    - 1 to 18 years

  - 19 to 65 years
  - >65 years and older
- Sex, defined at cohort entry date:
  - Overall
  - Male
  - Female

The variables for *objective 2* were as follows:

- Calendar period
  - Quarter of year
- Prespecified brands, including (if available):
  - Flebogamma DIF
  - Kiovig
  - Privigen
  - Octagam (5% and 10%)
  - Yimmugo
  - Ig vena
  - Intratect
  - Iqymune
  - Panzyga/Globiga
  - Gamunex
  - Hizentra
  - Hyqvia
  - Cuvitru
  - Cutaquig
  - Xembify
  - Gammagard
  - Nanogam/Optiglobin
  - Clairyg
  - Tegeline
  - Pentaglobin
  - Keycute/Naxiglo
  - Gammaplex
  - Beriglobin
  - Rhesonativ

- Rhophylac

The variables for characterisation of immunoglobulin users (*objective 4*) were as follows:

- Demographics, at index date:
  - Sex: Female/male
  - Age
  - Age group: 1 to 18 years, 19 to 65 years, >65 years and older
- Indication for use: Prespecified conditions were used as proxies to assess the indication for immunoglobulin use, including both authorised and non-authorised indications. The assessment windows were any time prior to 7 days after the index date [-inf, +7], 30 days prior to 7 days after the index date [-30, +7], and 7 days prior to 7 days after the index date [-7, +7].
  - Primary immunodeficiency syndrome, including:
    - Primary immunodeficiency syndromes
  - Secondary immunodeficiencies, including:
    - Secondary immunodeficiencies
  - Neurology, including:
    - Guillain Barré syndrome
    - Chronic inflammatory demyelinating polyradiculoneuropathy
    - Multifocal motor neuropathy
    - Myasthenia gravis
    - Stiff person syndrome
    - Lambert-Eaton myasthenia syndrome
  - Haematology, including:
    - Immune thrombocytopenia
    - Acquired von Willebrand disease
    - Foetal Neonatal Alloimmune Thrombocytopenia
  - Infectious diseases, including:
    - Measles
  - Solid organ transplantation, including:
    - Transplantation
  - Internal medicine, including:
    - Kawasaki's disease
    - Inflammatory myopathy
    - (Juvenile) dermatopolymyositis
    - ANCA vasculitis (replacement therapy)
    - Systemic lupus erythematosus

  - Hepatology, including:
    - Hepatitis A
  - Other indications, which were assessed overall and separately for each indication, where available, including:
    - Oncology
    - Autoimmune or paraneoplastic encephalitis
    - Epilepsy
    - Progressive systemic sclerosis
    - Sjögren's syndrome
    - COVID-19
    - Alzheimer's disease

- Comorbidities: The top 10 most frequent diagnostic codes (comorbidities) were identified through large-scale characterisation. These were assessed 30 days prior to the index date [-30, 0], 1 year prior to the index date [-365, 0], and any time prior the index date [-inf, 0].
- Common infections: Prespecified common infections among individuals initiating treatment with prespecified immunoglobulin brands were assessed up to 30 days post-index [0, +30] and up to 365 days post-index [0, +365]. The following types of infections [4]were assessed:
  - Systemic infections, including:
    - Gram negative sepsis
    - Bacteraemia
  - Bacterial infections, including:
    - Bacterial infectious disease
  - Central nervous system infections, including:
    - Meningitis
  - Respiratory & ear, nose, throat, ocular infections, including:
    - Otitis
    - Conjunctivitis
    - Bronchitis
    - Sinusitis
    - Respiratory tract infections
  - Fungal infections, including:
    - Opportunistic mycosis
    - Invasive fungal infection
  - Gastrointestinal & intra-abdominal infections, including:
    - Acute diarrhoea
    - Gastrointestinal infections

        - Peritonitis
    - Urinary infections, including:
        - Urinary tract infections
    - Viral infections:
        - Chronic enteroviral infections
        - Herpesvirus infections
- Antibiotic treatment: Exposure to prespecified antibiotics were assessed up to 30 days post-index [0, +30] and up to 365 days post-index [0, +365]. The following classes of antibiotic ingredients were assessed:
    - Tetracyclines
    - Amphenicols
    - Beta-lactam antibacterials, penicillins
    - Other beta-lactam antibacterials
    - Sulphonamides and trimethoprim
    - Macrolides, lincosamides, and streptogramins
    - Aminoglycoside antibacterials
    - Quinolone antibacterials
    - Other antibacterials

The final concept sets used for the identification of covariates are described in **ANNEX IV**. Final concept sets were defined following input from the EMA.

8.7. Study size

No sample size was calculated, as this was a characterisation and drug utilisation study with a descriptive design, which did not test a specific hypothesis. In addition, we used already available data to describe treatment and characteristics of individuals receiving immunoglobulins. Thus, the sample size was driven by the availability of data for individuals with a prescription for prespecified immunoglobulin types and brands.

8.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources and quality control checks were performed. Once all the tests passed (see **ANNEX III**), the final study codes package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the, by default, aggregated results.

The study results of all data sources were checked, after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

8.9. Statistical methods

8.9.1. Main statistical methods

Objective 1

Trends of immunoglobulin use during the study period were assessed based on OMOP CDM mapped data using the *IncidencePrevalence* R package (https://github.com/darwin-eu/IncidencePrevalence), developed by DARWIN EU®.

The prevalence of individuals with a recorded immunoglobulin prescription (expressed as the proportion of individuals with any immunoglobulin prescription in the general study population) is presented by immunoglobulin ingredient, route of administration, and stratified by sex and age.

Prevalence was calculated as overall and annual, which summarised the total number of individuals with recorded immunoglobulin use during a given period divided by the population at risk of receiving immunoglobulins during that period. Therefore, period prevalence provided the proportion of individuals exposed at any time during a specified interval. Binomial 95% confidence intervals were calculated.

Objective 2

Trends of immunoglobulin use during the study period were assessed based on OMOP CDM mapped data using the *IncidencePrevalence* R package (https://github.com/darwin-eu/IncidencePrevalence), developed by DARWIN EU®.

The quarterly prevalence of individuals with prescriptions for prespecified immunoglobulin brands was estimated per brand (expressed as the proportion of individuals prescribed each specific immunoglobulin brand among prevalent immunoglobulin users).

Prevalence was calculated as quarterly period prevalence, which summarised the total number of individuals with recorded immunoglobulin brand prescription during a quarter divided by the population of prevalent immunoglobulin users during that period. Therefore, period prevalence gave the proportion of individuals exposed to a specific brand at any time during the specified interval. Binomial 95% confidence intervals were calculated.

An illustration of the calculation of period prevalence is shown below in **Figure 3**. Between time t+2 and t+3, two of the five study participants received immunoglobulin treatment, giving a prevalence of 40%. Meanwhile, for the period t to t+1, all five also had some observation time during the year, with one of the five study participants having a recorded immunoglobulin prescription, giving a prevalence of 20%.

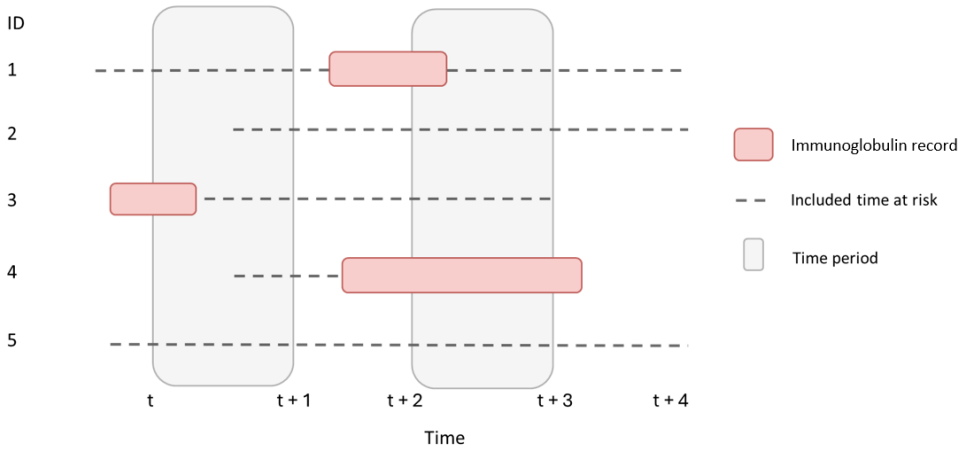


Figure 3. Prevalence.

Objective 3

The dose, duration of use, and number of immunoglobulin prescriptions were calculated per prespecified immunoglobulin brand based on OMOP CDM mapped data using the *DrugUtilisation* R package (https://github.com/darwin-eu/DrugUtilisation), developed by DARWIN EU®.

Drug exposure calculations

Drug eras were defined as follows: exposure started at the date of the first prescription of prespecified immunoglobulin brand during the study period. For primary care data sources, a washout period of 180 days was applied prior to inclusion. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the OMOP CDM, using the recorded start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed treatment episodes (drug eras) using the following specifications: two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤30 days. The time between the two joined eras was considered as exposed by the first era as shown in **Figure 4**, first row. The cumulative dose is the sum of defined daily doses (DDDs) multiplied by the number of days exposed to each dose, i.e. the total dose taken throughout the exposures considered in the time-window reported per prespecified immunoglobulin brand.

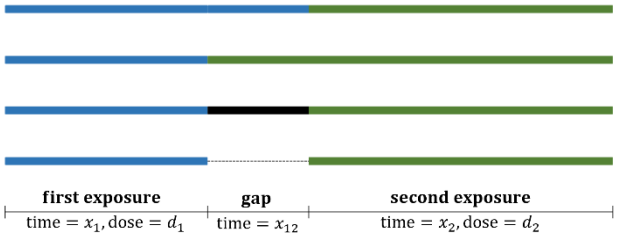
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 4. Gap era joint mode.

If two exposures overlapped, the overlap time was considered exposed to the first exposure (**Figure 5**). No time was added at the end of the combined drug era to account for the overlap. If two exposures started at the same date, the overlapping period was considered exposed to both.

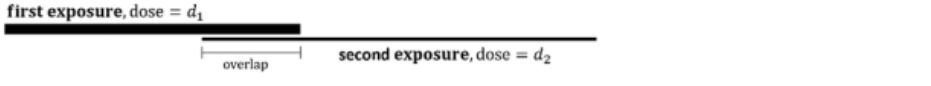
Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

Figure 5. Gap era overlap mode.

In cases where the end date was not explicitly available in the data, it may have been inferred during the ETL process using one of the following methods: (1) adding the value of treatment duration or days' supply to the start date, (2) using quantity divided by daily dose or concentration, or (3) applying predefined rules

such as assigning a default value of 29 days (which is a predefined OMOP convention) for written prescriptions or 89 days for mail-order prescriptions.

The number of prescriptions, initial and cumulative dose of the index drug, as well as duration of use, were provided per prespecified immunoglobulin brand as minimum, q25, median, q75, and maximum.

Objective 4

Characteristics of individuals were assessed in predefined time windows around the date of the first recorded prescription of immunoglobulins (index date) during the study period. For primary care data sources, a washout period of 180 days was applied. Characteristics were described for each prespecified immunoglobulin brand by means of large-scale characterisation and prespecified patient-level characteristics based on OMOP CDM mapped data using the *CohortCharacteristics* (https://github.com/darwin-eu/CohortCharacteristics) and *DrugUtilisation* (https://github.com/darwin-eu/DrugUtilisation) R packages, developed by DARWIN EU®.

Characteristics of interest were reported as counts and proportions for categorical variables and as minimum, q25, median, q75, and maximum for continuous variables. Demographic characteristics, including age and sex, were assessed at the date of first recorded prescription of immunoglobulins (index date) during the study period. Characterisation of prespecified indications for use was assessed any time prior to 7 days after the index date, 30 days prior to 7 days after the index date, and 7 days prior to 7 days after the index date. Large-scale characterisation of comorbidities prior to immunoglobulin treatment was assessed 30 days prior to the index date, 1 year prior to the index date, and any time prior to the index date. Characterisation of prespecified common infections and prespecified antibiotics treatment among immunoglobulin initiators was assessed up to 30 days post-index and up to 365 days post-index.

8.9.2. Missing values

We assumed that the absence of a prescription record in the data source means that the person did not receive the respective treatment. Similarly, for assessment of comorbidities, we assumed that the absence of a recorded diagnostic code for a given condition means that that condition was not present or not recorded in the context of routine clinical care. For data sources where treatment duration could not be calculated, due to e.g. missing information on quantity or dosing, treatment duration was not provided.

8.9.3. Sensitivity analysis

Not applicable.

8.10. Deviations from the protocol

None.

9. RESULTS

The full set of results for this study, including attrition per objective, overall prevalence, and results for all prespecified immunoglobulin ingredients and brands during the study period, is available through an interactive web-application Shiny app at EUPAS1000000823.

9.1. Participants

A total of 37,786,260 individuals were included in the study population to assess the prevalence of immunoglobulins (CDW Bordeaux: 1,723,887; IQVIA DA Germany: 29,757,040; CPRD GOLD: 6,305,333) (**Table 2**).

Table 2. Study attrition of individuals with a record of immunoglobulin prescription among the general study population, presented by data source (*objective 1*).

