SUPPLY PROJECT

"Strengthening voluntary non-remunerated plasma collection capacity in Europe"

REPORT ON THE RESULTS OF:

"A comparative analysis on the current use of immunoglobulins in individual countries: A clinical program"

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Glossary of acronyms

Acronym	Description
ABP	Activity-based pricing
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Health Products)
AIHA	Autoimmune haemolytic anaemia
AIE	Autoimmune encephalitis
AIFA	Italian Medicines Agency
ANSM	Agence nationale de sécurité du médicament et des produits de santé (French Health Products Safety Agency)
AT	Antibody titer - laboratory test that measures the level of antibodies in a blood sample
ATIH	Agence technique de l'information sur l'hospitalisation
BfArM	Bundesinsitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices)
CA	Competent Authority
CAPS	Catastrophic antiphospholipid syndrome
CAR-T	Chimeric antigen receptor - T cell therapy
CatSalut	Department of Health / Catalan Health Services
CDI	Clostridium difficile infection
CIDP	Chronic inflammatory demyelinating polyneuropathy
CLL	Chronic Lymphocytic Leukaemia
CNS	Centro Nazionale Sangue (Italian National Blood Centre)
DM	Dermatomyositis
DRG	Diagnostic-related group
DROM	Overseas departments and regions of France
EAN	European Academy of Neurology
EBA	European Blood Alliance
EDQM	European Directorate for the Quality of Medicines & Healthcare
EHA	European Hematology Association
EMA	European Medicines Agency
ENVI	European Parliament Committee on the Environment, Public Health, and Food Safety
EOEIAP	East of England Immunoglobulin Assessment Panel
ESID	European Society for Immunodeficiencies
EU	European Union
FAGG	Federal Agency for Medicines and Health Products
FMAIT/FNAIT	Foetal maternal/neonatal alloimmune thrombocytopenia
fSCIg	Facilitated subcutaneous immunoglobulins

GALD	Gestational allo-immune liver disease
GBS	Guillain-Barré syndrome
GHM	groupes homogenes de sejour, a group coding system for hospital reimbursement
GLAD	(Quality of) guideline adherence
gr	grams
HAS	Haute Autorité Sanitaire (French HTA agency - it evaluates the clinical benefit of drugs, medical devices, procedures and other health technologies, assessing added benefit over existing therapeutic strategies)
HLA	Human leukocyte antigen
HLH	Haemophagocytic lymphohistiocytosis or Haemophagocytic syndrome
HNIg	Human Normal Immunoglobulin
HSCT	Hematopoietic stem cell transplantation
HT	Health Technology
HTA	Health Technology Assessment - An intervention developed to prevent, diagnose, or treat medical conditions; promote health; provide rehabilitation; or organize healthcare delivery. The intervention can be a test, device, medicine, vaccine, procedure, programme, or system.
IdF	Ile-de-France (French region including Paris)
Ig	Immunoglobulins
IgRT	Immunoglobulin replacement therapy
INN	International non-proprietary name
IPINet	Italian Primary Immunodeficiencies Network
ITP	Idiopathic thrombocytopenic purpura
IU	International Unit
IVIg	Intravenous Immunoglobulin
KD	Kawasaki disease
kg	kilograms
l/L	litres
MA	Marketing Authorisation / Autorisation de mise sur le marché (AMM)
MDSAS	Medical Data Solutions and Services (UK)
MG	Myasthenia gravis
mg	milligrams
ML	Malignant myeloma
MM	Multiple myeloma
MMN	Multifocal motor neuropathy
MoH	Ministry of Health
MS	Member State(s)
NHL	Non-Hodgkin lymphoma
NHS	National Health Service

OMéDIT	Observatoires des médicaments, dispositifs médicaux et innovations thérapeutiques/ French Regional Healthcare Products Observatories
PAD	Primary antibody deficiency - These syndromes are defined as a group of rare disorders characterized by an inability to produce clinically effective immunoglobulin responses
PDMPs	Plasma-derived medicinal products - ex polyvalent immunoglobulins from whole blood (plasma, red blood cells, platelets) and from apheresis (source plasma)
PERMEDES	Platform for Exchange and Research on Blood-Derived Medicines and their Recombinant Analogues / French Plateforme d'Echange et de Recherche sur les Médicaments Derivés du Sang et leurs analogues recombinants
PI	Polyvalent immunoglobulins - Used for post-exposure prophylaxis as one aspect of the public health management of hepatitis A, rubella and measles.
PID	Primary immunodeficiency
PIMS-TS	Paediatric inflammatory multisystem syndrome temporally associated to COVID-19
PLEX	Plasma exchange
PM	Polymyositis
PMSI	Programme de Médicalisation des Systèmes d'Information
PNS	Paraneoplastic neurological syndromes
PNS	Peripheral Nerve Society
PNDS	Protocoles nationaux de diagnostic et de soins (French National Diagnostic and Care Protocols)
PUI	French regional Ig hospital pharmacists
REDIP	Spanish Registry of Primary Immunodeficiencies
REPER	Registry of Rare Disease Patients of Instituto de Salud Carlos
RPT	Registry of Treatments and Patients, Catalonia
SC/IMIg	Subcutaneous/intramuscular immunoglobulin
SCIg	Subcutaneous Immunoglobulin
SEFH	Spanish Society of Hospital Pharmacy
SFPC	Société Française de Pharmacie Clinique/ French Society of Clinical Pharmacy
SID	Secondary immunodeficiency
SISCAT	Catalonian comprehensive public healthcare system
SmPC	Summary of Product Characteristics
SOHO	Regulation on substances of human origin
SRIAP	Subregional immunoglobulin advisory panels (UK)

T2A	Funding system for all acute care services (including home hospitalisation) in public and private hospitals in France since 2005
TSS	Toxic-shock syndrome
UCD	unités communes de dispensation - a 7-digit code that classifies drugs into the smallest unit of dispensation available for a drug granted by the National Agency for the Safety of Medicinal Products and Health Products
UKPID	UK Primary Immunodeficiency Registry
vCJD	Variant Creutzfeldt-Jakob Disease
VITT	Covid Vaccine-induced thrombosis and thrombocytopenia
vWD	Acquired von Willebrand disease
WP	Work Package

Work Package 6 Overview

The aim of Work Package 6 (WP6) is to deliver a set of recommendations on the appropriate use of plasma-derived medicinal products (PDMPs) at baseline and on its prioritisation in times of crisis. Although several PDMPs are manufactured from plasma, emphasis is primarily on polyvalent immunoglobulin as this product determines the volume of plasma needed for European strategic independence.

This document D6.1 provides information on 1) the current indications and uses of Ig and 2) the differences in use of immunoglobulins in Europe whilst providing insights on potential reasons for these differences such as clinical practices, product supply and reimbursement, existing guidelines and differences between countries and adherence to the guidelines. These tasks will contribute towards task 6.2 with the final deliverable D6.2 due December 2023.

Executive Summary / Abstract

Introduction

Since demand for immunoglobulins (Ig) in Europe has more than doubled over the past 20 years, the SUPPLY project Working Package 6 (WP6) was assigned to assess the scope of Ig usage from individual European (EU) member states (MS), and the United Kingdom (UK), preferably by medical specialty, to gain insight of its use now, in the future, and in times of crises. A report on the current Ig use in individual EU MS will allow us to assess the appropriateness and how this differs between EU MS, to develop recommendations for optimising Ig use in the future.

Methods

To assess the scope of Ig usage across medical specialties and within different EU MS, a stepwise methodology was employed through a scoping review, survey, semi-structured interviews, and grey literature analysis. This was completed by real world data analysis on Ig usage on a patient level. A specific focus was placed on mitigation and prioritisation strategies in time of crises and the influence of the COVID-19 pandemic on shortages.

Results

Not all EU MS were represented, due to several reasons. The scoping and the grey literature review lacked information of all EU MS. Survey responses came back for mainly Italy (n=142), followed by Spain (n=15) and the Netherlands (n=12) and a small number of other countries. Sixteen respondents (14 clinicians and 2 pharmacists) from eight countries were interviewed and provided insights into the impact of the pandemic upon their prescription behaviour, described various mitigating measures, and the lessons learned. The survey revealed, that although the majority (52.3%) of prescribers adhere to guidelines, the ones who deviate from it was up to 20%, with new scientific evidence as the main reason (56%). Guidelines may be behind updated literature, which may also correlate to the second reason, namely the lack of information in existing guidelines (28%). EU MS reported shortages on different scales, and mitigation and prioritisation strategies were not widely available. Real world Ig data analysis on a patient level was only possible for France, which was the only EU MS that collected required Ig data on a national level.

Discussion

Integrating all information gathered, we propose a set of recommendations which will be further discussed with all relevant stakeholders, including health authorities, prescribers, and patient organisations. The first recommendation concerns better data collection on Ig use at a patient level, followed by harmonisation of regularly updated guidelines. More focus should be placed onto mitigation- and prioritisation planning and finally, shortage awareness should result in increased collaboration between EU MS.

Conclusions

In conclusion, Ig consumption is likely to increase. Therefore, it is urgently needed to benchmark patients' Ig use on a national level, for better insight and to be able to give guidance to possible inappropriate Ig use and shortages. In addition, harmonisation of Ig indications, mitigation and prioritisation strategies are critically important.

Chapter 1: Introduction

Immunoglobulins (Ig) are used for a wide range of disorders including primary immune deficiencies (PID) such as severe congenital immunodeficiency syndrome (SCID), and secondary immune deficiencies (SID) due to immunosuppressive therapies, such as CAR-T cell therapy or Rituximab that target subsets of B cells. Ig have also proved their efficacy as immunomodulatory agents in neuromuscular disorders such as multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP). Over time, use for Ig has increased tremendously as it is used for both on-label and off-label indications, and administration routes have expanded from intravenous (IVIg) to subcutaneous (SCIg) and facilitated subcutaneous (fSCIg).[1,2]

From 1999 to 2014, the demand for IVIg and SCIg preparations in Europe has more than doubled[3], and from 2014-2020, the European Ig market has grown by 6.7% annually,[4] which has led to many shortage issues. Ig use is predicted to increase by 5-7% yearly, although it is difficult to support with scientific evidence.[2] Ig determines the volume of plasma needed (as the driver) for European strategic independence. In response to this increasing demand, European regulatory institutions have created guidelines to provide the EU countries with harmonised guidance for Ig administration[5] with a range of other international, national, regional, and local initiatives, such as consensus documents, audits, and monitoring schemes.[6–8]
The SUPPLY project was assigned to collect data on the Ig usage from individual countries to gain insight of Ig use now and in the future, and in times of crises (WP6).