Criteria	CDW Bordeaux (n)*	IQVIA DA Germany (n)*	CPRD GOLD (n)*
Starting population	2,474,759	43,691,689	17,539,783
Year of birth present	2,474,759	43,691,689	17,539,783
Sex present	2,473,477	43,664,565	17,539,783
Satisfies age criteria during the study period based on year of birth, i.e. not born after the study period	2,461,416	43,646,103	17,532,323
Observed during study period	1,723,896	29,757,040	6,305,333
Observed during study period after applying age criteria	1,723,887	29,757,040	6,305,333

*n = number of individuals; CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; IQVIA DA Germany = IQVIA Disease Analyzer Germany; CPRD GOLD = Clinical Practice Research Datalink GOLD.

A total of 41,645 individuals received an immunoglobulin during the study period and were included in the study population to assess the prevalence of proportion of immunoglobulins brands among prevalent immunoglobulin users (CDW Bordeaux: 10,551; IQVIA DA Germany: 29,369; CPRD GOLD: 1,725) (**Table 3**).

Table 3. Study attrition of individuals with a prescription record of a prespecified immunoglobulin brand among prevalent immunoglobulin users, presented by data source (*objective 2*).

Criteria	CDW Bordeaux (n)*	IQVIA DA Germany (n)*	CPRD GOLD (n)*
Starting population with an immunoglobulin record anytime in the data source	16,054	53,787	72,013
Year of birth present	16,054	53,787	72,013
Sex present	16,054	53,730	72,013
Satisfies age criteria during the study period based on year of birth, i.e. not born after the study period	16,054	53,730	72,013
Observed during study period	10,551	29,369	1,725

*n = number of individuals; CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; IQVIA DA Germany = IQVIA Disease Analyzer Germany; CPRD GOLD = Clinical Practice Research Datalink GOLD.

The number of individuals who initiated treatment with a prespecified brand during the study period and were included in the study population to assess treatment and clinical characteristics (*objectives 3* and *4*) can be observed per brand in the Shiny app at EUPAS1000000823.

9.2. Main results

9.2.1. Prevalence of immunoglobulin use

Annual prevalence of overall immunoglobulin use remained low across all three data sources during the study period (2017–2024), with an overall prevalence of 0.6% in the hospital data source CDW Bordeaux (10,551 cases among 1,723,887 individuals), of 0.1% in the primary care data source IQVIA DA Germany (29,369 cases among 29,757,040 individuals), and of 0.03% in the primary care data source CPRD GOLD (1,725 cases among 6,305,333 individuals). In CDW Bordeaux, annual prevalence was 0.2% in 2017 and remained stable through 2019, followed by a slight decrease in 2020 and a subsequent increase from 2023 onwards, reaching 0.4% in 2024. In IQVIA DA Germany, annual prevalence remained 0.03% between 2017 and 2023, with an increase to 0.1% in 2024. In CPRD GOLD, annual prevalence was 0.02% in 2017 and decreased to approximately 0 during the remainder of the study period due to limited use (**Figure 6**).

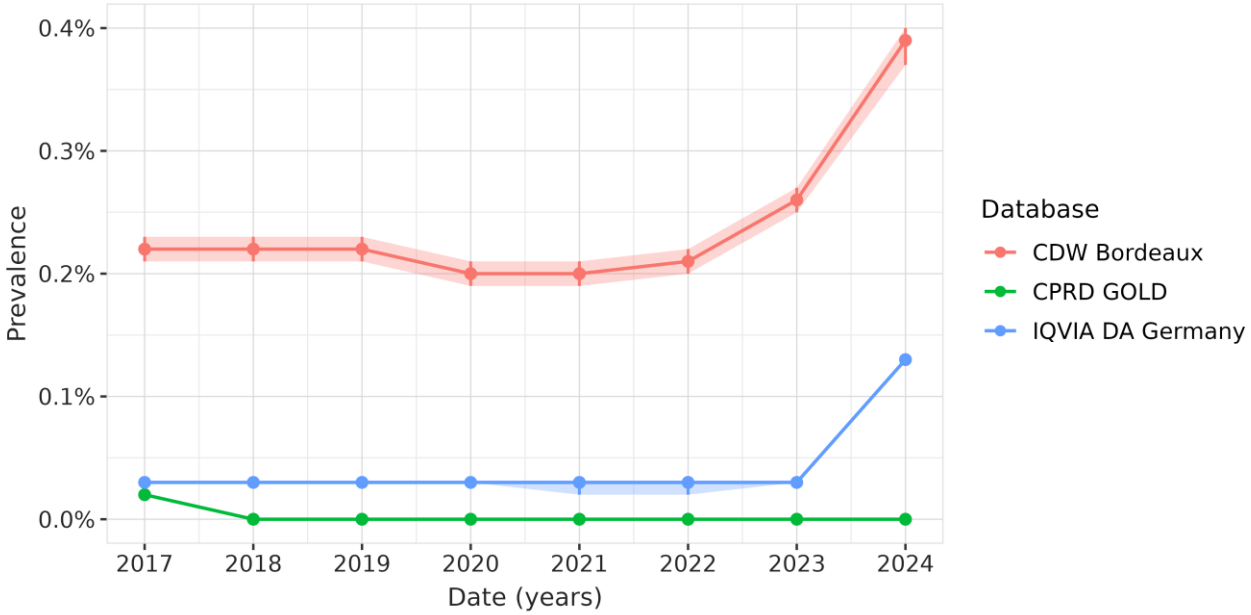


Figure 6. Annual prevalence of overall immunoglobulin use during 2017–2024, per data source.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; IQVIA DA Germany = IQVIA Disease Analyzer Germany; CPRD GOLD = Clinical Practice Research Datalink GOLD. Prevalence estimates are provided with binomial 95% confidence intervals.

Stratification by type of immunoglobulin resulted in varying prevalence estimates per ingredient across the data sources during the study period.

The annual prevalence of immunoglobulin G use in CDW Bordeaux was around 0.1%, with a slight decrease observed between 2020 and 2022. In IQVIA DA Germany, annual prevalence remained consistent at 0.02% during the study period, while in CPRD GOLD, prevalence was approximately around 0 due to limited use of this immunoglobulin throughout the study period (**Figure 7,** Shiny app at EUPAS1000000823).

The annual prevalence of immunoglobulin Rho(D) use was around 0.1% CDW Bordeaux, while the prevalence was either censored (<5 cases) or was approximately around 0 in IQVIA DA Germany and remained consistent at approximately 0 during the study period in CPRD GOLD (**Figure 7,** Shiny app at EUPAS1000000823).

For tetanus immunoglobulins, annual prevalence remained around 0 in CDW Bordeaux, IQVIA DA Germany, and CPRD GOLD, except for a prevalence of 0.01% in 2017 in CPRD GOLD and 0.01% in 2023 and 2024 in CDW Bordeaux (**Figure 7,** Shiny app at EUPAS1000000823).

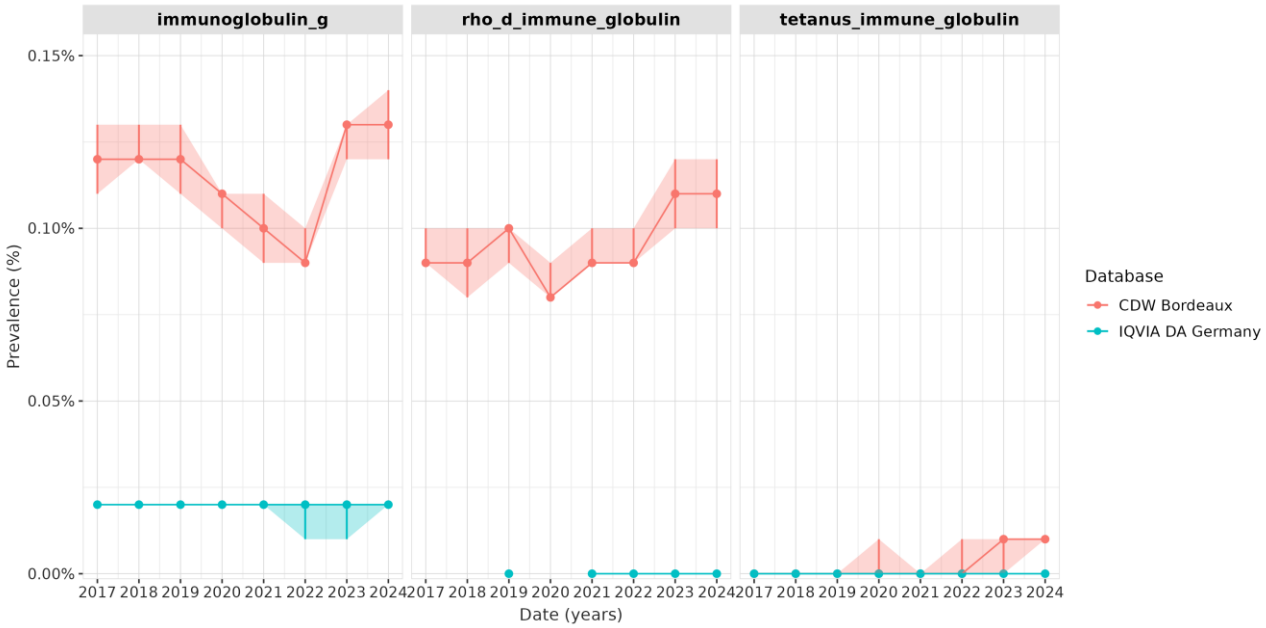


Figure 7. Annual prevalence of immunoglobulin use, stratified by ingredient, per data source.

CPRD GOLD = Clinical Practice Research Datalink GOLD. Prevalence estimates are provided with binomial 95% confidence intervals. Please note that the figure only shows immunoglobulin types for which the number of cases was sufficient enough to assess prevalence estimates over time. CPRD GOLD prevalence estimates are not shown, as it was approximately around 0 during the study period. Prevalence estimates for immunoglobulin based monoclonal antibodies are shown in **Figure S1**. Detailed information for the other immunoglobulin types can be found in the Shiny app. CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; IQVIA DA Germany = IQVIA Disease Analyzer Germany

The annual prevalence of immunoglobulins against hepatitis B, cytomegalovirus immunoglobulins, tickborne encephalitis immunoglobulins, immunoglobulins against varicella zoster virus, rabies immunoglobulins, and immunoglobulin A was 0 (no recorded users), censored (<5 cases), or approximately around 0 across the data sources, indicating sparse use.

There was no reported use of anthrax immunoglobulin, bacillus anthracis immunoserum rabbit, diphtheria antitoxin, freeze-dried polyethylene glycol-treated human normal immunoglobulin, freeze-dried pepsin-treated human normal immunoglobulin, freeze-dried ph4-treated human normal immunoglobulin, freeze-dried sulfonated human normal immunoglobulin, hepatitis A immunoglobulin (systemic), human vaccinia immune globulin, immunoglobulin anti-rubella, immunoglobulin M human, measles immunoglobulin (systemic), mumps immunoglobulin (systemic), pertussis immunoglobulin, ph4-treated acidic human normal immunoglobulin, ph4-treated acidic human normal immunoglobulin (for subcutaneous injection), polyethylene glycol-treated human normal immunoglobulin, respiratory syncytial virus immune globulin intravenous, staphylococcus aureus immunoserum, and staphylococcus epidermidis immunoserum rabbit in CDW Bordeaux, IQVIA DA Germany, and CPRD GOLD during the study period.

The only immunoglobulin types for which the number of cases per route of administration was sufficient enough for a prevalence assessment to be performed on were immunoglobulin G and immunoglobulin Rho(D). The observed route of administration of these ingredients was indicated as 'other', i.e. the level of granularity is not sufficient to classify a drug as intravenous, intramuscular, or subcutaneous, except for immunoglobulin G, which also had some records of subcutaneous administration in IQVIA DA Germany (overall prevalence around 0, corresponding to 23 cases among 29,757,040 individuals) (**Figure 8,** Shiny app at EUPAS1000000823). There were several immunoglobulin records for which the route of administration was not known. The overall prevalence of immunoglobulin types with an unknown administration route was 0.2% for immunoglobulin Rho(D) in CDW Bordeaux and 0.01% for tetanus immunoglobulins records in

CDW Bordeaux and CPRD GOLD during the study period. For the other immunoglobulin ingredients, the overall prevalence of records with an unknown route of administration was 0, censored (<5 cases) or around 0 due to a limited number of cases. The route of administration of immunoglobulin A could not be assessed due to the level of granularity, i.e. concepts were mapped to the ingredient level. All remaining prespecified ingredients were either not observed or were observed in fewer than five individuals when stratified by route of administration throughout the study period, resulting in annual prevalence estimates of zero. The annual prevalence results on these ingredients stratified by route of administration are available in the ShinyApp.