1.1 Objective

To deliver a report on the appropriate use of PDMPs of EU countries, focusing specifically on IVIg and SCIg I) at baseline and II) on its prioritisation in times of crisis.

The aim of this document is to report on the current use of Ig in individual countries, where possible by medical specialty, to allow us to collect and compare information on Ig use in EU countries. This task serves as a proof of principle to address the appropriate use and prioritisation of PDMPs from plasma and to feed into recommendations (Task 6.2) on different indications for Ig and proposals for prioritisation in times of crisis.

Chapter 2: Methodology

To assess the scope of Ig usage across medical specialties and within different European countries, a stepwise methodology was employed through a scoping review, survey, semi-structured interviews, and grey literature analysis. Instead of conducting a gap analysis of many European countries, due to constraints of data collection and time, a case study of France is underway using the French National Health Data System (SNDS; *Système National des Données de Santé*). Preliminary results of this analysis are included in this report.

2.1 Scoping review

A scoping review is a type of literature review that aims to provide an overview of the available evidence on current and future Ig use, including crisis preparedness, to map the identification of certain characteristics or concepts in the literature.[9] We had conducted previous work to collect information on the current and future demand of Ig for the Netherlands in which an international scoping review was part of the methodology.[5] The search strategy was replicated for this project. The same search algorithms were used (see Appendix I) on February 1, 2023 to the databases PubMed, Embase, Web of Science, and Cochrane Library for both full publications and meeting abstracts. A total of 132 new references were found (89 regular references and 43 meeting abstracts). All titles and abstracts were read but as most of these concerned Ig for COVID-19, only ten were deemed as potentially relevant articles, and six could be obtained full-text. Additional literature was shared from the WP members or interview respondents that were not found in the scoping review, but relevant to the objectives. These were also included.

2.2 Semi-structured interviews

From March through April 2023, interview requests were emailed to approximately 50 experts, medical organizations and scientific societies involved in Ig demand. In the email, a formal invitation letter was included that explained the SUPPLY project and aims of WP6. Experts were purposefully selected for their specific role and expertise in Ig usage. If they agreed to participate, each interview lasted approximately 20 to 60 minutes, carried out via video conference, and was recorded with consent on Microsoft Teams.

An interview guide was created in accordance with SUPPLY's W6 objectives and composed of seven sections: 1) hospital context (including trends/changes in usages, on- and off-label indications that are treated with Ig, and number of patients using Ig), 2) guidance documents used, 3) Ig approval during non-crisis scenario, 4) crisis scenarios (focusing on COVID shortages, Ig approval processes, and mitigating measures), 5) decreasing usage, 6) EU recommendations, and 7) obtaining Ig data (see Appendix II).

A semi-structured approach was adopted so that the interview guide was followed with additional probing and follow-up questions when appropriate to the response. This allowed for the interviews to be more conversational in nature, which is essential for such an exploratory topic.[10] We conducted these interviews in English (13/16) and French (3/16) to facilitate easier communication with the French respondents.

For the analysis, the interviews were transcribed verbatim and coded using qualitative software (MAXQDA 2020, VERBI Software GmbH). Thematic analysis was done in two steps: first-cycle coding was based on a predetermined coding scheme from the interview questions followed by second-cycle coding where categories were combined under emergent themes.[10]

2.3 Survey

We circulated two surveys: one addressed to hospital pharmacists, which was developed and kindly provided by the BEST Collaborative Group, and the other survey addressed to the clinicians as the prescribers of Ig, which we developed (see Appendix III). The survey was developed using the Qualtrics survey tool and used a skip logic method for convenience to the participants. Survey dissemination was performed using social media of the European Hematology Association (EHA), the European Blood Alliance (EBA), and the European Association of Hospital Pharmacist (EAHP) networks, as well as use of the personal network of WP6 members. One reminder was sent, and the inclusion period was for two months.
Due to a very low response from the hospital pharmacist survey (n=17), the results were not included in this report, since the numbers were not representative for the EU member states (MS), and too low for valid conclusions.

2.4 Grey literature analysis

Due to the limited time at our disposal, the choice was made first to restrict the main comparison between the five countries with the biggest Ig markets in the EU: France, Italy, England, Spain, and Germany.[11] Where possible, other countries found during

the grey literature search have been included. Various websites such as National Health Service websites, scientific societies, and regional health services websites, have been screened with key words such as “Immunoglobulins”, “IVIg”, “SCIg”, “shortages” in each country’s national language. Then regular internet searches were performed with the same keywords. The various resources found included press articles, reports, published papers, prioritisation guidelines, website information, green papers, white papers, and national reports, all which were combined.

2.5 Case study of Ig usage in France

Objectives

The aim of this analysis was to document the use of Ig in France between 2013 and 2022 with the following objectives:

- Describe the demographic profile of patients prescribed Ig;
- Calculate the quantities of Ig administered;
- Describe the type of Ig administered;
- Calculate the number of patients who received Ig, the quantities administered per patient and per indication;
- Describe the indications for which Ig was administered.

Method

We led a repeated cross-sectional study to describe trends in Ig use between 2013 and 2022.

The main steps involved were:

- Construction of the list of Ig reimbursed in France,
- Classification of indications,
- Ig usage data extraction and analysis.

Construction of the list of Ig reimbursed in France

There is not one single database available in the public domain that contains all the information that we required to document the Ig available for prescription in France. Thus, several sources had to be merged from different sources. We have been able to construct an exhaustive list of all the Ig commercialised in France during the last ten years with their corresponding indications, common unit of dispensing (UCD; *unités communes de dispensation*) codes, reimbursement regimes and prices.

The UCD code is a 7-digit code that classifies drugs into the smallest unit of dispensation available for a drug (e.g., a vial or tablet). This code is assigned to each refundable medicinal product with MA (Marketing Authorisation) granted by the National Agency for the Safety of Medicinal Products and Health Products (ANSM). It

is used in the context of hospital activity-based pricing (ABP) called T2A and in the distribution of Ig by hospital pharmacies to non-hospitalised patients. T2A has been the funding system for all acute care services (including home hospitalisation) in public and private hospitals in France since 2005. It involves allocating a budget to health care institutions based on their activity. With the introduction of T2A, most drugs are now included in the *groupes homogènes de séjour* (GHM) tariffs. However, certain expensive drugs (such as Ig) and devices are not included in the GHM tariff and are billed separately. The website of the "technical agency for hospital information" (ATIH) makes public the downloadable lists of these pharmaceutical specialities that are not included in the diagnostic-related group (DRG) tariffs (*liste en sus*) but are reimbursed in addition to the hospital services contained in the DRGs (https://www.atih.sante.fr/unites-communes-de-dispensation-prises-en-charge-en-sus).

In brief, we accessed these lists of pharmaceutical specialities on the ATIH website that are not included in the DRG tariffs (*liste en sus*) and found that the list linking the international non-proprietary name (INN) with the UCD codes and brand names was incomplete. To verify and to complete the information given on the ATIH website, we used:

- the French HTA agency (https://www.has-sante.fr/) website, where all the summary of product characteristics of the Ig that have been commercialised in France are easily accessible by searching for the INN « normal human immunoglobulin ».
- the database of medicines and price indications of the Health Insurance (http://www.codage.ext.cnamts.fr/codif/bdm_it//fiche/index_fic_ucd.php?p_code_cip=9403627&p_site=AMELI) where the missing UCD codes and price records were available.

Using the codes of the Ig available in France over the ten-year period to search the database allowed us to identify the diagnostic ICD-10 code for which they are prescribed. This is preferable to using other extraction parameters such as DRG codes. For example, the DRG [12] used for coding an outpatient infusion is non-specific (*Z5130 Séance de transfusion de produit sanguin labile* - labile blood product transfusion session) since it covers all types of labile blood product and does not give an indication or diagnosis. This table contained the characteristics of each drug: product UCD code, quantity, weight (g), laboratory, etc.

Classification of indications

We regrouped the diagnostic codes first by indications within the French MA for Ig therapies with a view to reporting our results by family of disease as per the EMA

recommendations. Several difficulties were encountered to regroup codes within some indications:

- Secondary Immunodeficiencies (SID) contains a wide variety of pathologies. For an Ig prescription to qualify for MA, it must be prescribed for an immune deficiency secondary to a disease, with defective Ig production and repeated serious infections. So potentially almost any ICD-10 code can fit. The underlying disease is not taken into consideration, even if most of SID are secondary to Multiple myeloma (MM) and chronic lymphocytic leukaemia (CLL). Thus, we chose to include not only these two diagnostics, but also any leukaemia, lymphoma and myeloma in this category, to attain the best estimate possible for off-label use.
- Some diagnostic codes are too vague to determine if the Ig prescription complied with the MA or, even to definitively class the diagnostic code in a defined indication. For example, the International Classification of Diseases (ICD)-10 code for "prophylactic immunotherapy" (Z291) is non-specific since Ig therapy is almost always used as a prophylaxis measure to avoid infections and so the prescriptions with the code Z291 have been included in the wider group of indications of SID. Another example is the ICD-10 codes for inflammatory polyneuropathies. There is a specific code for Guillain-Barré syndrome, an inflammatory polyneuropathy within the MA, but there are no specific codes for other inflammatory neuropathies within the MA such as chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy. We had to select the codes most likely to include the prescriptions for these diseases, with no means to further distinguish these two diseases from each other.

SNDS Ig Usage Data Extraction and Analysis

The rights of access to the SNDS database for SUPPLY were requested in March 2023 and access was given in May 2023. The data in this analysis concerned databases used to track Ig prescribed during hospital stays (in acute care, follow-up care and rehabilitation units and home hospitalisation), as well as during outpatient procedures and consultations (in acute care, follow-up care and rehabilitation units). The data also covered Ig to non-hospitalised patients (retrocession).

The SNDS extraction covered exhaustive data for French hospitalisations from 2013 to 2022. The data extracted included the following information: patient details (year of birth or age, gender, area of residence), sequential stay number, diagnosis at hospitalisation (for inpatients), month and year of administration, product UCD code, number of prescriptions, number of stays involved (for inpatients), total amount of Ig prescribed. We were able to construct a variable "indication" for Ig use indication for patients whose Ig was prescribed during a hospital stay, using the hospitalisation diagnoses. A new variable of the quantity of Ig administered was created by linking the SNDS tables with the list of Ig reimbursed in France.

We applied certain data filters as recommended by the SNDS online documentation (https://documentation-snds.health-data-hub.fr/snds/fiches/medicaments_de_la_liste_en_sus.html#presentation) and took into account possible repetition of the sequential length of hospital stay in order to calculate the quantities administered, the number of deliveries and the amount reimbursed. We then matched the various tables extracted with the list of lg reimbursed in France as described above.

Frequencies, means and standard deviations were calculated using SAS software (version 9.4) for data management, RStudio (version 2023.03.0-daily+82.pro2) for statistical analysis and Excel (Microsoft Office Professional Plus 2016) for the presentation of the results.

Chapter 3: Results

3.1 Scoping review

Of the six articles that were read fully, all but one was excluded due to the setting not being in Europe or the article's aims not meeting our aims and/or not having sufficient data to extract from. The one paper that was applicable was a white paper on pandemic preparedness in the blood supply which, although not specified to Ig, had seven key recommendations for actions at different levels (i.e., from blood bankers to policy makers). This included how to sustain or expand a sufficient donor base to international harmonisation of safety standards and resource sharing.[13]

In addition, our WP6 members highlighted two other papers that were relevant. One investigated the quality of guideline adherence (GLAD) in approved indications for IgG substitution for secondary immune deficiency (SID) in patients with CLL and MM in Germany.[14] There was an overall good GLAD in CLL (n=490) and MM (n=596) patients, documented from 86 centres. However, the subgroup with a mandatory indication for Ig replacement therapy (GLAD score =0) was relatively small (CLL n=86, MM n=77), and undertreated in 76.7% for CLL and 77.9% in MM, respectively. In this group, the hazard ratio (HR) for any infection was 4.49 (95% CI 3.72–5.42; $p < 0.001$) and for severe infections (grade ≥ 3) 10.64 (95% CI 7.54–15.00; $p < 0.001$). These results confirm the increased risk for infections when not treated with Ig. We can conclude that undertreatment is present and more Ig is warranted.

The second paper regarded clinical usage for Ig replacement therapy for Polish patients over a five-year period (January 2016 - 31 December 2020).[15] The authors analysed IgG consumption in total IgG use and number of patients reported to the National Health Fund and found that the total IgG used within five years increased by 27.48%. This was mostly attributed to PID (an increase of 72%) which was the result of increased awareness of PID, improved diagnostic tools, and reduction in diagnostic delay, with the introduction of a drug program for adult patients in 2015. Furthermore, the amount of Ig increased in three specialties: dermatology (+178%), rheumatology (+103%), and clinical transplantation (+82%). However, Ig decreased in paediatric and adult haematology (-13% and -11%, respectively), adult anaesthesiology and intensive care (–46%), internal medicine (–55%), pneumonology (–50%), paediatric clinical immunology (–50%), and gynaecology and obstetrics (–48%). In 2020, 35.5 % of IgG used was for neurological conditions, 25% for PID, and 39.3% for all other indications. SCIg was found to be the most common route of administration in PID patients. The authors recommended implementing evidence-based clinical guidelines to prioritise and rationalise Ig usage along with distributing periodical reports amongst different

specialties using Ig for updates on Ig's availability, efficacy, and possible alternatives. From these German and Polish papers, we can conclude that the future demand of Ig will increase due to the growing needs of patients.

3.2 Semi-structured interviews

3.2.1 Descriptives

A total of 16 respondents from eight countries were interviewed: 14 were clinicians (one of whom was a nurse practitioner) and two were hospital pharmacists. The clinicians represented three medical specialties (neurology, immunology, and haematology) with one respondent being a nurse practitioner in neurology, one respondent being a paediatric haematologist, and one being a paediatric immunologist. Their years of experience averaged 18 years. All the immunologists specialized in PIDs with two immunologists working in rare reference centres for specific autoimmune diseases. All worked in a university hospital setting and all worked in different hospitals except for two respondents from the Netherlands who worked at the same setting. A summary of their characteristics can be found in Table 3.2.1.

Table 3.2.1: Descriptives of interview respondents from eight countries

	Netherlands (N=3)	**Italy (N=2)**	**Spain (N=2)**	**UK (N=2)**	**France (N=3)**	**Finland[a] (N=2)**	**Denmark (N=1)**	**Portugal (N=1)**
Gender								
Male	1	1	2		3	2	1	
Female	2	1		2				1
Years of experience								
0-10	1		1	1			1	
11-20	2		1	1	1			1
21+		2			2	2		
Specialties								
Neurology	1	1	1				1	1
Immunology		1			3	2		
Haematology	1		1	1				
Pharmacy	1			1				
Number of patients treated with Ig								
0-20	1		1	1				
21-50			1		2		1	1
51-100	1	1				1		
100+	1	1		2				

	Netherlands (N=3)	Italy (N=2)	Spain (N=2)	UK (N=2)	France (N=3)	Finland[a] (N=2)	Denmark (N=1)	Portugal (N=1)
Pre-existing Ig approval process in their hospital	No	No	No	Yes	Yes	No	No	Yes
Shortage during COVID	Somewhat	Some-what	Yes	Yes	Yes (for 1); No (for 2)	Yes	No	No

[a]*One Finnish immunologist is currently not seeing patients or prescribing Ig directly*

The following results will be structured according to themes with the inclusion of direct quotations from the respondents as necessary.

3.2.2 Trends

When respondents were asked which trends or changes the respondents had observed in the recent years, two main themes arose: shortage mitigation measures and increased usage of Ig and/or number of patients using Ig. Several respondents reflected how they had experienced Ig shortages often before COVID, although the pandemic exacerbated the situation. Thus, they described the various actions that were undertaken to combat these shortages, such as having to switch brands more frequently; rounding down dosages; using the entirety of a vial to not lose a drop of Ig; creating a system of Ig monitoring; and for neurologists, using more plasma exchange (PLEX) as the default treatment instead of IVIG, such as with Guillain-Barré syndrome (GBS). Respondents particularly mentioned switching administration routes from IVIG to SCIg as SCIg was easier to acquire than IVIG (although one neurologist mentioned a complete shortage of SCIg at his hospital) and/or to protect them from being exposed to the virus (although one neurologist explained that most of his patients had been on SCIg for years prior to COVID). Some of these mitigating measures will be described more in detail further below.

Regarding the second trend of increased usage of Ig and/or increased number of patients using it, many respondents remarked on the increase of patients across the fields of neurology, immunology, oncology, haematology, and rheumatology. Furthermore, several emphasised the large rise of SID patients, particularly post-transplant or CAR-T, as Ig use in CAR-T is growing in popularity.
For two immunologists, they worried that this trend of increasing patients using Ig is due to a misperception or misunderstanding of Ig by other specialists that results in inappropriate or excessive use in their specialties. However, two other respondents believed that the trend of increased patients in their setting was appropriate as their

colleagues in other fields had “good understanding.” Conversely, two neurologists remarked how their patient populations have been relatively stable.

3.2.3 Guidance documents

When respondents were asked whether they use any guidance documents to guide their daily Ig prescription, their responses varied from using national, international, hospital protocols, published papers or consensus documents, or a combination thereof. For example, respondents from Denmark, France, the UK, and Italy alluded to using national guidelines and recommendations; the Netherlands has the Medicines Evaluation Board which mirrors the EMA guidelines. Other than the EMA, respondents named various international guidelines: all the neurologists referred to the European Society for Immunodeficiencies and the European Academy of Neurology (EAN) and Peripheral Nerve Society (PNS) guidelines, particularly for CIDP, and all the immunologists named the European Society of Immunodeficiencies (ESID). However, two clinicians remarked on how international guidelines are not being followed, which they considered a pity.

For those respondents in Portugal, Finland, Spain, and the Netherlands who primarily follow their hospital guidelines due to an absence of national guidelines (or an absence of specific protocols for their patient group), they stated that these hospital guidelines are based on international guidelines, published papers, specialty consensus documents, and even the clinicians’ experiences themselves. Consequently, several clinicians spoke of the variability of these hospital protocols for the same specialty or indication throughout the same country. For example, both haematologists in CAR-T and cellular therapies reported that the paucity of evidence for their patient group results in variability of treatment due to this uncertainty. Spanish respondents spoke of Spain’s many autonomous communities and the variety of protocols and guidance documents thereof. Furthermore, two clinicians stated that they heavily rely on clinical expertise, especially after one has been practising for decades.

Because of these factors, several respondents described how clinician-prescribing practices vary accordingly and could reflect on experiencing those differences when treating patients. For example, a UK paediatric haematologist described having a French patient who was accustomed to monthly infusions for idiopathic thrombocytopenic purpura (ITP), which was not the case in the UK.
Furthermore, a hospital’s way of doing things is what a clinician described as “the practice you are used to.” Several respondents with decades of experience described how important clinical experience is to using Ig wisely and how mentoring or advising a younger clinician in Ig prescription is very beneficial to appropriate use of Ig.

3.2.4 Pre-existing Ig approval process

When respondents were asked whether an Ig monitoring system existed before the pandemic, their answers varied.

Respondents from the UK, Portugal, and France spoke of the pre-existing Ig monitoring systems in place. UK respondents spoke of the UK guidelines that clearly define indications for Ig prescription to the presence of subregional Ig advisory panels (SRIAP), for all other indications. Both could share their positive experiences of working within this system, and the pharmacist shared the benefits of the Medical Data Solutions and Services (MDSAS) national Ig database and being a member of a SRIAP. The Portuguese neurologist stated how a triple check system had been in place in hospitals for more than a decade; for all other indications except for GBS, CIDP, and myasthenia gravis (MG), a clinician needed to present to and get approval from an internal commission, the ethical committee, and the medical director.
Finnish respondents shared how PIDs are an on-label indication that needed no further approval but knew their neurology colleagues need to obtain internal approval before any prescription because neurology indications were not a preapproved national indication from the national insurance organisation.

Respondents from the Netherlands, Denmark, and Italy said that there were no further internal or external checks regarding off-label usage; they were able to freely prescribe for off-label indications. The Italian neurologist spoke of the "trust" the pharmacies had in their clinicians, and the Danish neurologist clarified that Ig prescription is only available in regional hospitals. However, the Dutch pharmacist clarified that though he had never stopped a clinician from prescribing for an off-label indication, clinicians can submit evidence from expert consensus documents or expertise organisations that justify Ig usage for off-label indications: "*if the professional organisation says it's allowed, then the pharmacy will also allow it.*"
Spanish respondents were not aware of a pre-existing Ig approval process; the haematologist stated that he submits Ig prescriptions to the pharmacy with no additional checks; there is no internal or external monitoring entity or activity that checks his usage that he is aware of or has experienced.
The neurologist conveyed to the changes that were established due to COVID-19 which will be described further below.

3.2.5 Shortages during COVID-19 and mitigating measures

Eleven respondents from the Netherlands, Italy, Spain, the UK, Finland, and France had experienced some sort of shortage in their setting since the pandemic began (Table 3.2). This ranged from a shortage of one type of product for a few months up to

a year (e.g., Nanogam® in the Netherlands and Hizentra® in Finland) to a severe shortage where such little Ig was available that patients went without (i.e., Spain). Their mitigating measures varied.