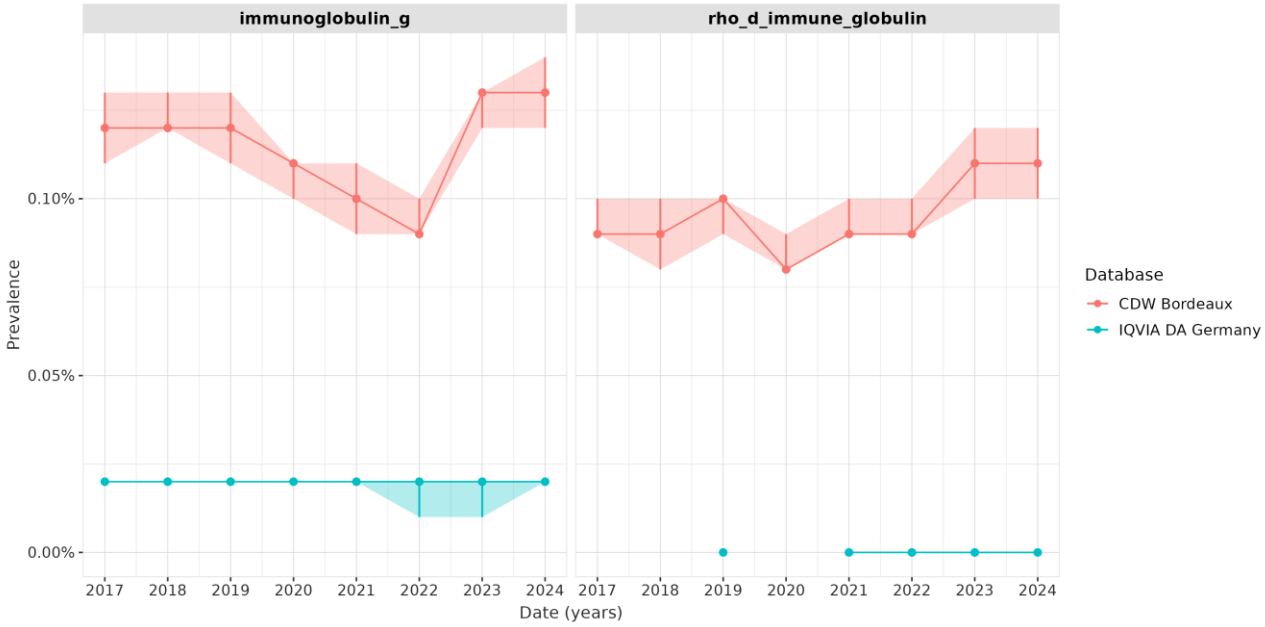


Figure 8. Annual prevalence of immunoglobulin use, stratified by ingredient and route of administration, per data source.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; IQVIA DA Germany = IQVIA Disease Analyzer Germany. Prevalence estimates are provided with binomial 95% confidence intervals. Please note that figure only shows immunoglobulin types for which the number of cases per route of administration was sufficient to assess prevalence estimates over time. CPRD GOLD prevalence estimates are not shown, as it was approximately around 0 during the study period. Prevalence estimates for immunoglobulin based monoclonal antibodies are shown in **Figure S2.** Detailed information for the other immunoglobulin types stratified by route of administration can be found in the Shiny app.

Sex-stratified analyses revealed higher annual prevalence estimates of immunoglobulin G use among females compared to males in IQVIA DA Germany, ranging from 0.04% in 2017 to 0.03% in 2024 among females and around 0 among males throughout the study period. CDW Bordeaux and CPRD GOLD exhibited negligible sex-related differences for immunoglobulin G. In CDW Bordeaux, the prevalence estimates of immunoglobulin Rho(D) among females was around 0.2%, while there was no recorded use among males during the study period, indicating female predisposition. The prevalence of immunoglobulin Rho(D) in IQVIA DA Germany and CPRD GOLD was too low to assess sex-related differences. CDW Bordeaux, IQVIA DA Germany, and CPRD GOLD exhibited negligible sex-related differences for the other types of immunoglobulins (**Figure 9**).

Figure 9. Annual prevalence of immunoglobulin use, stratified by ingredient and sex.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; IQVIA DA Germany = IQVIA Disease Analyzer Germany. Prevalence estimates are provided with binomial 95% confidence intervals. Please note that figure only shows immunoglobulin types for which the sex-stratified number of cases was sufficient to assess prevalence estimates over time. Detailed information for the other immunoglobulin types stratified by sex can be found in the Shiny app.

In CDW Bordeaux, age-stratified analyses revealed the highest prevalence estimates of immunoglobulin G among older adults (≥66 years), which was stable around 0.2%, followed by adults aged 19–65 years, and children and adolescents (1–18 years). In IQVIA DA Germany, adults aged 19–65 years exhibited the highest prevalence of immunoglobulin G, which was stable around 0.03%, while the annual prevalence was approximately around 0 among older adults (≥66 years) and children and adolescents (1–18 years) throughout the study period.

In CPRD GOLD, the age-stratified prevalence of immunoglobulin G remained low and exhibited negligible age-related differences.

In CDW Bordeaux, the highest prevalence of immunoglobulin Rho(D) was observed among adults aged 19–65 years, which was around 0.2%, followed by children and adolescents (1–18 years), ranging from 0.02% in 2017 to 0.03% in 2024. There was no reported use of immunoglobulin Rho(D) among older adults (≥66 years) in CDW Bordeaux.

In IQVIA DA Germany and CPRD GOLD the age-stratified prevalence remained low and exhibited negligible age-related differences.

Age-related differences were negligible in all three data sources for varicella zoster immunoglobulin, except for a higher prevalence estimate among older adults (≥66 years) in 2017 (0.03%) compared to a prevalence around 0 among adults aged 19–65 years and children and adolescents (1–18 years) in CPRD GOLD. The observed prevalence of tetanus immunoglobulin was higher among adults aged 19–65 years and older adults (≥66 years) in 2017 (0.01% in both age groups) compared to children and adolescents (1–18 years) in CPRD GOLD, while age-related differences were negligible in the remaining years and in CDW Bordeaux and IQVIA DA Germany (**Figure 10**). CDW Bordeaux, IQVIA DA Germany, and CPRD GOLD exhibited negligible age-related differences for the other types of immunoglobulins.

The prevalence of immunoglobulins based monoclonal antibodies is described in **ANNEX V**.

Figure 10. Annual prevalence of immunoglobulin use, stratified by ingredient and age, per data source.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; IQVIA DA Germany = IQVIA Disease Analyzer Germany; CPRD GOLD = Clinical Practice Research Datalink GOLD. Prevalence estimates are provided with binomial 95% confidence intervals. Some age strata with very low or zero values may not be visible in the figure due to overlapping prevalence estimates; corresponding values are reported in the text/tables. Please note that figure only shows immunoglobulin types for which the age-stratified number of cases was sufficient to assess prevalence estimates over time. Prevalence estimates for immunoglobulin monoclonal antibodies are shown in **Figure S3.** Detailed information for the other immunoglobulin types stratified by age can be found in the Shiny app.

9.2.2. Proportion of immunoglobulin brand use amongst prevalent immunoglobulin users

Quarterly proportion of use for pre-specified immunoglobulin brands amongst prevalent users of immunoglobulins was concentrated in a limited number of brands, with clear differences in brand distribution between the data sources during the study period. Among the prespecified brands, Beriglobin, Cutaquig, Cuvitru, Gamunex, Hizentra, Intratect, Kiovig, Octagam, Privigen, Rhesonativ, and Rhophylac were observed with at least five users in at least one calendar quarter. All remaining prespecified brands were either not observed or were observed in fewer than five individuals throughout the study period, resulting in quarterly estimates of zero. The results for all brands are available in the ShinyApp. In CDW Bordeaux, Kiovig, Privigen, and Rhophylac were the most frequently observed brands (**Figure 11**). The quarterly use for Kiovig showed early variability, with a maximum of 13.9% of prevalent users in the second quarter of 2017, followed by a decline to 1.3% in the second quarter of 2018 and no users observed during the rest of the study period. For Privigen the proportion of users fluctuated across quarters, ranging from 61.2% in 2017 to 60.0% in the second quarter of 2021, with short-term increases typically observed in the first quarters followed by decreases. This pattern persisted until 2021. From mid-2021 onward, a pronounced decline was observed, reaching 13.3% in the first quarter of 2022. Subsequently, quarterly estimates ranged from 21.1% in the second quarter of 2022 to 23.3% of prevalent users in the third quarter of 2023, followed by a decline to 10.2% and 6.4% in the last two quarters of 2024. Quarterly use of Rhophylac ranged from 27.8% in 2017 to 24.7% of prevalent users in the third quarter of 2024 and 14.1% in the last quarter of 2024. There were no users of the other brands observed in CDW Bordeaux.

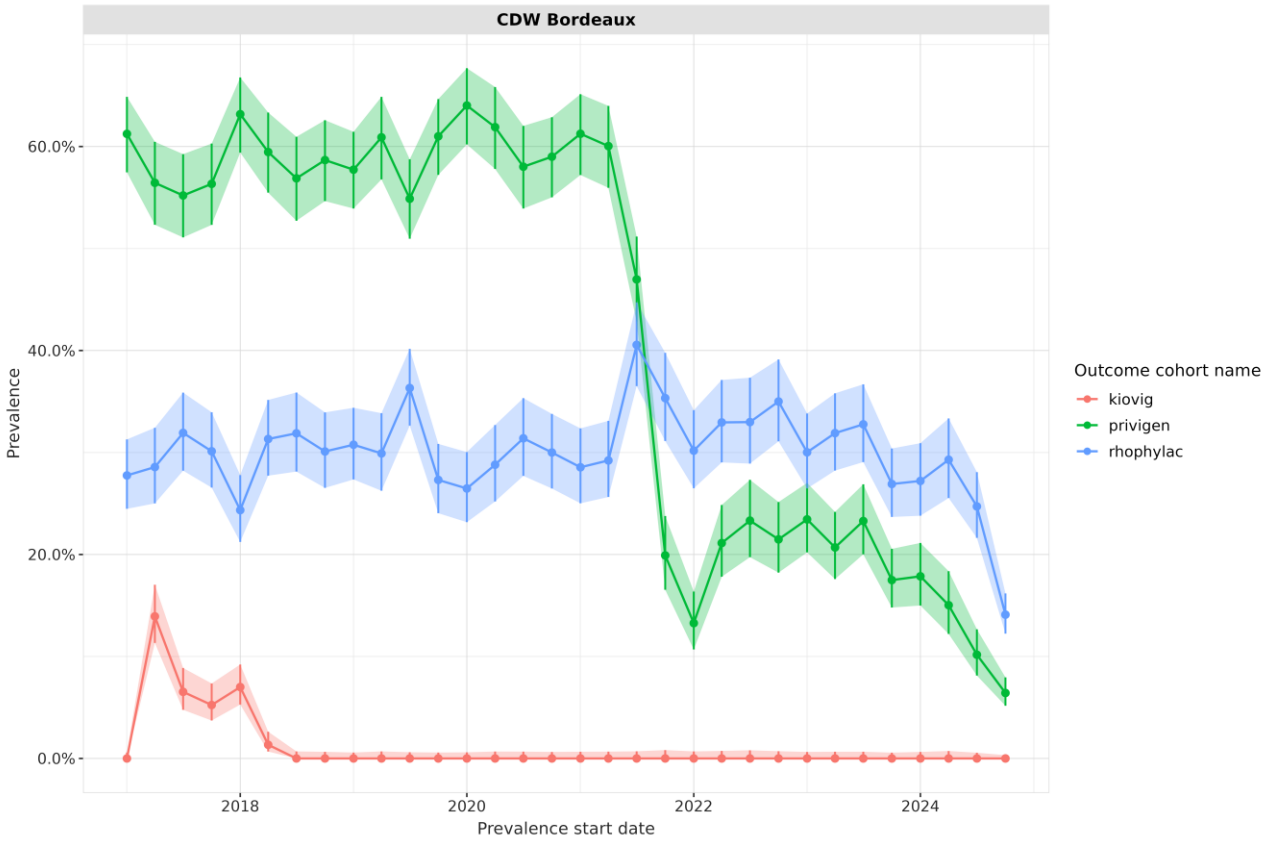


Figure 11. Quarterly proportion of immunoglobulin brand use amongst prevalent users of immunoglobulins, in CDW Bordeaux.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital. Prevalence estimates are provided with binomial 95% confidence intervals. Please note that figure only shows immunoglobulin brands for which the number of cases was sufficient to assess prevalence estimates over time. Detailed information for the other immunoglobulin brands can be found in the Shiny app.

The quarterly proportion of immunoglobulin brand use in IQVIA DA Germany can be observed in **Figure 12** and **Figure S4**. Quarterly use of Beriglobin was 4.7% during the first quarter of 2017, fluctuated over time, and reached 2.4% of prevalent users in the third quarter and 0.4% in the final quarter of 2024. For Cutaquig, the quarterly use was 0 from 2017 to 2020, increased from 0.5% in the final quarter of 2020 to 1.2% in the second quarter of 2022, and was censored during the remaining intervals. The number of users for Cuvitru was low during the study period over time, with no more than 6 users per quarterly interval. The quarterly proportion of Gamunex users was 1.8% in 2017, peaked at 4.3% in 2023, followed by a fluctuating decline to 1.6% in third quarter, and 0.2% in the final quarter of 2024. A similar pattern was observed for Hizentra, the quarterly use was 0.6% in 2017, peaked at 2.4% in 2023, followed by a fluctuating decline to 1.1% in the third quarter, and 0.2% in the final quarter of 2024. The quarterly use of Intratect fluctuated over time, starting at 0.5% in 2017, followed by some intervals with low number of users (<5 cases) and increased from 0.5% in the second quarter of 2020 to 1.4% in the second quarter of 2024, followed by a decline to 0.4% in the third quarter and 0.1% in the final quarter of 2024. The quarterly proportion of Kiovig users was censored during most of the intervals until 2019, was 0.7% in the third quarter of 2019, peaked at 2.2% in 2022 and the second quarter of 2024, followed by a decline to 1.1% in the third quarter and 0.1% in the final quarter of 2024, with fluctuations during the study period. Octagam use was limited at the beginning of study period (<5 cases) but increased over time, with quarterly estimates ranging from 0.9% in 2019 to 1.2% in the third quarter and 0.2% in the final quarter of 2024. The quarterly use of Privigen was stable at the beginning of the study period, ranging from 1.0% in 2017 to 1.1% in 2019, with a subsequent increase to 5.5% in the third quarter of 2020, followed by fluctuating estimates

with short-term increases typically observed in the second and third quarters followed by decreases. The proportion was 5.0% in the second quarter of 2024 and declined to 2.7% in the third quarter and 0.3% in the final quarter. Quarterly use of Rhesonativ fluctuated throughout the years, ranging from 9.1% in 2017 to 0.5% in the final quarter of 2023 and 1.0% in the second quarter of 2024, with other quarters of 2024 censored due to low counts (<5 cases). Quarterly proportions of Rhophylac ranged from 40.4% in 2017 to 54.3% in the second quarter of 2024, with short-term increases typically observed in the second and third quarters, followed by a decline to 23.5% in the third quarter and 3.3% in the final quarter of 2024. Of note, the proportion estimates in the final quarter of 2024 are affected by a substantial increase in the denominator population, i.e. the number of prevalent immunoglobulin users almost doubled in CDW Bordeaux, and there was a more than 6-time increase observed in IQVIA DA Germany. This increased denominator population is likely affected by the increased number of cases with a nirsevimab record.

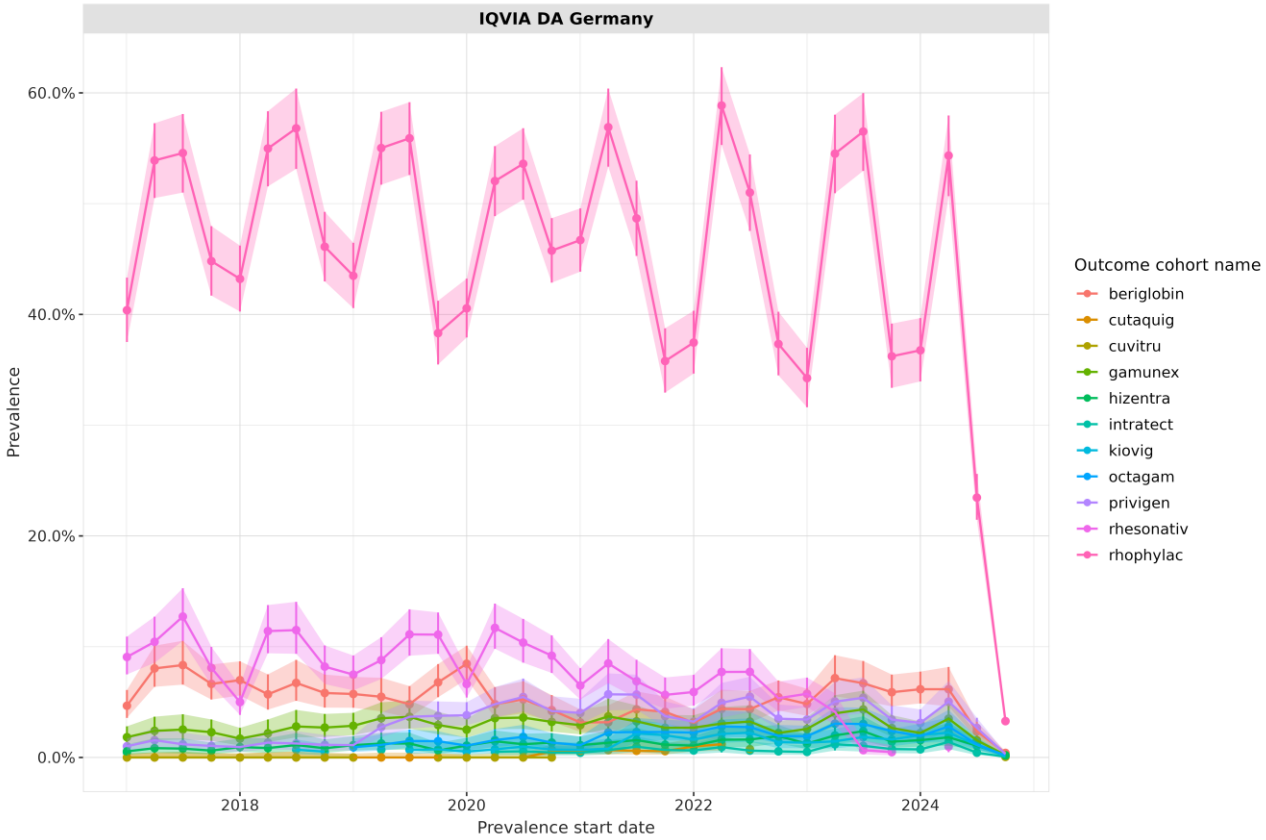


Figure 12. Quarterly proportion of immunoglobulin brand use amongst prevalent users of immunoglobulins, in IQVIA DA Germany.

IQVIA DA Germany = IQVIA Disease Analyzer Germany. Prevalence estimates are provided with binomial 95% confidence intervals. Please note that figure only shows immunoglobulin brands for which the number of cases was sufficient to assess prevalence estimates over time. Figure S4 shows the prevalence of these immunoglobulins brands excluding Rhophylac. Detailed information for the other immunoglobulin brands can be found in the Shiny app.

In CPRD GOLD, the 0.5% of prevalent immunoglobulin users had a record for Hizentra, and 0.6% had a record for Privigen during the study period. The quarterly proportion of users for these brands could not be assessed, as the intervals were either zero or censored due to low counts (<5). Detailed information can be observed in the Shiny app.

9.2.3. Treatment duration, dose, and number of prescriptions of immunoglobulin brands

The median number of exposures, i.e. a prescription or dispensing records, during the study period was 1 for Beriglobin (IQVIA DA Germany), Cuvitru (IQVIA DA Germany), Hizentra (IQVIA DA Germany and CPRD GOLD), Intratect (IQVIA DA Germany), Rhesonativ (IQVIA DA Germany), and Rhophylac (CDW Bordeaux and IQVIA DA Germany). The median number of exposures of 1.5 was observed for Cutaquig (IQVIA DA Germany), while Gamunex and Octagam each showed a median of 2 exposures (IQVIA DA Germany). The highest median number of exposures was 5 for Hyqvia in IQVIA DA Germany. For Privigen, the median number of exposures ranged from 1 (CPRD GOLD) to 2 (IQVIA DA Germany) and 3 (CDW Bordeaux), whereas Kiovig showed a median ranging from 1 exposure (CPRD GOLD) to 2 exposures (IQVIA DA Germany and CDW Bordeaux).

For Hizentra and Rhophylac, the median duration varied, ranging from 1 day in CPRD GOLD and CDW Bordeaux, respectively, to 30 days in IQVIA DA Germany. The median treatment duration for Privigen ranged from 3 days in CDW Bordeaux to 21 days in CPRD GOLD and 33.5 days in IQVIA DA Germany, while Kiovig showed median durations of 1 day in CDW Bordeaux and CPRD GOLD and 58 days in IQVIA DA Germany. The median treatment duration of 30 days was observed for (collapsed) drug eras in IQVIA DA Germany for Beriglobin, Cuvitru, Cutaquig, Intratect, Octagam, and Rhesonativ during the study period. The corresponding IQR treatment duration of Beriglobin, Rhesonativ, and Rhophylac prescriptions were all 30 days in IQVIA DA Germany, which likely reflects limited variability or imputed values of duration and therefore may not represent true treatment duration for these immunoglobulins.

The dose per ingredient varied substantially between brands and across data sources. The median initial dose of immunoglobulin G ranged from 0.01 milligrams for Rhesonativ (IQVIA DA Germany) and Rhophylac (IQVIA DA Germany) to 30,000 milligrams for Kiovig (CDW Bordeaux). The median cumulative dose of immunoglobulin G ranged from 0.3 milligrams for Rhesonativ (IQVIA DA Germany) and Rhophylac (IQVIA DA Germany) to 160,000 milligrams for Cuvitru (IQVIA DA Germany). The median initial and cumulative dose of immunoglobulin Rho(D) was 0.2 milligrams for Rhophylac in CDW Bordeaux (**Table 4–6**). Treatment characteristics of other brands could not be assessed, as the number of initiators per brand was either zero or censored due to low counts (<5).

Table 4. Number of immunoglobulin prescriptions, treatment duration, and dose (initial, cumulative) of immunoglobulin use during the study period, per immunoglobulin brand, in CDW Bordeaux.

Variable	Format	Kiovig	Privigen	Rhophylac
Number of subjects	N	144	3,234	4,675
Number of exposures	Median [q25 – q75]	2 (2 – 4)	3 (2 – 7)	1 (1 – 1)
Days exposed	Median [q25 – q75]	1 (1 – 8)	3 (1 – 5)	1 (1 – 1)
Immunoglobulin G				
Initial dose milligram	Median [q25 – q75]	30,000.00 (20,000.00 – 40,000.00)	10,000.00 (7,500.00 – 40,000.00)	–
Cumulative dose milligram	Median [q25 – q75]	40,000.00 (25,000.00 – 90,000.00)	30,000.00 (10,000.00 – 80,000.00)	–
Rho(D) immune globulin				
Initial dose milligram	Median [q25 – q75]	–	–	0.19 (0.19 – 0.19)
Cumulative dose milligram	Median [q25 – q75]	–	–	0.19 (0.19 – 0.19)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital. Minimum and maximum values can be found in the Shiny app. – = no results available. Treatment characteristics of other brands are not presented as the number of initiators per brand was either zero or censored due to low counts (<5).

Table 5. Number of immunoglobulin prescriptions, treatment duration, and dose (initial, cumulative) of immunoglobulin use during the study period, per immunoglobulin brand, in IQVIA DA Germany.

Variable	Format	Beriglobin	Cutaquig	Cuvitru	Gamunex	Hizentra	Hyqvia	Intratect	Kiovig	Octagam	Privigen	Rhesonativ	Rhophylac
Number of subjects	N	723	20	15	68	56	6	17	36	63	100	1,244	7,044
Number of exposures	Median [q25 – q75]	1 (1 – 1)	1.5 (1 – 2)	1 (1 – 2)	2 (1 – 4)	1 (1 – 2)	5 (2 – 19)	1 (1 – 4)	2 (1 – 5)	2 (1 – 4)	2 (1 – 6)	1 (1 – 1)	1 (1 – 1)
Days exposed	Median [q25 – q75]	30 (30 – 30)	30 (30 – 46)	30 (30 – 35)	36 (30 – 118)	30 (30 – 66)	122.5 (36 – 534)	30 (30 – 85)	58 (30 – 146)	30 (30 – 86.5)	33.5 (30 – 134.5)	30 (30 – 30)	30 (30 – 30)
immunoglobulin G ingredient													
Initial dose milligram	Median [q25 – q75]	5.33 (5.33 – 10.67)	2,640.00 (1,800.00 – 2,640.00)	2,666.67 (1,333.33 – 5,333.33)	3.33 (3.33 – 7.50)	3,333.33 (1,333.33 – 3,333.33)	666.67 (666.67 – 916.67)	150.00 (16.67 – 666.67)	666.67 (583.33 – 1,333.33)	6.67 (3.33 – 333.33)	–	0.01 (0.01 – 0.01)	0.01 (0.01 – 0.01)
Cumulative dose milligram	Median [q25 – q75]	160.00 (160.00 – 320.00)	79,200.00 (79,200.00 – 103,500.00)	160,000.00 (60,000.00 – 160,000.00)	300.00 (100.00 – 600.00)	100,000.00 (40,000.00 – 170,000.00)	110,000.00 (30,000.00 – 490,000.00)	6,900.00 (750.00 – 30,000.00)	40,000.00 (10,000.00 – 140,000.00)	893.00 (100.00 – 15,900.00)	–	0.33 (0.33 – 0.33)	0.33 (0.33 – 0.33)

IQVIA DA Germany = IQVIA Disease Analyzer Germany. Minimum and maximum values can be found in the Shiny app. – = no results available. Treatment characteristics of other brands are not presented as the number of initiators per brand was either zero or censored due to low counts (<5).

Table 6. Number of immunoglobulin prescriptions, treatment duration, and dose (initial, cumulative) of immunoglobulin use during the study period, per immunoglobulin brand, in CPRD GOLD.

Variable	Format	Hizentra	Privigen
Number of subjects	N	7	10
Number of exposures	Median [q25 – q75]	1 (1 – 1)	1 (1 – 1)

Variable	Format	Hizentra	Privigen
Days exposed	Median [q25 – q75]	1 (1 – 1)	21 (1 – 21)
Immunoglobulin G ingredient			
Initial dose milligram	Median [q25 – q75]	1,000.00 (1,000.00 – 1,000.00)	476.19 (476.19 – 15,625.00)
Cumulative dose milligram	Median [q25 – q75]	1,000.00 (1,000.00 – 1,000.00)	10,000.00 (10,000.00 – 20,000.00)

CPRD GOLD = Clinical Practice Research Datalink GOLD. Minimum and maximum values can be found in the ShinyApp. Treatment characteristics of other brands could not be assessed, as the number of initiators per brand was either zero or censored due to low counts (<5).