In the Netherlands, one of the pharmacists recalled that there had been Ig shortages for IV products since approximately 2020; however, it was only very recently they faced a large shortage of Nanogam,® that they were now seeking to switch most of their patients to SCIg since there was not a shortage of subcutaneous products. The pharmacist shared how they would reserve the remaining IVIG for specific neurology patients who needed large amounts of it; everyone else would be switched to SCIg. The pharmacist and clinicians had several meetings to create an overview of all the patients who received according to the type of Ig product and an action list in case of insufficiency. The haematologist located at a different hospital stated that it was only in the recent months that she recalled getting a notification from the pharmacy about a shortage of Ig products.

In Italy, the immunologist stated that a majority (70%) of PID patients were switched over to SCIg since the beginning of the pandemic so that patients did not have to travel to the hospital. The neurologist, meanwhile, stated that there was a significant shortage of SCIg in his hospital centre so that his patients had to switch to IVIg; however, apart from that, there were not major issues in his centre, but he had heard of worse scenarios elsewhere. The neurologist participated in clinical trials for drugs such as Rituximab to find an alternative to Ig.

In the UK, one pharmacist in charge of high-cost drugs stated that the pre-existing Ig shortages were exacerbated by the pandemic, so that an allocation system was created to avoid stockpiling. Hospitals were required to forecast their Ig needs every month and allowed to order up to that amount; if they required more, they could buy extra products from other hospitals through a mutual aid system. The paediatric haematologist shared how great care was taken with doses so that not a drop was wasted, and how dosages for her ITP patients were slightly decreased (e.g., from 1 g/kg to 0.8 g/kg).

In Finland, the immunologists did experience a slight shortage with one specifying it as Hizentra® for several months up to a year but still managed well. They had heard of how other specialties in the country faced worse circumstances and had to reduce dosages for their patients.

In France, one immunologist who was aware of and involved in national demand issues and initiatives explained how shortages had been prevalent in the country for years, but as it was exacerbated by the pandemic, a national collaboration was undertaken

between different medical specialties, patient representatives, medical societies, and a range of other stakeholders, to update a national consensus document on prioritising indications. This work was described as very fruitful and resulted in helpful amendments.

For those respondents in France, Denmark, and Portugal who did not experience a shortage in their setting, they stated that they still felt the supply tensions and preventive measures were still taken. In France, two immunologists did not have difficulties with obtaining Ig, but recalled their pharmacists giving prescription recommendations. In Portugal and Denmark, the neurologists were cautioned by their pharmacies of the potential for shortage; therefore, the Portuguese neurologist described the great care not to waste a drop from each vial. The Danish neurologist reported how all chronic patients on maintenance therapies were reassessed to see if lowering their dosages were possible, along with stricter control over off-label indications.

In Spain, the respondents' experiences varied as they were in different autonomous communities. The haematologist recalled a few moments in which the pharmacist stated that there was shortage in certain brands or concentrations, but it did not happen often. However, the neurologist was still experiencing a severe shortage that required governmental intervention and major changes in hospital protocols. As this was the most extreme example of a shortage found in the interviews, this scenario will be described in detail.

3.2.6 The Spanish shortage scenario

For the neurologist in Catalonia, there was such a severe shortage of Ig products overall that patients in smaller hospitals were left without treatment and could not get it elsewhere: "*an avalanche of patients that were left without treatment with neither intravenous nor subcutaneous immunoglobulins for some time in the smaller hospitals. And then the physicians in those hospitals asked the bigger ones like us to [take over] those patients thinking that [those patients] would get supplied, which was not true because we were not allowed to receive any new patients that were not already under treatment*."

Therefore, a series of new external and internal actions were taken by the government and by the neurologist's hospital. Externally, the government centralised the purchasing of Ig (previously, each hospital was responsible for purchasing its own) and distributed it according to the number of patients within each hospital. Additionally, the Spanish government created a form that listed the approved (reimbursable) indications according to grades of evidence (grades A-C). Indications that were considered grade

'C' or not on the list need to get permission from a hospital committee for that patient to be treated with Ig. Therefore, the hospital created an internal committee formed of various clinicians and a pharmacist to review the cases. Furthermore, in his hospital, treatment paradigms were altered: for all indications but MMN and GBS, steroids became the first treatment option. For GBS, the first line of treatment is PLEX. These protocols are still in place today.
Additionally, with Ig (nearly) out of the picture, the neurologist and fellow colleagues began to rapidly enrol their patients into clinical trials with other drugs to see if it would benefit them, which included CAR-T and complement inhibition.

However, the neurologist emphasised his belief that the shortage was so drastic in Spain because of Ig's cheaper market price. To explore this hypothesis, the neurologist distributed his own survey regarding the severity of Ig shortages to networks in North America and Europe. He found a clear contrast: amongst his networks in the U.S., they were not experiencing shortage, whereas in Europe, there was a gradient of shortages with ascending severity and Spain at the top of the list: "*there was this gradient, which means, very clearly that, yes, there might be less immunoglobulins to give away, but they were maximising those countries that paid more for the immunoglobulins…I think Spain, within Europe, was one of the countries that had the worst shortage because the cost of immunoglobulins was clearly lower than in other countries."* Because of this price factor linked to other market dynamics, the neurologist was sure that future shortages will occur and anticipates the retention of the governmental and hospital mitigation measures.

3.2.7 Priority protocols

When respondents were asked if there was a priority protocol in case of shortages, only the clinicians from Italy, France, and Portugal affirmed it. The French priority protocols were published in 2018 prior to the pandemic; the Italian one was published in 2022; and the Portuguese neurologist stated that this was written during the pandemic for neurology patients.

3.2.8 Lessons learnt

When respondents were asked what they learnt from the pandemic, several key lessons were shared.

For the Spanish neurologist, the treatment paradigm changes resulted in drastically reducing the number of patients treated with Ig by half (from 60% to 30%). This advantage is one reason why, though the shortage has improved in his community,

these mitigation measures will continue to stay in place to safeguard for upcoming shortages.

Multi-faceted communication was a recurring theme, between clinicians and pharmacists and even to donors. Timely communication was key, especially emphasised by the pharmacists, in communicating to other pharmacists and clinicians about shortage alerts and brand changes. These "short lines" were advantageous in awareness and actions. Additionally, careful communication was emphasized in how important information regarding Ig is relayed, even amongst and between clinicians, to avoid even a slight misunderstanding that could lead to detrimental actions, such as suspending Ig treatment. Furthermore, the UK pharmacist spoke of the importance of making the clinicians feel involved as active participants in the process: "*one of the most important things is to have the clinicians involved in the discussions so they understand why these systems are in place because it can feel a little bit like pharmacy just saying 'no'...[that's why we try] to get [the clinicians] involved, present their data, come to the panels, to make them feel part of the process rather than it's a process being done to them."* Additionally, communicating the right information to donors regarding plasma donation was thought of as an important step to overcoming supply shortages. Respondents emphasized how donors need to be made aware and motivated to donate, and this was acutely illustrated in Spain, as multiple patient associations and medical societies rallied together for a national campaign to improve the plasma donation and management system.

3.2.9 EU recommendations

When respondents were asked what recommendations they would provide, several key themes arose regarding guidelines, clinician practices/behaviours, evidence, and Ig alternatives.

With regards to guidelines, respondents shared the importance of having national recommendations that are comparable to international guidelines. However, one respondent understood the challenges that arise with such a step:
"*The problem is if they can [implement these recommendations]. But for this, they have to fight with the regulatory agency. Or maybe in some place, they have to fight against their own hospital."* UK respondents spoke of the benefits of having a centralised monitoring database and system with checkpoints in, such as the presence of gatekeepers and panels to help monitor Ig usage. With regards to the EMA guidelines, one respondent mentioned how it could be improved by being more precise particularly with its recommendations for SCID; the haematologists also referred to this same point as the generalised terminology leaves it open for interpretation, and thus, variability in implementation.

With regards to clinician practices/behaviours, the subtheme that was discussed the most, however, was the need to bridge specialties and improve mutual understanding of Ig use. Several of the immunologists mentioned how they feared that other specialties, particularly in neurology, have a misunderstanding or misperception of what Ig does and hence use it liberally or inappropriately. Therefore, respondents suggested that having access to good immunologists is paramount to understanding how to best prescribe Ig along with supporting inexperienced clinicians with more experienced colleagues when they are in the early years of Ig prescription.

Several respondents highlighted multiple ways for using Ig appropriately in daily practice ("*stick to the evidence").* All neurologists spoke of abiding by EAN/PNS guidelines to increase interval periods and/or reduce dosages to stable patients; they all affirmed the importance of monitoring the patients to see if their doses could be reduced effectively over time.

Furthermore, regarding evidence, several respondents emphasised the crucial need for more clinical trials to provide evidence especially where there is a paucity, such as using Ig for cellular therapies or transplants. Linked to this, the idea of having a European database that could capture pertinent information regarding Ig usage was mentioned, with the clarification that it would require monetary commitment and sufficient manpower and time to enable such a step.

Lastly, several respondents emphasised the need to continue exploring Ig alternatives to reduce dependency upon Ig as there is still increasing demand and limited supply.

3.3 Doctors' Survey

A copy of the doctors' survey can be found in Appendix III.

3.3.1 Descriptives of the doctors' survey

A total of 193 responses were collected, most came from Italy (n=142), where respondents worked in the field of neurology, haematology, immunology, and general medicine (60%), 30% came from the paediatric specialty (all subspecialties), and 10% from other areas, mainly rheumatology. In Spain (n=15), haematology and neurology was represented in 80%; in the Netherlands (n=12), 83% came from haematology, neurology and paediatrics; the other countries had very low responses, varying from 1-3 responses from Austria, Belgium, Bulgaria, Czech Republic, Denmark, Ireland, Romania, Serbia and Sweden (one response), Finland, Greece and Portugal (two

responses), Croatia, Germany and France (three responses) (n=24), over 90% came from haematology and paediatrics. The countries were categorised into four groups: Italy, Spain, The Netherlands and “other” countries. Overall, since Italy had the highest response rate, this country had the best representation of Ig usage among all EU MS.

As shown in Table 3.3.1, mainly university hospitals (n=114) and general hospitals (n=59) are represented: specialised hospitals, for example oncology centres (n=13), were also among the respondents. Smaller hospitals (rural (n=2) and community hospitals (n=3)) are not very well represented and will be further excluded from this analysis.

Overall, the haematological specialty is the most represented in this survey (n=60), followed by paediatrics (n=47; all specialties, not categorised) and neurology (n=45). In addition, among the respondents were also rheumatologists, dermatologists, and nephrologists, for which Ig are used for kidney transplants for desensitisation in case of human leukocyte antigen (HLA) incompatibility and antibody-mediated rejection. In Italy, which had the most responses, general medicine is also represented, where haemato-oncology patients are being treated in general hospitals.