9.2.4. Characterisation of immunoglobulin initiators

9.2.4.1. Demographic characteristics

The demographic characteristics of immunoglobulin initiators are provided per brand for CDW Bordeaux (**Table 7**), IQVIA DA Germany (**Table 8**), and CPRD GOLD (**Table 9**). The median age of immunoglobulin initiators ranged between 30 years among 4,675 Rhophylac initiators in CDW Bordeaux and 64 years among 100 Privigen initiators in IQVIA DA Germany (**Table 7–9**). Across all data sources, the majority of participants were adults aged 19–65 years, ranging between 49.4% of all 3,234 Privigen initiators in CDW Bordeaux and 99.1% of all 1,244 Rhesonativ initiators in IQVIA DA Germany. The sex distribution varied per brand and data source. For example, 45.7% of Privigen initiators in CDW Bordeaux were female, while the sex distribution was equal among the 10 Privigen initiators in CPRD GOLD, and females represented the majority (54.0%) of all Privigen initiators in IQVIA DA Germany. The vast majority of all 4,675 Rhophylac initiators in CDW Bordeaux and of all 7,044 Rhophylac initiators in IQVIA DA Germany were female (99.98% and 99.7%, respectively).

For several prespecified brands, the demographic characteristics of initiators could not be assessed, as the number of initiators per brand was either zero or censored (<5) in the data sources. The number of recorded subjects is provided per brand in the Shiny app.

Table 7. Demographic characteristics of individuals initiating immunoglobulin therapy at index date, per immunoglobulin brand, in CDW Bordeaux.

Variable name	Estimate name	Kiovig	Privigen	Rhophylac
Subjects	N	144	3,234	4,675
Age	Median [q25 – q75]	63 [50 – 71]	56 [31 – 69]	30 [25 – 34]
	Range	0 to 89	0 to 96	0 to 51
Age group				
• 1 to 18	N (%)	<5	461 (14.25%)	200 (4.28%)
• 19 to 65	N (%)	79 (54.86%)	1,598 (49.41%)	4,464 (95.49%)
• 66 to 150	N (%)	61 (42.36%)	1,034 (31.97%)	0
• None	N (%)	<5	141 (4.36%)	11 (0.24%)
Sex				
• Female	N (%)	77 (53.47%)	1,479 (45.73%)	4,674 (99.98%)
• Male	N (%)	67 (46.53%)	1,755 (54.27%)	<5

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital. Demographic characteristics of other brands could not be assessed as the number of initiators per brand was either zero or censored due to low counts (<5).

Table 8. Demographic characteristics of individuals initiating immunoglobulin therapy at index date, per immunoglobulin brand, in IQVIA DA Germany.

Variable name	Estimate name	Beriglobin	Cutaquig	Cuvitru	Gamunex	Hizentra	Hyqvia	Intratect	Kiovig	Octagam	Privigen	Rhesonativ	Rhophylac
Subjects	N	723	20	15	68	56	6	17	36	63	100	1,244	7,044
Age	Median [q25 – q75]	56 [39 – 69]	47 [23 – 63]	48 [22 – 63]	58 [42 – 69]	58 [37 – 65]	44 [20 – 61]	57 [49 – 65]	61 [54 – 73]	62 [55 – 75]	64 [54 – 74]	31 [28 – 35]	32 [29 – 36]
	Range	3 to 91	7 to 81	1 to 81	4 to 85	4 to 87	15 to 75	35 to 83	24 to 87	30 to 87	20 to 89	0 to 57	1 to 74
Age group													
• 1 to 18	N (%)	24 (3.32%)	<5	<5	<5	<5	<5	0	0	0	0	10 (0.80%)	65 (0.92%)
• 19 to 65	N (%)	473 (65.42%)	13 (65.00%)	9 (60.00%)	44 (64.71%)	39 (69.64%)	<5	13 (76.47%)	22 (61.11%)	35 (55.56%)	54 (54.00%)	1,233 (99.12%)	6,976 (99.03%)
• 66 to 150	N (%)	226 (31.26%)	<5	<5	23 (33.82%)	13 (23.21%)	<5	<5	14 (38.89%)	28 (44.44%)	46 (46.00%)	0	<5
• None	N (%)	0	0	0	0	0	0	0	0	0	0	<5	0
Sex													
• Female	N (%)	425 (58.78%)	10 (50.00%)	10 (66.67%)	32 (47.06%)	28 (50.00%)	<5	8 (47.06%)	14 (38.89%)	30 (47.62%)	54 (54.00%)	1,242 (99.84%)	7,023 (99.70%)
• Male	N (%)	297 (41.08%)	10 (50.00%)	5 (33.33%)	36 (52.94%)	28 (50.00%)	<5	9 (52.94%)	22 (61.11%)	33 (52.38%)	46 (46.00%)	<5	14 (0.20%)
• None	N (%)	<5	0	0	0	0	0	0	0	0	0	0	7 (0.10%)

IQVIA DA Germany = IQVIA Disease Analyzer Germany. Demographic characteristics of other brands could not be assessed as the number of initiators per brand was either zero or censored due to low counts (<5).

Table 9. Demographic characteristics of individuals initiating immunoglobulin therapy at index date, per immunoglobulin brand, in CPRD GOLD.

Variable name	Estimate name	Hizentra	Privigen
Subjects	N	7	10
Age	Median [q25 – q75]	62 [51 – 66]	50 [13 – 76]
	Range	28 to 83	2 to 86
Age group			
• 1 to 18	N (%)	0	<5
• 19 to 65	N (%)	5 (71.43%)	<5
• 66 to 150	N (%)	<5	<5
• None	N (%)	0	0
Sex			
• Female	N (%)	<5	5 (50.0%)
• Male	N (%)	<5	5 (50.0%)

CPRD GOLD = Clinical Practice Research Datalink GOLD. Demographic characteristics of other brands could not be assessed as the number of initiators per brand was either zero or censored due to low counts (<5).

9.2.4.2. Indication of use

The indication of use varied per immunoglobulin brand and across data sources within the predefined time window (30 days before to 7 days after treatment initiation) (**Table 10–11,** Shiny app at EUPAS1000000823).

Among Beriglobin initiators, oncology was the most frequently observed diagnosis (2.9%), followed by COVID-19 (0.8%), and primary immunodeficiency syndrome indications (0.7%) in IQVIA DA Germany.

Among Kiovig initiators, oncology was the most frequently observed diagnosis (41.7%), followed by primary immunodeficiency syndrome indications (16.7%), indications related to internal medicine (9.0%), neurology indications (3.5%), and Sjögrens syndrome (3.5%) in CDW Bordeaux.

Among Privigen initiators in CDW Bordeaux, oncology was the most frequently observed diagnosis (29.8%), followed by neurology indications (11.4%), primary immunodeficiency syndrome indications (5.1%), indications related to internal medicine (5.0%), and several other prespecified indications diagnosed in less than 3.0% of the initiators. In IQVIA DA Germany, neurology indications were recorded in 6.0% of Privigen initiators, while the frequency of other prespecified indications was either zero or censored (<5 cases).

Among Rhesonativ initiators in IQVIA DA Germany, 'other indications' was the most frequently observed diagnosis (0.5%), but counts were too low (<5 cases) to assess which specific indications.

Among Rhophylac initiators in CDW Bordeaux, oncology was the most frequently observed diagnosis (1.2%), followed by epilepsy (0.6%), COVID-19 (0.2%), and primary immunodeficiency syndrome indications (0.1%). In IQVIA DA Germany, oncology indications, epilepsy and COVID-19 were recorded in in 0.1% of Rhophylac initiators, while the frequency of the other prespecified indications was either zero or censored (<5 cases).

The number of recorded indications of use among individuals initiating treatment with Cutaquig, Cuvitru Gamunex, Hizentra, Hyqvia, Intratect, Kiovig, and Octagam in IQVIA DA Germany was either zero or censored due to low counts (<5), and was zero among Hizentra, Kiovig, Octagam, and Privigen initiators in CPRD GOLD (Shiny app at EUPAS1000000823).

Overall, widening the time window to any time prior to 7 days following treatment initiation increased the prevalence of pre-specified indications of use (**Table 10–11,** Shiny app at EUPAS1000000823).

Indications of use for other brands and data sources could not be assessed, as the number of initiators per brand was either zero or censored (<5) during the study period.

Table 10. Indications of use of individuals initiating immunoglobulin therapy during the study period, per immunoglobulin brand, in CDW Bordeaux. Indications with 0 or <5 users are not included in the tables.

	Any time prior to 7 days after index date [-inf, +7]	30 days prior to 7 days after the index date [-30, +7]	7 days prior to 7 days after the index date [-7, +7]
Indication of use	**n (%)**	**n (%)**	**n (%)**
Kiovig			
Internal medicine	15 (10.42)	13 (9.03)	13 (9.03)
Neurology	7 (4.86)	5 (3.47)	5 (3.47)
Other indications*	79 (54.86)	66 (45.83)	66 (45.83)
Other indications: epilepsy	5 (3.47)	<5	<5
Other indications: oncology	71 (49.31)	60 (41.67)	60 (41.67)
Other indications: Sjögren's syndrome	7 (4.86)	5 (3.47)	5 (3.47)
Primary immunodeficiency syndrome	33 (22.92)	24 (16.67)	23 (15.97)
Privigen			
Hepatology	9 (0.28)	<5	<5
Infectious diseases	15 (0.46)	15 (0.46)	15 (0.46)
Internal medicine	178 (5.50)	162 (5.01)	162 (5.01)
Neurology	391 (12.09)	368 (11.38)	365 (11.28)
Other indications*	1,232 (38.10)	1,079 (33.36)	1,062 (32.84)
Other indications: COVID-19	54 (1.67)	40 (1.24)	39 (1.21)
Other indications: epilepsy	125 (3.87)	94 (2.91)	87 (2.69)
Other indications: oncology	1,095 (33.86)	963 (29.78)	950 (29.38)
Other indications: progressive systemic sclerosis	13 (0.40)	8 (0.25)	6 (0.19)
Other indications: Sjögren's syndrome	36 (1.11)	28 (0.87)	27 (0.83)
Primary immunodeficiency syndrome	206 (6.37)	165 (5.10)	161 (4.98)
Secondary immunodeficiencies	16 (0.49)	13 (0.40)	11 (0.34)
Rhophylac			
Internal medicine	6 (0.13)	<5	<5
Other indications*	121 (2.59)	90 (1.93)	87 (1.86)
Other indications: COVID-19	14 (0.30)	10 (0.21)	8 (0.17)
Other indications: epilepsy	38 (0.81)	27 (0.58)	26 (0.56)
Other indications: oncology	72 (1.54)	54 (1.16)	54 (1.16)
Primary immunodeficiency syndrome	8 (0.17)	5 (0.11)	5 (0.11)

The frequency of prespecified indications of use was assessed any time prior to 7 days after immunoglobulin initiation [-inf, +7], 30 days prior to 7 days after immunoglobulin initiation [-30, +7], and 7 days prior to 7 days after immunoglobulin initiation [-30, +7]. * = Frequencies of 'Other indications' are provided overall and per individual indication; CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital. Indications of use of other brands could not be assessed as the number of initiators per brand was either zero or censored due to low counts (<5).

Table 11. Indications of use of individuals initiating immunoglobulin therapy during the study period, per immunoglobulin brand, in IQVIA DA Germany. Indications with 0 or <5 users are not included in the tables.

	Any time prior to 7 days after index date [-inf, +7]	30 days prior to 7 days after the index date [-30, +7]	7 days prior to 7 days after the index date [-7, +7]
Indication of use	**n (%)**	**n (%)**	**n (%)**
Beriglobin			
Other indications*	161 (22.27)	28 (3.87)	18 (2.49)
Other indications: COVID-19	60 (8.30)	6 (0.83)	<5
Other indications: epilepsy	12 (1.66)	<5	<5
Other indications: oncology	100 (13.83)	21 (2.90)	15 (2.07)
Primary immunodeficiency syndrome	11 (1.52)	5 (0.69)	<5
Gamunex			
Other indications*	10 (14.71)	<5	<5
Hizentra			
Neurology	5 (8.93)	<5	<5
Other indications*	11 (19.64)	<5	<5
Other indications: oncology	7 (12.50)	<5	<5
Primary immunodeficiency syndrome	10 (17.86)	<5	<5
Kiovig			
Other indications*	13 (36.11)	<5	<5
Other indications: oncology	12 (33.33)	<5	<5
Octagam			
Other indications*	26 (41.27)	<5	<5
Other indications: oncology	24 (38.10)	<5	<5
Privigen			
Neurology	13 (13.00)	6 (6.00)	6 (6.00)
Other indications*	26 (26.00)	<5	<5
Other indications: oncology	21 (21.00)	<5	0
Rhesonativ			
Other indications*	29 (2.33)	6 (0.48)	<5
Other indications: epilepsy	12 (0.96)	<5	<5
Other indications: oncology	14 (1.13)	<5	0
Rhophylac			
Other indications*	132 (1.87)	17 (0.24)	9 (0.13)
Other indications: COVID-19	20 (0.28)	5 (0.07)	<5
Other indications: epilepsy	18 (0.26)	5 (0.07)	<5
Other indications: oncology	96 (1.36)	7 (0.10)	<5

The frequency of prespecified indications of use was assessed any time prior to 7 days after immunoglobulin initiation [-inf, +7], 30 days prior to 7 days after immunoglobulin initiation [-30, +7], and 7 days prior to 7 days after immunoglobulin initiation [-30, +7]. * = Frequencies of 'Other indications' are provided overall and per individual indication; IQVIA DA Germany = IQVIA Disease Analyzer Germany. Indications of use for Cutaquig, Cuvitru, Hyqvia, and Intratect could not be provided as the number of users per indication was either zero or censored due to low counts (<5). Indications of use of other brands could not be assessed as the number of initiators per brand was either zero or censored due to low counts.