Furthermore, the majority of the respondents treated less than 20 patients, 33% of respondents treated between 21 and 50 patients, and only 6% treated more than 100 patients. Most patients are treated in the outpatient clinic or directly at home, and on average only in 30-40% of patients the administration of Ig takes place in hospital. The majority (54,9%) use only IVIg and vary from 50 to 60% between countries. The exclusive use of SCIg varies from 2,4% to 50% of respondent countries. As confirmed in literature, respondents prescribed Ig for the well-known indications, as replacement therapy for primary or secondary immune deficiencies, or for its immunomodulatory effect (see Appendix IV, Table 3.3.2A).

Fifty-five percent of respondents use only IVIg (n=106), 43% (n=83) uses both SCIg and IVIg. Of the latter group, 70% (49 of 70 responders, 13 missing) reported no dosage differences between the two routing strategies. This latter group also did not change routing from IV to SC during 2019 to 2021: for all years, 70% of Ig use was IV and 30 % was SC (n=67 responders).

Of note, respondents were allowed to provide multiple answers for several questions.

Table 3.3.1 Descriptives of the clinician respondents

Main category	Sub-category	**Italy (n=142) N (%)**	**Spain (n=15) N (%)**	**Netherlands (n=12) N (%)**	**Others (n=24) N (%)**	**Totals (n=193) N (%)**
Hospital type	University	73 (52)	11 (73)	11 (92)	19 (79)	114 (59)
	General	51 (36)	3 (20)	1 (8)	4 (17)	59 (31)
	Specialised	12 (9)	1 (7)			13 (7)
	Community	3 (2)				3 (2)
	Rural	2 (1)				2 (1)
	Missing	*1*			*1*	*2*
Clinical Specialty	Haematology	27 (19)	10 (67)	5 (42)	18 (75)	60 (31)
	Paediatrics (all specialties)	42 (30)		1 (8)	4 (17)	47 (24)
	Neurology	39 (28)	2 (13)	4 (33)		45 (23)
	Immunology	16 (11)				16 (8)
	General medicine	4 (3)				4 (2)
	Infectious diseases	1 (1)	1 (7)		1 (4)	3 (2)
	Rheumatology	1 (1)				3 (2)
	Dermatology	1 (1)				1 (.5)
	Nephrology	1 (1)				1 (.5)
	Other[a]	8 (6)	2 (13)	2 (17)	1 (4)	13 (7)
Patients treated with Ig per year	Up to 20	65 (46)	10 (67)	10 (83)	16 (67)	101 (52)
	21-50	53 (37)	5 (33)	1 (8)	5 (21)	64 (33)
	51-100	15 (11)			2 (8)	17 (9)
	More than 100	9 (6)		1 (8)	1 (4)	11 (6)
Setting	Inpatient median (IQR)	40 (15-81)	29 (10-50)	44 (9-95)	29,5 (13,5-50,8)	40 (15-80)
	Outpatient median (IQR)	60 (19-85)	71 (50-90)	55 (5-91)	70 (49-86,5)	60 (20-85)
Routes of administration	Only IVIG	77 (55)	9 (60)	6 (50)	14 (58)	106 (55)
	Only SCIg	3 (2)	6 (40)	6 (50)	10 (42)	3 (2)
	Both	61 (43)				83 (43)
	Missing	*1*				*1*

[a] *Other specialties include Critical Care, Gastroenterology, Paediatric and Adult Gastroenterology, Gastroenterology and Hepatology, Pathology, Primary Immunodeficiencies Referral Centre (tertiary referral hospital), Resuscitation and Transfusion Medicine*

3.3.2 Indications for which Ig is prescribed

The main causes of SID, after selecting the Ig-prescribers for SID (n=89), were B cell depletion therapy (83%) and other immunosuppressive therapy (58%), and secondary to underlying diseases such as MM (35%), CLL (46%) and malignant lymphoma (34%). CAR-T cell therapy is found as a minor cause of Ig use (12%), however, may be upcoming in the near future (see Appendix IV, Table 3.3.2B).

3.3.3 IVIg prescription in accordance with guidelines

The majority (52.3%) of respondents use Ig exclusively according to the guidelines, followed by a further 30.6% who prescribe outside the guidelines in up to 20% of cases without differences between countries (Appendix IV, Table 3.3.3). With regards to reasons why, most responses refer to new scientific evidence as the main reason (56%), as guidelines may be behind updated literature, which may be also correlated to the second reason, namely the lack of information in existing guidelines (28%) (Appendix IV, Table 3.3.3A). For both reasons, the majority of responses deviate from the guidelines in less than 20% of prescriptions (Appendix IV, Table 3.3.3B).

3.3.4 Dosage adherence for replacement therapy and immunomodulation

Dosage adherence for Ig replacement therapy is mostly based on international or local hospital guidelines, which are approved by government agencies or recognized scientific societies, or SPC labelling instructions, which must also comply with the indications for which they were authorised. Remarkably, a relatively large percentage (13%, 22 out of 171 responses) based dosage adherence to their own clinical expertise, coming mostly from Italy and “other” countries (Appendix IV, Table 3.3.4A).

Dosage adherence for Ig immunomodulation showed a similar adherence to the international guidelines (39% versus 41%). For this indication type, the respondents provided more multiple answers than for immune-deficiency indications, which may reflect the prescription behaviour for the different indications within this group (Appendix IV, Table 3.3.4B).

3.3.5 Dosing strategies for specific indications

Regarding dosing strategies for specific diseases, the answers highly matched with the existing guidelines (94% for PID, 91% for SID, 92% for ITP, 100% for GBS and Kawasaki disease, 96% for CIDP and 94% for MMN respectively).

Most respondents always (60%) and sometimes (27%) perform dose adjustments to the individual patient, which is reflected in all responding countries. When analysed per hospital type, this is more performed in university and specialised hospitals (64.6%

and 66.7%, respectively always; 22.9% and 33.3%, respectively sometimes) compared to general hospitals (49.1% always; 30.9% sometimes).
For those who indicated “sometimes,” several provided reasons why for those who work in neurology, immunology, haematology, and paediatrics (see Appendix V). When analysed per specialty, the majority perform dose adjustments, however, with slightly variations per specialty (Appendix IV, Table 3.3.5).

3.3.6 Alternative therapies and reassessment

Overall, the majority of responders (n=110) use alternative therapies before or after Ig usage (57%, varying from 53.3% to 75% per country category). Different from Italy, other countries tend to prescribe other alternative therapies before Ig therapy (in 2/3) more often than after Ig therapy (1/3) (Appendix IV, Table 3.3.6). Spanish respondents stated this 100%. There was no difference between hospital types or between specialties. In Italy (with the most responses) it was 1/3 versus 2/3, respectively; especially neurology, haematology and paediatrics use Ig as first line therapy, and secondly, alternative therapy after Ig has failed.

Of the 89 respondents who treat patients for SID, the vast majority reassess the Ig treatment (79 of a total of 81 responses, n=8 missing), of which 62% (n=49) at six months follow up, 31.6% (n=25) at the end of the treatment cycle, and 21,5% (n=17) yearly. This is found in all country groups.

3.3.7 Trends in Ig use from 2019-2021

By asking respondents to comment on changes in Ig usage during the pandemic years (2020 and 2021 compared to 2019), there was no evident trend of pandemic influence regarding Ig usage (Appendix IV, Table 3.3.7). However, shortages were increasingly present. (See Figures 3.3.9 A and B, and Appendix IV Figures 3.3.9C 3.3.9E).

3.3.8 Clinical prescription behaviour and Ig approval process

From 2017 to 2021, the majority (n=100, 51,8% of total) of clinicians did not change their prescription behaviour for use of IGs, which is overall consistent between countries and between hospital types (n=146 responses). When respondents do change their prescription behaviour, this is mostly done in university hospitals (29/46= 63%).

Regarding the approval process, most Ig requests are being approved either by the clinician together with the pharmacist or by the department manager and/or the clinician. Since multiple answers were possible, the combination of these

aforementioned individuals was most prevalent. Also, the combination of choosing both dual clinician-pharmacist and the requesting department/clinician was most prevalent (n=15, multiple answers were possible). Overall, the same score was reflected by country type and by specialty type (Appendix IV, Table 3.3.8).

The criteria for approving Ig therapy are mainly: a. guidelines (mainly EMA guidelines or national guidelines, depending on the country) (136 respondents, 58.5% of 193) and b. expert opinions/multidisciplinary meetings (82 respondents, 42.5% of 193) These can be seen in Appendix IV, Tables 3.3.8 A and 3.3.8B. However, costs and own clinical input may also be a factor of importance. There were no differences between specialties.

3.3.9 Shortages, mitigating measures, and prioritisation strategies

From 2019 to 2021 shortages were increasingly present from 12.4% to 42% (overall), and especially in Italy from 13.4 to 44.4%) and Spain (from 13.3 to 46.7%). Both countries confirmed that the COVID-19 pandemic influenced shortages (in 84%), see Figures 3.3.9A and 3.3.9B below.