9.2.4.3. Comorbidities

The most commonly diagnosed comorbidities among immunoglobulin initiators varied substantially between brands and data sources (**Tables 12–13**). In the year prior to treatment initiation, acute upper respiratory infection was most frequently recorded among individuals initiating treatment with Beriglobin (11.8%), immunodeficiency disorder among Cuvitru initiators (33.3%) and Hizentra initiators (17.9%), and chronic obstructive pulmonary disease among Gamunex initiators (22.1%) in IQVIA DA Germany. Illness (i.e. life expectancy limiting condition, terminal illness, or viral syndrome) was most frequently recorded among Cutaquig initiators (25.0%), Hizentra initiators (17.9%), Octagam initiators (15.9%), and Privigen initiators (18.0%) in IQVIA DA Germany, while essential hypertension was most frequently recorded among Privigen initiators (34.0%) in CDW Bordeaux. Essential hypertension was also most frequently recorded among Kiovig initiators (43.1%) in CDW Bordeaux, while polyneuropathy was most common among Kiovig initiators (22.2%) in IQVIA DA Germany. Rhesonativ initiators most often had a noninflammatory disorder of the vagina (26.0%), while the most recorded conditions among Rhophylac initiators were first degree perineal laceration in CDW Bordeaux (23.3%) and pregnancy in IQVIA DA Germany (42.1%) in the year prior to index date.

Counts were too low (<5) to assess which comorbidities were most frequent among individuals initiating treatment with Hyqvia or Intratect in IQVIA DA Germany, and with Hizentra or Privigen in CPRD GOLD within the year prior to treatment initiation.

Overall, widening the time window to any time prior to treatment initiation increased the prevalence of recorded conditions, while narrowing the time window to 30 days prior to treatment initiation decreased the prevalence of recorded conditions (**Table S5**).

Table 12. Top 10 recorded conditions in individuals initiating immunoglobulin therapy, prior to the index date, per immunoglobulin brand, in CDW Bordeaux.

One year prior to the index date [-365, 0]		
Kiovig	**Privigen**	**Rhophylac**
Condition, n (%)	**Condition, n (%)**	**Condition, n (%)**
Essential hypertension, 62 (43.06)	Essential hypertension, 1,099 (33.98)	First degree perineal laceration, 1,089 (23.29)
White blood cell disorder, 55 (38.19)	Headache, 841 (26.00)	Anemia in mother complicating pregnancy, childbirth AND/OR puerperium, 965 (20.64)
Hypogammaglobulinemia, 49 (34.03)	Nausea and vomiting, 779 (24.09)	Gestational edema, 744 (15.91)
Localized edema, 48 (33.33)	Hypokalemia, 751 (23.22)	Labor and delivery complicated by fetal heart rate anomaly, 640 (13.69)
Dyspnea, 45 (31.25)	White blood cell disorder, 729 (22.54)	Hemorrhoids in puerperium, 513 (10.97)
Headache, 39 (27.08)	Hypo-osmolality and or hyponatremia, 727 (22.48)	Obesity, 484 (10.35)
Nausea and vomiting, 37 (25.69)	Hyponatremia with decreased serum osmolality, 727 (22.48)	Prem rupture of membranes onset of labor within 24 hours, 470 (10.05)
Obesity, 37 (25.69)	Fever, 714 (22.08)	Tobacco dependence syndrome, 444 (9.50)
Cough, 36 (25.00)	Dyspnea, 655 (20.25)	Cracked nipple in pregnancy, the puerperium or lactation, 411 (8.79)
Hypokalemia, 34 (23.61)	Localized edema, 647 (20.01)	Gestational diabetes mellitus, 404 (8.64)

Comorbidities of initiators of several prespecified brands could not be assessed as the number of initiators per brand was either zero or censored due to low counts (<5). The other time windows can be observed in **Table S5**. CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital.

Table 13. Top 10 recorded conditions in individuals initiating immunoglobulin therapy, prior to the index date, per immunoglobulin brand, in IQVIA DA Germany.

One year prior to the index date [-365, 0]									
Beriglobin	**Cutaquig**	**Cuvitru**	**Gamunex**	**Hizentra**	**Kiovig**	**Octagam**	**Privigen**	**Rhesonativ**	**Rhophylac**
Condition, n (%)	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**
Acute upper respiratory infection, 163 (11.76)	Illness*, 5 (25.00)	Immunodeficiency disorder, 5 (33.33)	Chronic obstructive pulmonary disease, 15 (22.06)	Illness*, 10 (17.86)	Polyneuropathy, 8 (22.22)	Illness*, 10 (15.87)	Illness*, 18 (18.00)	Noninflammatory disorder of the vagina, 323 (25.96)	Pregnancy, 2,966 (42.11)
Essential hypertension, 124 (10.65)	-	-	Acute bronchitis, 10 (14.71)	Immunodeficiency disorder, 10 (17.86)	-	Immunodeficiency disorder, 8 (12.70)	Polyneuritis, 15 (15.00)	Pregnancy, 307 (24.68)	Noninflammatory disorder of the vagina, 2,232 (31.69)
Illness*, 85 (9.54)	-	-	Heart disease, 8 (11.76)	Polyneuritis, 8 (14.29)	-	Multiple sclerosis, 7 (11.11)	Polyneuropathy, 14 (14.00)	Symptomatic disorders in pregnancy, 291 (23.39)	Unplanned pregnancy, 1,687 (23.95)
Acute bronchitis, 84 (8.71)	-	-	Illness*, 8 (11.76)	Polyneuropathy, 6 (10.71)	-	Polyneuritis, 5 (7.94)	Essential hypertension, 9 (9.00)	Lower abdominal pain, 237 (19.05)	Lower abdominal pain, 1,465 (20.80)
Nerve root disorder, 77 (6.50)	-	-	Polyneuropathy, 8 (11.76)	Acute bronchitis, 5 (8.93)	-	Polyneuropathy, 5 (7.94)	Acute upper respiratory infection, 6 (6.00)	Secondary amenorrhea, 225 (18.09)	Disorder of pregnancy, 1,341 (19.04)
Bronchitis, 69 (6.09)	-	-	Polyneuritis, 7 (10.29)	Infectious disease, 5 (8.93)	-	-	Immunodeficiency disorder, 5 (5.00)	Unplanned pregnancy, 205 (16.48)	Threatened miscarriage, 1,152 (16.35)
Immunodeficiency disorder, 63 (5.67)	-	-	Viral disease, 7 (10.29)	-	-	-	Multiple sclerosis, 5 (5.00)	Mild hyperemesis gravidarum, 166 (13.34)	Illness, 1,083 (15.37)

One year prior to the index date [-365, 0]									
Beriglobin	**Cutaquig**	**Cuvitru**	**Gamunex**	**Hizentra**	**Kiovig**	**Octagam**	**Privigen**	**Rhesonativ**	**Rhophylac**
Condition, n (%)	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**	**Condition, n (%)**
Chronic obstructive pulmonary disease, 53 (5.53)	-	-	Asthma, 6 (8.82)	-	-	-	Neuralgia, 5 (5.00)	Threatened miscarriage, 156 (12.54)	Rhesus isoimmunization affecting pregnancy, 1,025 (14.55)
Inflammatory disorder of digestive tract, 47 (5.26)	-	-	Acute exacerbation of chronic obstructive pulmonary disease, 5 (7.35)	-	-	-	Paraplegia, 5 (5.00)	Illness*, 123 (9.89)	Mild hyperemesis gravidarum, 1,012 (14.37)
Pure hypercholesterolemia, 44 (5.12)	-	-	Allergic asthma, 5 (7.35)	-	-	-	Pneumonia, 5 (5.00)	Cervical incompetence, 121 (9.73)	Amenorrhea, 953 (13.53)

Brands with only censored counts for comorbidities (i.e. Hyqvia and Intratect) were not included in the table. Comorbidities of Clairyg, Flebogamma DIF, Gammagard, Gammaplex, Ig vena, Iqymune, Nanogam, Panzyga, Pentaglobin, Tegeline, Xembify and Yimmugo initiators could not be assessed as the number of initiators per brand was either zero or censored due to low counts (<5). The other time windows can be observed in **Table S5**. - = Counts for comorbidities were zero or censored (<5); IQVIA DA Germany = IQVIA Disease Analyzer Germany. * = Illness includes life expectancy limiting condition, terminal illness, and viral syndrome concepts.

9.2.4.4. Infections

The prevalence of infections among immunoglobulin initiators varied substantially between brands and data sources (**Table 14–15,** Shiny app at EUPAS1000000823). 'Respiratory & ear, nose, throat, ocular infections' were most frequently observed among individuals initiating treatment with Beriglobin (18.7%), Gamunex (7.4%), Hizentra (10.7%) in IQVIA DA Germany, and Kiovig (16.7%) in CDW Bordeaux within the 30 days after treatment initiation. Both bacterial infections (22.1%) and 'Respiratory & ear, nose, throat, ocular infections' (21.8%) were frequently recorded among Privigen initiators in CDW Bordeaux, bacterial infections were also most frequent among Rhophylac initiators (4.6%) in CDW Bordeaux, and urinary infections were most frequently recorded among Rhesonativ initiators (3.6%) and Rhophylac initiators (3.3%) in IQVIA DA Germany within the 30 days after treatment initiation.

The number of recorded types of infections among individuals initiating treatment with Cutaquig, Cuvitru Hyqvia, Intratect, Kiovig, Octagam, and Privigen in IQVIA DA Germany, and of Hizentra and Privigen in CPRD GOLD was either zero or censored due to low counts (<5) within the 30 days after treatment initiation.

Overall, widening the time window to the year following treatment initiation increased the prevalence of pre-specified infections (**Table 14–15,** Shiny app at EUPAS1000000823).

Table 14. Common infections among individuals who initiated immunoglobulin therapy during the study period, provided per immunoglobulin brand, in CDW Bordeaux.

	Kiovig	Privigen	Rhophylac
Infections	**n (%)**	**n (%)**	**n (%)**
First month following treatment initiation [0, +30]			
Bacterial infections	22 (15.28)	714 (22.08)	217 (4.64)
Central nervous system infections	<5	69 (2.13)	<5
Fungal infections	0	18 (0.56)	0
Gastrointestinal & intra-abdominal infections	<5	104 (3.22)	23 (0.49)
Respiratory & ear, nose, throat, ocular infections	24 (16.67)	705 (21.80)	40 (0.86)
Systemic infections	7 (4.86)	282 (8.72)	36 (0.77)
Urinary infections	6 (4.17)	196 (6.06)	122 (2.61)
Viral infections	10 (6.94)	190 (5.88)	38 (0.81)
First year following treatment initiation [0, +365]			
Bacterial infections	43 (29.86)	1,014 (31.35)	262 (5.60)
Central nervous system infections	<5	93 (2.88)	<5
Fungal infections	<5	29 (0.90)	<5
Gastrointestinal & intra-abdominal infections	9 (6.25)	194 (6.00)	36 (0.77)
Respiratory & ear, nose, throat, ocular infections	51 (35.42)	1,038 (32.10)	65 (1.39)
Systemic infections	13 (9.03)	402 (12.43)	46 (0.98)
Urinary infections	19 (13.19)	333 (10.30)	144 (3.08)
Viral infections	17 (11.81)	300 (9.28)	52 (1.11)

The frequency of prespecified infections was assessed during the first month following immunoglobulin initiating [0, 30] and the first year following treatment initiation [0, +365]. Infections of initiators of several brands could not be assessed as the number of initiators per brand was either zero or censored due to low counts (<5). CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital.

Table 15. Common infections among individuals who initiated immunoglobulin therapy during the study period, provided per immunoglobulin brand, in IQVIA DA Germany. Common infection types identified for 0 or <5 users are not included in the table.

	Beriglobin	Cuvitru	Gamunex	Hizentra	Octagam	Privigen	Rhesonativ	Rhophylac
Infections	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
First month following treatment initiation [0, +30]								
Bacterial infections	19 (2.63)	0	0	<5	<5	<5	5 (0.40)	39 (0.55)
Respiratory & ear, nose, throat, ocular infections	135 (18.67)	<5	5 (7.35)	6 (10.71)	<5	<5	13 (1.05)	58 (0.82)
Urinary infections	6 (0.83)	0	<5	<5	0	<5	45 (3.62)	231 (3.28)
Viral infections	24 (3.32)	0	0	<5	<5	<5	<5	9 (0.13)
First year following treatment initiation [0, +365]								
Bacterial infections	44 (6.09)	<5	<5	<5	<5	<5	23 (1.85)	151 (2.14)
Gastrointestinal & intra-abdominal infections	7 (0.97)	<5	0	0	0	0	<5	16 (0.23)
Respiratory & ear, nose, throat, ocular infections	301 (41.63)	6 (40.00)	17 (25.00)	13 (23.21)	11 (17.46)	13 (13.00)	46 (3.70)	174 (2.47)
Urinary infections	52 (7.19)	<5	<5	<5	0	<5	105 (8.44)	666 (9.45)
Viral infections	43 (5.95)	0	0	<5	<5	<5	9 (0.72)	39 (0.55)

The frequency of prespecified infections was assessed during the first month following immunoglobulin initiating [0, 30] and the first year following treatment initiation [0, +365]. Infections of initiators of several brands could not be assessed as the number of initiators per brand was either zero or censored due to low counts (<5). IQVIA DA Germany = IQVIA Disease Analyzer Germany.