Figure 3.3.9A: Trends in total Ig shortages from 2019-2021

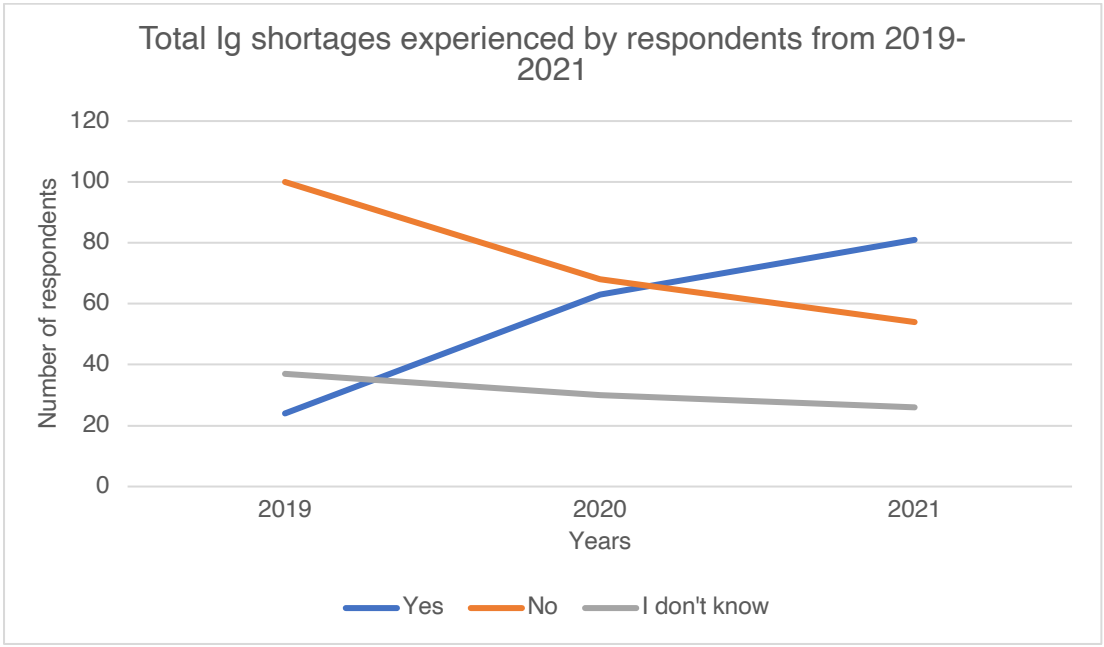
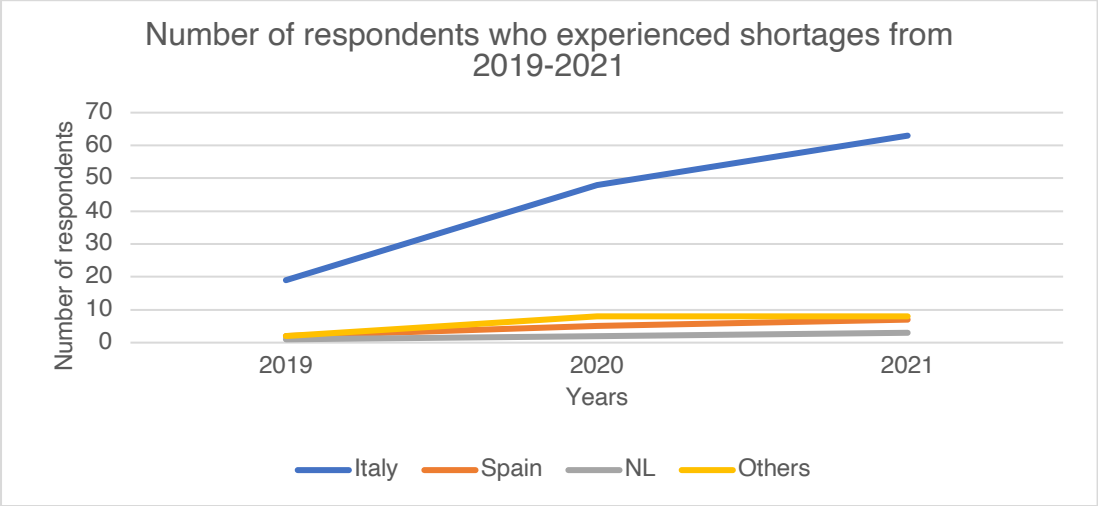


Figure 3.3.9B: Trends in those who experienced shortages from 2019-2021



Therefore, respondents shared their mitigating strategies. Their answers confirm that there is similarity between countries. The top four answer choices are: switching to a lower dose (n=88), substitution with other drugs (n=70), change of brand (n=54) and delay of treatment (n=55). These four options are also mostly used as combined strategies (see Table 3.3.9A).

Table 3.3.9A Mitigating measures in case of a shortage (multiple answers could be chosen)

What are mitigation measures in case of a shortage?	**Italy**	**Spain**	**NL**	**Other**	**Totals N (%)**
Referral to another hospital	16	1	-	1	18 (5)
Lower dose or longer time interval between doses	63	9	2	14	88 (25)
Substitution with other drugs/treatments/products	48	9	2	11	70 (20)
Delay of treatment	39	5	1	10	55 (16)
Importing product from another country	13	1	1	6	21 (6)
Change of brand	34	3	6	11	54 (16)
Switch administration route	20	5	1	7	33 (10)
Other	4	1	1	1	7 (2)
Total responses	237	34	14	61	346 (100)

Importing Ig from other countries (n=21) or changing the brand may only be a solution when there is no overall shortage. An example from the Netherlands was put forward in one of the interviews, where switching to SCIg (which was abundantly available) was performed due to IVIg shortages. The same trend is also consistent among the different

specialties. Regarding prioritisation strategies, most clinicians follow some type of guidelines (70.8%), which can be European/international, national or local, which are usually consented by government or specialist societies. However, still 27,5% uses their own experience to prioritise, which can be seen in all countries (Table 3.3.9B below), and in the main represented specialties neurology, haematology, and paediatrics (Appendix IV, Table 3.3.9).

Table 3.3.9B: Prioritisation strategies (multiple answers could be chosen)

How do you prioritise which patients receive Ig? (Multiple answers possible)	**Italy**	**Spain**	**NL**	**Other**	**Totals N (%)**
Use of hospital-based priority protocols	41	9	2	8	60 (25)
Use of national-based priority protocols	45	8	4	7	64 (27)
Use of European-based priority protocols	35	5	1	2	43 (18)
My own clinical judgement	49	2	4	10	65 (28)
Other	2	-	1	1	4 (2)
Total responses	172	24	12	28	236 (100)

Future shortages are expected in 51% of responses, highest from the Spanish respondents (77%) (Table 3.3.9C). Several clarified why they answered 'yes' or 'no' (see Appendix VI).

Table 3.3.9C: Expectation of future shortages by respondents

Do you expect future shortages?	**Italy**	**Spain**	**NL**	**Other**	**Totals N (%)**
Yes	58	10	2	11	81 (51)
No	17	1	-	3	21 (13)
I do not know	43	2	6	7	58 (36)
Totals	118	13	8	21	160 (100)

3.3.10 How Ig is paid for in different countries

Payment structure for Ig varies per country, governmental budgets were high in Italy and Spain (71.6% and 83.2%, respectively), and payment by the health insurance mainly in the Netherlands (92.4%) and "other" countries (53%).

Due to a very low response rate, questions (Q32d) regarding change of routing from IVIg to SCIg (n=17 responses) were not analysed further.

3.4 Grey literature analysis

3.4.1 Comparison of on-label indications

Due to the limited time at our disposal, the choice was made first to restrict the main comparison between the five countries with the biggest Ig markets in the EU: France, Italy, England, Spain, and Germany.[11] Table 3.4.1 provides an overview of on-label indications for these countries. “On-label" use refers to the indications listed in a drug's MA. There are two major categories for on-label use:

1) Use as replacement therapy. In this case, Ig are administered to restore immunoglobulin levels to normal in patients with immunodeficiency;
2) Use as immunomodulating agents in some autoimmune diseases. Autoimmune diseases result from a dysfunction of the immune system, leading it to attack the body's normal constituents. The mechanism of immunomodulation is complex and not yet fully understood. Moreover, the efficiency of the use of Ig as immunomodulatory agents has not been proven in all autoimmune diseases, of which there are many.

“Off-label” use falls outside the scope of the indications and conditions of administration laid down in the MA. This may involve administration:

1) For a disease not covered by the MA;
2) At doses or in a schedule unlike those specified in the MA;
3) On a patient population different from that approved in the MA (e.g., paediatric population).

MAs may differ from country to country, so the use within the framework of the MA in France may be considered off-label in another country. It is to be noted that, in addition to the indications listed in the table below, further conditions not enumerated here must be met for on-label use (patient population or doses, for example).

TABLE 3.4.1 General overview of clinical approved and reimbursed indications

	France[16]	**Italy**[17]	**England**[18,19]	**Spain**[20]	**Germany**[21]	**EU**
Immunodeficiencies						
Replacement therapy for primary Immunodeficiencies	x	x	x	x	x	x
Neurology						
Acute idiopathic/autoimmune dysautonomia/ganglionopathy			x			
Autoimmune encephalitis (AIE)			x			
Guillain Barre syndrome (GBS)	x	x	x	x	x	x

	France[16]	**Italy**[17]	**England**[18,19]	**Spain**[20]	**Germany**[21]	**EU**
Chronic inflammatory demyelinating polyneuropathy (CIDP)	x	x	x	x	x	x
Multifocal motor neuropathy (MMN)	x	x	x	x	x	x
Myasthenia gravis (MG)	x	x	x		x	
Autoimmune encephalitis and neurological paraneoplastic syndromes, including: - Lambert-Eaton; - Stiff man syndrome			x			
IgM Paraprotein-associated demyelinating neuropathy			x			
Opsoclonus-myoclonus syndrome			x			
Paraneoplastic neurological syndromes (PNS)			x			
Neuromyotonia (Isaacs syndrome)			x			
Non-MS CNS inflammatory disease covering the clinical phenotype of AQP4 ab disease, NMOSD, ADEM (with or without encephalopathy, including brainstem attacks), MOGAD, TM, ON			x			
Rasmussen's Encephalitis			x			
Haematology/Immunology						
Idiopathic thrombocytopenic purpura (ITP)	x	x	x	x	x	x
Post-transfusion purpura			x			
Aplastic anaemia associated with chronic infection with parvovirus B19			x			
Acquired von Willebrand disease (VWD)			x			
Covid Vaccine-induced thrombosis and thrombocytopenia (VITT)			x			

	France[16]	Italy[17]	England[18,19]	Spain[20]	Germany[21]	EU
Replacement therapy for secondary immune deficiencies: Chronic lymphocytic leukaemia (CLL), Multiple myeloma (MM) and all other secondary immune deficiencies with severe or bacterial infections, ineffective antibiotic treatment and either proven specific antibody failure or serum IgG<400	x	x	x	x	x	x
>Post-transfusion hyperhaemolysis >Prevention of haemolysis in patients with a history of transfusion-associated hyperhaemolysis >Prevention of delayed haemolytic transfusion reaction			x			
Hematopoietic stem cell transplantation (HSCT)	x	x	x	x	x	x
Autoimmune haemolytic anaemia (AIHA, including Evans syndrome)			x			
Alloimmune thrombocytopenia (foetal maternal/neonatal) (FMAIT NAIT)			x		x	
Haemolytic disease of the newborn			x			
Thymoma with immunodeficiency			x			
Haemophagocytic syndrome (Haemophagocytic lymphohistiocytosis or HLH)			x			
Infectious Diseases						
Recurrent infections in HIV-infected children	x			x	x	
Measles post-exposure prophylaxis for some patients (pregnant women, immunodeficient patients, infants)			x			x