9.2.4.5. Antibiotics

The prevalence of antibiotics among immunoglobulin initiators varied substantially between brands and data sources (**Table 16–17**). Macrolides, lincosamides, and streptogramins were most frequently recorded among individuals initiating treatment with Beriglobin (7.1%) and Gamunex (10.3%) in IQVIA DA Germany and Quinolone antibacterials among Hizentra initiators (8.9%) in IQVIA DA Germany within the 30 days after treatment initiation. Both 'Beta-lactam antibacterials, penicillins' (12.7%) and 'Sulphonamides and trimethoprim' (13.1%) were frequently recorded among Privigen initiators in CDW Bordeaux, and 'Sulphonamides and trimethoprim' antibiotics were also most frequently recorded among Privigen initiators (5.0%) in IQVIA DA Germany and Kiovig initiators (13.9%) in CDW Bordeaux. 'Other antibacterials' were most frequent among Rhophylac initiators (5.3%) in CDW Bordeaux, and among Rhesonativ initiators (1.4%) and Rhophylac initiators (1.8%) in IQVIA DA Germany within the 30 days after treatment initiation.

The number of antibiotic records among individuals initiating treatment with Cutaquig, Cuvitru, Hyqvia, Intratect, Kiovig, and Octagam in IQVIA DA Germany, and of Hizentra and Privigen in CPRD GOLD was either zero or censored due to low counts (<5) within the 30 days after treatment initiation (Shiny app at EUPAS1000000823). Overall, widening the time window to the year following treatment initiation increased the records of pre-specified antibiotics (**Table 16–17,** Shiny app at EUPAS1000000823).

Table 16. The frequency of antibiotics prescribed among individuals initiating immunoglobulin therapy during the study period, provided per immunoglobulin brand, in CDW Bordeaux. Antibiotics identified for 0 or <5 users are not included in the table.

	Kiovig	Privigen	Rhophylac
Antibiotics	**n (%)**	**n (%)**	**n (%)**
First month following treatment initiation [0, +30]			
Aminoglycoside antibacterials	<5	75 (2.3)	20 (0.43)
Beta-lactam antibacterials, penicillins	8 (5.56)	409 (12.65)	129 (2.76)
Macrolides, lincosamides, and streptogramins	<5	91 (2.81)	49 (1.05)
Other antibacterials	<5	107 (3.31)	247 (5.28)
Other beta-lactam antibacterials	6 (4.17)	319 (9.86)	56 (1.20)
Quinolone antibacterials	0	51 (1.58)	5 (0.11)
Sulphonamides and trimethoprim	20 (13.89)	424 (13.11)	10 (0.21)
Tetracyclines	0	10 (0.31)	<5
First year following treatment initiation [0, +365]			
Aminoglycoside antibacterials	10 (6.94)	202 (6.25)	26 (0.56)
Beta-lactam antibacterials, penicillins	22 (15.28)	770 (23.81)	174 (3.72)
Macrolides, lincosamides, and streptogramins	9 (6.25)	211 (6.52)	55 (1.18)
Other antibacterials	7 (4.86)	244 (7.54)	269 (5.75)
Other beta-lactam antibacterials	17 (11.81)	571 (17.66)	78 (1.67)
Quinolone antibacterials	<5	120 (3.71)	10 (0.21)
Sulphonamides and trimethoprim	29 (20.14)	643 (19.88)	19 (0.41)
Tetracyclines	<5	20 (0.62)	<5

The frequency of prespecified antibiotic prescriptions was assessed during the first month following immunoglobulin initiating [0, 30] and the first year following treatment initiation [0, +365]. Antibiotics recorded among initiators of several prespecified brands could not be assessed as the number of initiators per brand was either zero or censored due to low counts (<5). CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital.

Table 17. The frequency of antibiotics prescribed among individuals initiating immunoglobulin therapy during the study period, provided per immunoglobulin brand, in IQVIA DA Germany. Antibiotics identified for 0 or <5 users are not included in the table.

	Beriglobin	Cutaquig	Cuvitru	Gamunex	Hizentra	Hyqvia	Intratect	Kiovig	Octagam	Privigen	Rhesonativ	Rhophylac
Antibiotics	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
First month following treatment initiation [0, +30]												
Aminoglycoside antibacterials	<5	0	0	0	<5	0	0	0	0	0	0	0
Beta-lactam antibacterials, penicillins	33 (4.56)	0	<5	0	0	0	<5	<5	<5	0	10 (0.80)	44 (0.62)
Macrolides, lincosamides, and streptogramins	51 (7.05)	<5	<5	7 (10.29)	<5	0	0	0	<5	0	5 (0.40)	49 (0.70)
Other antibacterials	8 (1.11)	0	0	0	<5	0	0	0	0	0	17 (1.37)	127 (1.80)
Other beta-lactam antibacterials	40 (5.53)	0	0	<5	<5	0	<5	0	0	<5	<5	48 (0.68)
Quinolone antibacterials	31 (4.29)	0	0	6 (8.82)	5 (8.93)	<5	<5	0	<5	<5	0	7 (0.10)
Sulphonamides and trimethoprim	5 (0.69)	0	0	0	<5	0	0	<5	<5	5 (5.00)	0	<5
Tetracyclines	19 (2.63)	0	0	<5	0	0	0	<5	0	<5	0	28 (0.40)
First year following treatment initiation [0, +365]												
Aminoglycoside antibacterials	15 (2.07)	0	0	<5	<5	0	<5	0	0	0	0	<5
Beta-lactam antibacterials, penicillins	91 (12.59)	<5	<5	9 (13.24)	<5	<5	<5	<5	9 (14.29)	<5	49 (3.94)	269 (3.82)
Macrolides, lincosamides, and streptogramins	130 (17.98)	<5	<5	16 (23.53)	8 (14.29)	<5	<5	<5	<5	<5	18 (1.45)	119 (1.69)
Other antibacterials	35 (4.84)	0	<5	<5	<5	0	0	<5	<5	0	77 (6.19)	458 (6.50)
Other beta-lactam antibacterials	101 (13.97)	0	<5	11 (16.18)	<5	<5	<5	0	5 (7.94)	<5	29 (2.33)	180 (2.56)
Quinolone antibacterials	81 (11.20)	0	<5	11 (16.18)	8 (14.29)	<5	<5	<5	7 (11.11)	9 (9.00)	<5	19 (0.27)
Sulphonamides and trimethoprim	26 (3.60)	0	<5	0	<5	<5	<5	<5	<5	8 (8.00)	<5	20 (0.28)
Tetracyclines	35 (4.84)	0	0	<5	0	0	0	<5	0	<5	9 (0.72)	41 (0.58)

The frequency of prespecified antibiotic prescriptions was assessed during the first month following immunoglobulin initiating [0, 30] and the first year following treatment initiation [0, +365]. Antibiotics recorded among initiators of several prespecified brands could not be assessed as the number of initiators per brand was either zero or censored due to low counts (<5). IQVIA DA Germany = IQVIA Disease Analyzer Germany.

10. DISCUSSION

10.1. Key results

Prevalence of immunoglobulin use

A total of 37,786,260 individuals across 3 European data sources were included to assess immunoglobulin use between 2017 and 2024. The overall immunoglobulin use remained low across all three data sources during the study period. In the hospital data source CDW Bordeaux, annual prevalence was 0.22% in 2017 and remained stable through 2019, decreased slightly in 2020, and then increased from 2023 onwards, reaching 0.4% in 2024. In IQVIA DA Germany, annual prevalence remained 0.03% between 2017 and 2023, with an increase to 0.1% in 2024. In CPRD GOLD, annual prevalence was 0.02% in 2017 and decreased to approximately 0 during the remainder of the study period due to limited use.

Stratification by type of immunoglobulin revealed that annual prevalence was concentrated in a limited number of ingredients. One of the most prevalent immunoglobulin ingredients was immunoglobulin G, with annual prevalence estimates consistent in CDW Bordeaux (0.1% in 2017 to 2024, with a slightly decrease between 2020 and 2022) and IQVIA DA Germany (0.02%). The annual prevalence of immunoglobulin Rho(D) use ranged from 0.09% in 2017 to 0.1% in 2024 in CDW Bordeaux, while it was censored or approximately 0 in IQVIA DA Germany and CPRD GOLD.

The indicated route of administration of immunoglobulin G and immunoglobulin Rho(D), during the study period was frequently registered in the data source as 'other', i.e. not specifically intravenous, intramuscular, or subcutaneous. The number of cases with records for the other ingredients and routes of administration was either zero or too low to assess prevalence estimates.

Sex-stratified prevalence analyses revealed a female predisposition for immunoglobulin G use in IQVIA DA Germany and for immunoglobulin Rho(D) in CDW Bordeaux. Sex-related differences were negligible for the other ingredients.

Age-stratified analyses revealed the highest prevalence estimates of immunoglobulin G among older adults (≥66 years) in CDW Bordeaux and among adults aged 19–65 years in IQVIA DA Germany. The highest prevalence of immunoglobulin Rho(D) was observed among adults aged 19–65 years in CDW Bordeaux. The age-stratified annual prevalence was similar among the age groups in all three data sources for tetanus immunoglobulins and varicella zoster immunoglobulin. CDW Bordeaux, IQVIA DA Germany, and CPRD GOLD did not exhibit other age-related differences regarding the prevalence of immunoglobulin ingredients.

Proportion of individuals with a prespecified immunoglobulin brands prescription among prevalent immunoglobin users

Among the prespecified brands, Beriglobin, Cutaquig, Cuvitru, Gamunex, Hizentra, Intratect, Kiovig, Octagam, Privigen, Rhesonativ, and Rhophylac were observed with at least five users in at least one calendar quarter. Privigen and Rhophylac were one of the most frequently observed immunoglobulin brands overall in CDW Bordeaux and IQVIA DA Germany, respectively. In CDW Bordeaux, the quarterly proportion of Privigen users ranged from 61.2% of immunoglobulin users in 2017 to 60.0% in the second quarter of 2021, followed by a pronounced decline reaching 13.3% in the first quarter of 2022. Subsequently, quarterly estimates ranged from 21.1% of immunoglobulin users in the second quarter of 2022 to 23.3% in the third quarter of 2023, followed by a decline to 10.2% and 6.4% in the last two quarters of 2024. Other human normal immunoglobulin brands showed generally low use and variable quarterly estimates were predominately observed in IQVIA DA Germany and minimal or no observed use in CDW Bordeaux. For Rhophylac and Rhesonativ, the Rho(D) immunoglobulin brands, the proportion of immunoglobulin users varied across the products and data sources. Quarterly use of Rhophylac ranged from 27.8% in 2017 to 24.7% of immunoglobulin users in the third quarter of 2024 and 14.1% in the last

quarter of 2024 in CDW Bordeaux and ranged from 40.4% in 2017 to 54.3% in the second quarter of 2024, followed by a decline to 23.5% in the third quarter and 3.3% in the final quarter of 2024 in IQVIA DA Germany. Rhesonativ use fluctuated throughout the years, ranging from 9.1% in 2017 to 0.5% in the final quarter of 2023 and 1.0% in the second quarter of 2024 in IQVIA DA Germany, while no use was observed in CDW Bordeaux.

Treatment initiation, dose, and treatment duration

In general, the number of exposures was low across immunoglobulin brands and data sources. The median number of exposures ranged from 1 time to 5 times, depending on the brand and data source. The median treatment duration and dose varied substantially between brands and across data sources. For example, a median treatment duration of 1 day was reported for Hizentra (CPRD GOLD), Kiovig (CDW Bordeaux), and Rhophylac (CDW Bordeaux), while it was 122.5 days for Hyqvia (IQVIA DA Germany). The median initial dose of immunoglobulin G ranged from 0.01 milligrams for Rhesonativ (IQVIA DA Germany) and Rhophylac (IQVIA DA Germany) to 30,000 milligrams for Kiovig (CDW Bordeaux). The median cumulative dose of immunoglobulin G ranged from 0.3 milligrams for Rhesonativ (IQVIA DA Germany) and Rhophylac (IQVIA DA Germany) to 160,000 milligrams for Cuvitru (IQVIA DA Germany). The median initial and cumulative dose of immunoglobulin Rho(D) for Rhophylac was 0.2 milligrams in CDW Bordeaux.

Characterisation of immunoglobulin initiators

The characteristics of individuals who initiated treatment with prespecified immunoglobulin brands were assessed during the study period.

The median age of immunoglobulin initiators ranged between 30 years for Rhophylac in CDW Bordeaux and 64 years for Privigen in IQVIA DA Germany, and the majority of participants were adults aged 19–65 years across all data sources. The majority of individuals initiating treatment with Beriglobin, Cuvitru, Rhesonativ, or Rhophylac were female, the majority of Gamunex, Intratect, or Octagam initiators were male, and the sex distribution of Cutaquig or Hizentra initiators was equal across the data sources. For Kiovig initiators, females were predominant in CDW Bordeaux, while males were predominant in IQVIA DA Germany. For Privigen initiators, males were predominant in CDW Bordeaux, females in IQVIA DA Germany, and the sex distribution was equal in CPRD GOLD.

The indication of use could be assessed for five of the prespecified brands. Within 30 days prior to 7 days following treatment initiation, oncology was the most frequently recorded condition among Beriglobin, Kiovig, and Rhesonativ initiators. Oncology was also the most prevalent condition among Privigen initiators in CDW Bordeaux, while neurology was the most prevalent condition in IQVIA DA Germany. Among Rhesonativ initiators, ‘other indications’ was the most frequently observed diagnosis, but counts were too low to assess which specific indication.

The most commonly diagnosed comorbidity among immunoglobulin initiators varied substantially between brands and data sources. In the year prior to treatment initiation, acute upper respiratory infection was most frequently recorded among Beriglobin initiators, immunodeficiency disorder among Cuvitru and Hizentra initiators, and chronic obstructive pulmonary disease among Gamunex initiators in IQVIA DA Germany. Illness (i.e. life expectancy limiting condition, terminal illness, and viral syndrome concepts) was most frequently recorded among individuals initiating treatment with Cutaquig, Octagam, and Privigen in IQVIA DA Germany, while essential hypertension was most frequently recorded among Privigen initiators in CDW Bordeaux. Essential hypertension was also most frequently recorded among Kiovig initiators in CDW Bordeaux, while polyneuropathy was most common among Kiovig initiators in IQVIA DA Germany. Rhesonativ initiators most often had a noninflammatory disorder of the vagina, while the most recorded conditions among Rhophylac initiators were first degree perineal laceration in CDW Bordeaux and pregnancy in IQVIA DA Germany.

The most common infections among immunoglobulin initiators, within 30 days after treatment initiation, were 'Respiratory & ear, nose, throat, ocular infections' among initiators of Beriglobin, Gamunex, and Hizentra in IQVIA DA Germany, and of Kiovig in CDW Bordeaux. Both bacterial infections and 'Respiratory & ear, nose, throat, ocular infections' were frequently recorded among Privigen initiators in CDW Bordeaux, bacterial infections were also most frequent among Rhophylac initiators in CDW Bordeaux, and urinary infections were most frequently recorded among Rhesonativ initiators and Rhophylac initiators in IQVIA DA Germany.

The most frequently recorded antibiotics were 'Macrolides, lincosamides, and streptogramins' among Beriglobin and Gamunex initiators and 'Quinolone antibacterials' among Hizentra initiators in IQVIA DA Germany within 30 days following treatment initiation. Both 'Beta-lactam antibacterials, penicillins' and 'Sulphonamides and trimethoprim' were frequently recorded among Privigen initiators in CDW Bordeaux, and 'Sulphonamides and trimethoprim' antibiotics were also most frequently recorded among Privigen initiators in IQVIA DA Germany and Kiovig initiators in CDW Bordeaux. 'Other antibacterials' were most frequent among Rhophylac initiators in CDW Bordeaux, and among Rhesonativ initiators and Rhophylac initiators in IQVIA DA Germany, although the prevalence was low.

10.2. Strengths and limitations of the research methods

Strengths

This study leveraged several real-world data sources from three European countries, including France, Germany, and the United Kingdom, covering primary care and hospital care data sources. These data sources enable a comprehensive assessment of immunoglobulin use and patient characteristics across varied healthcare settings. Use of the OMOP CDM ensures standardised data structuring, harmonised variables, and consistent cohort definitions across sources. This facilitated reproducible analyses and enabled robust characterisation of demographic and clinical profiles of individuals initiating immunoglobulin treatment and trends of immunoglobulin use during the study period.

Limitations

The study was informed by routinely collected healthcare data, which introduces several important considerations that may have influenced the interpretation of the findings.

The study included data from three European countries. As such, the results reflect only the populations captured within these data sources and may not be generalisable to other countries or healthcare systems. CPRD GOLD does not capture medications prescribed in hospital settings. As immunoglobulins are typically initiated or administered in specialist care, their use is likely under-captured in this data source.

Electronic health records are primarily designed for clinical purposes rather than research, and as such, may contain incomplete, inconsistent, or variably recorded information. Therefore, the documentation of comorbidities, necessary for patient-level characterisation, may vary across data sources. The actual clinical indication for prescribing immunoglobulins is not directly linked to the prescription or dispensing record in the data sources. Instead, proxy measures based on diagnosis codes around the time of the first treatment during the study period were used. Consequently, the estimation of potential indications may be incomplete or imprecise as this might not have been recorded in all patients. To minimise incompleteness, different time windows around the immunoglobulin prescription date were applied to assess the indication of use.

Additionally, a recorded prescription did not guarantee that the medication was dispensed or consumed, therefore assumptions of actual use have been made. Furthermore, the type of health care setting may have affected the prevalence of prescriptions of specific immunoglobulin types, e.g. intravenous immunoglobulins are predominantly administered in a hospital setting and not in primary care. The study population which was included to estimate the prevalence of immunoglobulin use may have also been

affected by the type of health care setting and the definition of the observation period by each data source. Primary care data sources generally encompassed a broader cohort of individuals, observed from registration until deregistration (CPRD GOLD) or from first to last recorded event (IQVIA DA Germany), while the hospital data source (CDW Bordeaux) comprised individuals requiring inpatient care which were observed from their first to last visit.

Some data sources may face challenges in reliably determining treatment duration due to documentation gaps. End-of-treatment dates may not always be consistently available, and when direct observation was not possible, imputation methods using fixed duration assumptions (aligned with OMOP CDM conventions) may be applied during the ETL process. While this promoted consistency across sources, it may not fully captured true treatment variability and should be interpreted with caution.

To ensure comprehensive characterisation of all incident individuals, a minimum of 180 days of prior data availability was required for primary care data sources. This criterion may have reduced the study size in the primary care sources, but it was not applied for hospital-based settings, where patients typically seek care for acute or specialised conditions and might, as a result, not have had a long duration of longitudinal registration, as would be expected in a primary care setting data source. Consequently, for CDW Bordeaux, it is uncertain whether included individuals were true incident users. As two of the brands that were captured in CDW Bordeaux, i.e. Kiovig and Privigen, are indicated for conditions that require frequent administration, it is likely that Kiovig and Privigen users were not all incident, while Rhophylac initiators were.[5-7] Moreover, only a subset of included individuals from hospital-based settings may have contributed to time windows prior to the index date. The prior observation requirement may have also implied selection bias favouring chronic indications, i.e. data in some pathological conditions may have been limited or absent.

Of note, certain brands of interest could not be assessed in the current study due to limitations, such as market authorisation occurring after the study period or the unavailability of an RxNorm code for those specific brands.

10.3. Interpretation

This multi-country study provides real-world evidence on use of immunoglobulins across three European healthcare systems. Overall immunoglobulin use remained low across all three data sources during the study period, with the lowest prevalence observed in CPRD GOLD. This low prevalence is likely driven by under-capture of immunoglobulin use, as medications prescribed in hospital settings are not recorded in this data source. Although the overall immunoglobulin use was low during the majority of the study period, there was a steep increase in the annual prevalence observed in CDW Bordeaux and IQVIA DA Germany towards end of the study period. Stratification by type of ingredient suggest that this increase in part results from an increased annual prevalence of nirsevimab. Nirsevimab is the active substance of Beyfortus, a medicine used to prevent Respiratory Syncytial Virus, which received market authorisation in October 2022.[8] The most prevalent immunoglobulin type in both the hospital data source CDW Bordeaux and primary care data source IQVIA DA Germany is immunoglobulin G, with use of immunoglobulin Rho(D) also observed in CDW Bordeaux only

For the majority of the immunoglobulin types recording of the indicated route of administration was not specific. Of note, this does not confirm that these immunoglobulins are not administered intravenous, intramuscular, or subcutaneous, as the level of granularity might not be sufficient to assess the route of administration, e.g. the indicated clinical drug form can be ‘prefilled syringe’, ‘injection’, or ‘injectable solution’. There are also immunoglobulins which can be orally administered, such as immunoglobulin G.[12]

Sex-stratified prevalence analyses revealed a female predisposition for immunoglobulin G use in IQVIA DA Germany and for immunoglobulin Rho(D) in CDW Bordeaux. As immunoglobulin G can be used for various indications, it is difficult to explain the higher prevalence rates among females compared to males.

Immunoglobulin Rho(D) can be used for antenatal and postnatal prophylaxis to prevent Rho(D) immunisation in Rh(D) negative women [13], potentially explaining the large female predisposition. This is supported by the observation that the highest prevalence of immunoglobulin Rho(D) was observed in adults aged 19–65 years, which matches the average age of mothers at childbirth.[14]

The use of pre-specified immunoglobulin brands was concentrated in a limited number of brands, with clear differences in brand distribution between the data sources during the study period. Privigen was one of the more prevalent immunoglobulins in CDW Bordeaux, although estimates steeply decreased after 2021, possibly caused by alternative treatment options or a supply shortage. Rhophylac was also one of the more prevalent brands in CDW Bordeaux and IQVIA DA Germany, with comparable estimates across these data sources. Of note, the proportion estimates in the final quarter of 2024 are affected by a substantial increase in the denominator population, i.e. the number of prevalent immunoglobulin users almost doubled in CDW Bordeaux and there was a more than 6 times increase observed in IQVIA DA Germany. This increased denominator population is likely affected by the increased number of cases with a nirsevimab record.

The number of exposures and treatment duration varied across immunoglobulin brands and data sources. While one exposure and a treatment duration of 1 day suggests that the immunoglobulin was administered as a single as immunomodulating dose, routine administration of immunoglobulin is required as replacement therapy in immunodeficient patients.[2] Discrepancies between the number of recorded exposures and the indication of use, e.g. as is observed for Hizentra, can arise from various causes. For example, an individual might have switched to another brand, or the subsequent treatment was prescribed or dispensed by another healthcare provider. The dose varied substantially between brands and across data sources and can be influenced by indication of use and body weight, but also prescribing practices and data capture methods.

The characterisation of initiators of prespecified immunoglobulin brands revealed that, irrespective of the brand, the majority of individuals were adults aged 19–65 years. The highest sex-related predisposition was observed for Rhesonativ and Rhophylac, i.e. >99% females, which aligns with their indication to treat Rh(D) negative women.

The variety in the observed indications of use for the prespecified brands, which were assessed by using diagnostic codes recorded in the prespecified time windows as proxies, is consistent with clinical practice.[3] However, as the indications are assessed by proxies, it is also possible that the recorded indication is in fact a comorbidity. For example, the most frequent indication of use among Rhophylac initiators is oncology, while Rho(D) immunoglobulins are indicated for immune thrombocytopenic purpura and Rh isoimmunization suppression and oncology has been recorded in less than 2% of the initiators. It is important to note that the indication of use was not captured in a large proportion of individuals who initiated treatment with the prespecified brands, even after widening the time window. Possibly, this may reflect initiation of immunoglobulin treatment for indications that were not included in the current study or limitations in the recording of diagnostic information in routine healthcare data. In particular, diagnostic codes may lack sufficient specificity or may be recorded outside the assessed window or care setting, resulting in misclassification or under-recording of indications. While several of the reported comorbidities match with the indicated use of the immunoglobulins brands, e.g. immunodeficiency disorder or pregnancy, conditions such as essential hypertension recorded prior to the index date may be unrelated to the treatment initiation.

The various infection-related comorbidities, prespecified infections, and antibiotics recorded among immunoglobulin brand initiators suggest that initiators may experience infections around treatment initiation.

10.4. Generalisability

While our study comprised data from three data sources across European countries, and covered primary care and hospital care, findings from this study are not to be generalised to other countries or data sources and only reflect the situation in the specific region and setting covered by the respective data source.

11. CONCLUSION

This multi-country study provides real-world evidence on immunoglobulin use across three European healthcare systems. The overall prevalence of immunoglobulins was low during the complete study period (CDW Bordeaux: 10,551 cases among 1,723,887 individuals; IQVIA DA Germany: 29,369 cases among 29,757,040 individuals; CPRD GOLD: 1,725 cases among 6,305,333 individuals), and use was concentrated in a limited number of ingredients and brands. Nevertheless, temporal variations were observed across products and data sources. The number of nirsevimab cases rose from 0 in 2022, the year when it was authorised, to 854 (CDW Bordeaux) and to 10,748 (IQVIA DA Germany) in 2024, which caused an increase in the overall prevalence of immunoglobulin use. The quarterly proportion of Privigen initiators decreased by more than half within a year (CDW Bordeaux). Such increases may have resulted from market authorisation or expansion of approved indication of use, whereas decreases may have been influenced by shortages, availability issues, or differences in prescribing practices. While some immunoglobulin brands were administered only once (e.g. Rhesonativ and Rhophylac), others were routinely administered (e.g. Hyqvia and Kiovig). These varying treatment characteristics potentially result from different indications of use and accompanying treatment regimens or from differences in prescribing practices and data capture methods. For example, among Kiovig initiators, 41.7% had a recorded oncology-related diagnostic code, and 16.7% had a record of primary immunodeficiency syndrome around the index date in CDW Bordeaux. Although the observed indications of use for the prespecified brand were consistent with clinical practice, indications were not captured in a large proportion of individuals who initiated treatment with the prespecified brands, even after widening the time window. Several of the reported comorbidities, infections, and antibiotics suggest that immunoglobulin users experience infections around treatment initiation. Overall, the study illustrates the value of real-world data for understanding patterns of immunoglobulin use in clinical practice and how these evolve over time. While such data captures trends and changes in utilisation, they also come with limitations, including heterogeneous data capture and limited insight into the underlying drivers of observed changes.

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13. ANNEXES

Please see the separate document for Annexes.