	France[16]	Italy[17]	England[18,19]	Spain[20]	Germany[21]	EU
Hepatitis A			x	x		x
Polio			x			
Severe or recurrent Clostridium difficile infection (CDI) colitis			x			
Staphylococcal (including PVL-associated sepsis) or streptococcal toxic shock syndrome (TSS)			x			
Suspected tetanus case (IVIg) and Tetanus prone injury (prophylaxis)			x			
Varicella zoster			x			
Viral pneumonitis post-transplantation: HSCT and solid organ			x			
Solid organ transplants						
Treatment of graft rejection			x			
Internal medicine						
Allo-immune neonatal haemochromatosis or gestational allo-immune liver disease (GALD)			x			
ANCA-associated systemic vasculitis (AAV)			x			
Autoimmune uveitis			x			
Catastrophic antiphospholipid syndrome (CAPS)			x			
Immunobullous diseases			x			
Paediatric inflammatory multisystem syndrome temporally associated to COVID-19 (PIMS-TS)			x			
Prevention of autoimmune congenital heart block (anti-Ro)			x			
Kawasaki disease (KD)	x	x	x	x	x	x
Ophthalmology						
Birdshot retinochoroiditis	x					
Dermatology						
Dermatomyositis (DM), Polymyositis (PM)			x		x	

Sources:

- *France: authorised and reimbursed indications listed by the Transparency Commission on the French HTA agency (Haute Autorité de Santé;HAS) website.* [22]
- *Italy: authorised and reimbursed indications in Italy, listed in the paragraph 4.1 of the Summary of Product Characteristics - SmPC.* [17]
- *England: indications listed as "routinely commissioned" by the NHS (National Health Service) in the updated commissioning criteria for the use of therapeutic immunoglobulin* [19]*. In the UK, high-cost drugs can be put on the commissioning list. These medicines are then not reimbursed through national prices but instead directly commissioned by the NHS or by Clinical commissioning groups.* [18]
- *Spain: indications reimbursed and approved by Spanish agency for medicines and health products (AEMPS).* [20]
- *Germany: approved and reimbursed indications listed by the German Federal Institute for Drugs and Medical Devices Bundesinsitut für Arzneimittel und Medizinprodukte.* [21]

The approved reimbursed indications by country shown in Table 3.4.1 do not strictly follow the EMA guidelines (in the table listed as EU).[23,24] In addition, they do not always reflect the real Ig usage since they are also increasingly used in certain off-label situations, including for rare or orphan disorders. The level of evidence in favour of the use of Ig in this context is often limited to non-comparative studies or expert opinions. Off-label use can be difficult to quantify and should be assessed for evidence-based approaches rather than market-driven behaviour.[25]

"Accepted" indications not included in the regulatory approvals but for which substantial clinical evidence has been collected are not shown in this table. These accepted indications are nevertheless considered "off-label" from a regulatory point of view. These off-label uses can still have a reimbursement in some countries by validating additional requirements on a patient-by-patient basis. For example, in the UK, "not routinely commissioned" indications have not been included because to use Ig for these indications, a clinician needs to fill an Individual Funding Request for the patient to fund the Ig therapy.

3.4.2 Comparison between the five countries

There is a comprehensive overview of each country's characteristics in Appendix VII. In the following chapter, a comparative assessment analysis will be presented, focusing on the countries' elements of national consumption, guidelines, national Ig management plans, prioritisation strategies, data collection methodologies, and communication approaches employed in response to Ig shortages.

3.4.2.1 National consumption

England and Northern Ireland together have the lowest Ig consumption of the analysed countries with an estimated use of 90 grams per 1,000 inhabitants in 2021-2022. The recorded Ig volumes used declined from 5.8 million grams in 2017-2018 to almost 5.25 million grams in 2021-2022.[26,8]

On the contrary, Germany experienced a significant growth in Ig consumption during the last decade, increasing from 5.64 million grams in 2012 to 13.28 million grams in 2021.[27] At the population level, this country had the highest Ig consumption with 159.6 gram per 1,000 inhabitants.

In Spain, Ig consumption showed a steady increase since 2012, with consumption evaluated at 3.76 million grams in 2017, reaching 5.09 million grams in 2021.[28] At the population level, this country uses 107.9 million grams per 1,000 inhabitants in 2021. However, there was a relative stagnation in consumption during the 2019-2020 period.[28]

In Italy, the total Ig demand also experienced a stagnation during the 2019-2020 period, with only a small increase from 6.41 million grams to 6.76 million grams.[29] When reported per population, Ig demand was 113.4 grams per 1,000 inhabitants in 2020.

Finally, in France, Ig consumption continued to increase until 2017, with a relative stabilisation covering a bigger period than the two previous countries, from 2017 to 2020. Consumption ranged from 10.41 million grams in 2017 to 10.84 million grams in 2020. The average Ig use in France in 2021 was 107 grams per 1,000 population.
The decline in recorded Ig volumes used observed in some countries corresponded to the COVID-19 crisis. Germany was the least impacted country, maybe because they locally collect a vast quantity of plasma (almost 3 million litres collected per year).[27]

In all five countries, Germany included, local manufacturing production and capacities are not always sufficient and/or directed to serve the national needs, and importing the finished Ig products is required to meet demand. In the UK, the external dependency is also related to plasma acquisition because it has only started collecting plasma for fractionation after April 2021 as a restriction was previously put in place due to risk of variant Creutzfeldt–Jakob disease (vCJD) disease transmission.[30]

3.4.2.2 Guidelines

On the topic of guidelines and recommendations for Ig use in each country, in France, the ANSM has edited national recommendations in 2018, updated in 2019, to enhance

the control of Ig prescriptions.[31] French clinicians have access to an easy-to-use printable booklet called "Plasma-derived medicinal products derived from plasma and associated recombinants," which is updated every two years.[32] It provides guidance to healthcare professionals on Ig specialties, indications, good practices, and recommended dosages. For rare diseases, there are more detailed guidelines called National Diagnostic and Care Protocols (PNDS), developed by reference and competence centres for rare diseases.[33]

In Italy, there are regional guidelines, such as those for the Toscana region, adapted from the NHS - Scotland Clinical Guidelines for Immunoglobulin use (2012).[34] Specialised guidelines for PID are also being developed by the Italian Registry for Primary Immunodeficiencies (IPINet), which is a network consisting of Italian hospitals collaborating to check and update recommendations.[35] Italy has also issued a national guideline for the use of Ig in situations of shortage.[17] For specific diseases like CIDP, international guidelines from the European Academy of Neurology and Peripheral Nerve Society are also used.[36]

In Spain, the shortages as a result of COVID-19 resulted in two new prioritisation documents, one at a national level led by the Agencia Española del Medicamento (AEMPS) [37] and another at regional level led by the Comunidad de Madrid [38] with the participation and consensus of multiple scientific associations. However, individual hospitals may have their own local guidelines that are not standardised.[39,40,41] Consensus documents on the diagnosis and management of patients with specific diseases, like PID, are created by the coordination of several Spanish academic societies.[42]

In the UK, there is a national guideline, the Updated Commissioning Criteria for the use of Therapeutic Immunoglobulin (2021), which is utilised by all UK hospitals to provide standardised recommendations and doses.[19]

In Germany, guidelines are developed by scientific societies specific to medical specialties. For example, the "Evidence-based Practice Guidelines of the German Society for Neurology" (2018)[43] cover neurological indications, and the "Guideline for Primary Antibody Deficiency Diseases"[44] is tailored to PID and is elaborated from the Working Group of Scientific Medical Societies. Nevertheless, cross-sectional guidelines like the ones for therapy with blood components and Plasma Derivatives, updated in 2020, have been elaborated by the Executive Board of the German Medical Association and aim to improve medical care through the presentation of current knowledge of the medical profession through clear recommendations.[45]

In summary, each country has its own guidelines and recommendations for Ig use. France has national recommendations and booklets, Italy has regional and specialised guidelines, Spain has national and local guidelines, the UK has national commissioning criteria, and Germany has guidelines from scientific societies and the German Medical Association.

3.4.2.3 National Ig management plan

The analysed European countries have taken proactive measures to address the issue of Ig supply and manage potential shortages. These countries have implemented various strategies to ensure an organised supply chain and establish expert committees or data collection systems.

In 2008, France legislated to monitor Ig supplies and manage supply tensions, including the establishment of a steering committee and systems to collect supply data and to check Ig availability.[46] The steering committee, with input from Ig manufacturers, aims to prevent and manage shortages by implementing a better Ig distribution, by defining emergency stock thresholds, and by establishing referral contact points directly in the hospitals.

Germany has the German Transfusion Act, implemented in 1998, which ensures self-sufficiency and secured collection of blood and blood components, including plasma.[47] The Paul-Ehrlich-Institute collects data and publishes reports on blood and plasma collection, production of blood components (including plasma proteins), and importation of blood products. [48] These data are focused on the products but not on the patient's side.

The Italian Ministry of Health has established a national programme for plasma and plasma-derived medicinal products, along with a self-sufficiency programme for blood and blood products.[49] Yearly reports on the demand for plasma-derived medicinal products, including Ig, provide comprehensive information on brands, demand quantification, and regional variations.[29]

In Spain, the AEMPS Medicine Supply Guarantee Plan addresses medicine supply issues, including blood products, but not specifically focused on Ig supply.[50] The "Spanish consensus for the sufficiency of plasma and its by-products" aims to improve Ig management and achieve self-sufficiency in blood products. It highlights the need for better planning and reduced dependence on external sources.[51]
The UK implemented the National Demand Management Program for Immunoglobulin in 2006, consisting of a demand management plan, a national Ig database, and clinical guidelines for Ig use.[6] This programme addresses Ig supply issues by providing

procedures for shortages, collecting data for consistent standards of care, and offering comprehensive guidelines for Ig use across various diseases.
These initiatives demonstrate the efforts made by these countries to ensure a secure and sustainable supply of Ig, and to manage potential shortages.

3.4.2.4 National prioritisation plans

Some European countries have developed prioritisation plans in case of Ig shortages (see the comparative Table 3.4.2.4 below).

The country with the highest number of most prioritised indication is the UK. Interestingly, the match between the three prioritisation plans is low: only four indications are prioritised in all three plans (Idiopathic thrombocytopenic purpura, foetal-maternal and neonatal alloimmune thrombocytopenia, Kawasaki disease, Guillain-Barré syndrome) and three are prioritised in two plans (Primary Immunodeficiencies, Acquired von Willebrand disease, Measles in subjects at risk). The particularity of the UK highly prioritised indications (= class I indications): is that they are only short-term indications, for which typically, a single course of Ig is given. If there is a need for a treatment of a chronic disease, then the indication is considered no more than a “class II” indication, on a scale of V. Even for PID patients for which Ig used at a low dosage and are considered as a life-saving medication.

In the UK, the national guidelines classify Ig indications into routinely commissioned and non-routinely commissioned categories.[19] Routinely commissioned indications include prioritised indications, conditions with evidence for Ig use, and indications with limited evidence. Regional clinical guidelines provide additional information,[52] with the indication being divided into five classes, from the most prioritised indications, to classes up for usage review or modification during shortages, and to the final class regrouping indications for which Ig are not recommended for use.

The French National recommendations prioritise indications for Ig use in case of shortages by classifying them into three categories: red (priority), blue (reserved for emergencies or failure of alternatives), and black (not a priority). Prioritisation considers clinical and biological criteria, minimum effective dosage, guidelines/recommendations, and specialist opinion or rare disease network validation.[31]

Italy has an interesting take at the supply problem management. Instead of a clearly established hierarchy between the different conditions, the Italian guidelines provide a description of different inventory phases based on the availability of Ig, and Ig allocation criteria based on the different inventory phases. [17] Criteria for appropriate and priority

use of Ig are specified, with increasing restrictions during shortages, especially for indications with the lowest priority. The Ig use can even be forbidden for these indications in case of severe shortage. This is a more flexible system, but as there is room for interpretation, it could be difficult to take a common concerted action.

In Spain, several prioritisation documents exist. Through email communication with Spanish experts, we were informed of AEMPS creating an internal document ("Priorizacion del uso de Inmunoglobulina Humana Inespecifica") that is only to be used in times of shortages.[37] Additionally, the "Guía Clínica para el Uso de Inmunoglobulinas" elaborated by the Sociedad Española de Farmacia Hospitalaria, and the Grupo Español de Medicamentos Hemoderivados is a national guide, publicly available, with a colour-coded prioritisation system.[53] Red indicates the highest priority diseases, blue represents conditions with other treatment options, and grey denotes conditions with weak evidence. Local guidelines with hierarchisation can also be found, like for example the Guide of the Comunidad de Madrid elaborated with the participation and consensus of multiple scientific associations. It has been updated in 2020, and also contains a colour-coded classification.[38] Therefore, Table 3.4.2.4 shows the public guidelines from the Sociedad Española de Farmacia Hospitalaria and the Grupo Español de Medicamentos Hemoderivados, and excludes the AEMPS one as it is unpublished.

These countries have implemented different approaches to prioritise indications for Ig use during shortages, ranging from colour-coded systems to inventory-based criteria. In contrast, no prioritisation system for Ig indications has been found in Germany.

Table 3.4.2.4: Comparative table of the highest prioritised indications

Indications	**France[30]**	**UK*[52]**	**Spain[53]**
Immunodeficiencies			
Primary Immunodeficiencies	X		X
Haematology/Immunology			
Idiopathic thrombocytopenic purpura (ITP)	X	X	X
Low serum IgG concentrations after HSCT due to neoplasia			X
Autoimmune haemolytic anaemia (AIHA) including Evans syndrome		X	
Acquired von Willebrand disease (vWD)	X	X	
Erythroblastopenia (= red cell aplasia) associated with chronic parvovirus B19 infection	X		

Indications	France[30]	UK*[52]	Spain[53]
Haemolytic disease of the newborn		X	
Alloimmune thrombocytopenia (foetal-maternal / neonatal)	X	X Only neonatal	X
Post-transfusion hyperhaemolysis		X	
Post-transfusion purpura		X	
VITT (post Covid-vaccine)		X	
Internal medicine			
Kawasaki disease	X	X	X
Infectious Diseases**			
Hepatitis A		X	
Measles (if subjects at risk)	X	X	
Polio		X	
Staphylococcal or streptococcal toxic shock syndrome		X	
Tetanus prone injury or suspected Tetanus		X	
Transplant (solid organ)			
Antibody Mediated Rejection (AMR)	X		
cytomegalovirus-induced pneumonitis			X
Neurology			
Dermatomyositis			X
Demyelinating neuropathy associated with paraproteins (IgG or IgA)			X
Chronic inflammatory demyelinating polyneuropathy (CIDP)			X
Guillain-Barré syndrome	X	X	X
Myasthenia Gravis crisis		X	
Dermatology			
Toxic epidermal necrolysis Stevens-Johnson syndrome			X
Total (nb)	9	16	11

**Only for short-term indications*

***May include specific antibodies, directed to the indicated disease*

3.4.2.5 Data collection on Ig use

The UK has developed the National Immunoglobulin Database under the National Demand Management Programme, to support long-term planning and to provide data on the use of Ig in rare disorders. This database, launched in 2008, analyses Ig usage across England and Northern Ireland.[54] Although access is reserved for NHS employees, annual reports have been published since 2008 and made available to the public. The database provides monthly and yearly data, allowing for trend analysis and long-term planning. The data supports too commissioning decisions and therapy initiatives related to Ig usage, helping ensure alignment with guidelines and optimising resource allocation. However, the lack of linkage to discharge summaries makes patient follow-up challenging, resulting in a decline in recorded outcomes over the years.[8]

In the region of Catalonia, Spain, the Registry of Treatments and Patients (RPT) has been employed since 2012 to document comprehensive information on the indications and usage of hospital medications for outpatient purposes.[55] The RPT also collects data on the effectiveness and safety of drugs, including Ig. Spain has also established the National System for Transfusion Safety to ensure self-sufficiency in blood and blood derivatives, including plasma and Ig.[56] Although not directly accessible to the public, annual reports are published.[28] Nevertheless, this national database does not provide specific patient-level information or linkage to discharge data, which could hinder detailed analysis and follow-up. However, patient-level information is beginning to be documented at a national level in the Spanish Registry of Primary Immunodeficiencies (REDIP) that has just been implemented within the Registry of Rare Disease Patients (REPER) of Instituto de Salud Carlos.[57]

In Germany, the Paul-Ehrlich-Institute collects data on healthcare facilities, blood and tissue establishments, and blood products. Annual reports provide information on plasma collection, import/export, processing, and the marketing and consumption of Ig.[27] While these reports offer a general overview of Ig consumption and trends in Germany, they lack detailed patient-specific or clinical data, unlike data gathered by the German National Registry of Primary Immunodeficiencies, which only focus on PID patients.[58]

Italy provides easy access to the analysis of demand for plasma-derived medicinal products through reports that assess self-sufficiency levels and costs sustained by the Italian National Health Service.[29] The reports include data on national and regional demand for Ig but do not include clinical patient-specific data, unlike the IPINet national registry for PIDs.[35] This registry collects clinical data from PID centres and provides insights into the epidemiology, diagnosis, and progression of these disorders.

French data on Ig use can be accessed through surveys conducted by the OMEDIT (regional structures for support and vigilance). These surveys include evaluations of Ig consumption in hospitals and analyses of collected data.[59] Additionally, the French National Health Data System (SNDS) provides a national database for extracting data related to the delivery of Ig. These data are used to assess Ig utilisation, stock management, and resource allocation.

In summary, these countries employ various national Ig databases and systems to gather data on usage, indications, and to a lesser extent on patient outcomes. While each country has its own approach and levels of detail in data collection, these databases play a crucial role in contingency planning, evaluating therapies, and improving the utilisation of Ig. The big limitation of these database is the lack of consolidation at the national level and of detailed patient-level medical information. Except in the case of France, it is difficult to have comprehensive information on the use of Ig by disease at a patient-level.

3.4.2.6 Communication methods for shortage awareness

In the UK, NHS communicates supply shortages to Ig providers through letters, providing information on impacted products and guidance on switching treatments.[60] The NHS also distributes leaflets to healthcare structures and patient associations, warning about Ig shortages and their potential repercussions.[61] There is also an “allocation system" introduced during the pandemic to prevent hoarding of Ig products by using monthly predictions. Additionally, hospitals had a collaborative mutual support arrangement in place to provide extra Ig if needed.

The Spanish Agency for Medicines and Health Products publishes semi-annual reports on medicine shortages, including non-specific IgG medicines.[62] Patient awareness is raised through journal communications, emphasising the impact of shortages and promoting plasma donations.[63] Regional initiatives, such as in Catalonia with the SISCAT that merges different healthcare networks into a single public system, facilitate communication and coordination among hospitals to address supply issues.[55]

In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) collects and provides information on reported supply shortages through a public database.[64] Pharmaceutical companies report supply bottleneck information to the BfArM, ensuring comprehensive coverage on those issues.

The Italian Medicines Agency (AIFA) website offers accessible information on medicine shortages and unavailability, including chapters on actions to take when a

drug is missing and import procedures in case of shortages.[65] AIFA provides guidance to both clinicians and patients, aiming to address the complexity of shortage situations.

In France, OMEDITs serve as information points during health crises, such as the COVID-19 pandemic, to address supply tensions.[66] Alarms were raised regarding the increased consumption of SCIg, switch from IVIg to SCIg, and movement of confined patients, potentially aggravating shortages. Patient cards have been developed to improve information sharing among healthcare professionals, but do not specifically address Ig shortages.[32] Real-time information on shortages is available on the ANSM website, with pharmaceutical laboratories notifying the ANSM of potential or actual stock-outs.[67]

In conclusion, efforts to raise patient and professional awareness, promote plasma donations, and optimise information sharing are observed in multiple countries, but improving the timeliness and specificity of supply information remains a desirable goal for all countries to ensure continuity of patient care during normal situations and Ig shortages.

3.4.3 EU initiatives to prevent supply problems

3.4.3.1 EMA guidelines

To prevent supply problems, some initiatives have been taken at the EU level including guidelines as well as databases. The EMA has elaborated EU guidelines that have the advantage of being accessible to every Ig prescriber in the EU. They put a prescription framework for all the principal Ig indications, with specific dosages to use for each one.[23,24] Nevertheless, they do not cover all the indications for which Ig are used in all the European countries and are not systematically used in all European countries. Many EU countries seems to prefer using their own national guidelines, adapted to their healthcare system, and drafted in their national language, or guidelines from scientific societies specific of their clinical specialty, as they are more precise than the EMA version and often tailored to specific indications. As an example, Table 3.4.3.1 shows the difference in guidelines for five countries for replacement therapy.

By comparing guidelines from a few European countries to the EMA, it is interesting to note that all these guidelines differ from each other in terms of indications and dosages, which highlights the need for a harmonised set of guidelines covering a comprehensive set of indications for which Ig are used across the EU.

3.4.3.2 European database/registry on Ig usage

It is difficult to find aggregated patient data on Ig use in the EU. Nevertheless, in the field of PID, European initiatives have allowed a significant increase in the awareness and diagnosis of new patients by the creation of databases. A notable measure was the launch by the European Society for Immunodeficiencies (ESID) of the European online-PID registry in 2004, which has successfully registered over 20,000 cases by January 2014.[68]

Three different levels of information can be gathered in the ESID PID registry, only the first one being mandatory. Information should be updated once a year, to establish a follow-up of the patients. The dataset of the first level includes:

- Personal information about the patient;
- Date of diagnosis;
- Affected gene(s);
- First PID-related symptom(s);
- Onset of symptoms;
- Information about different therapies used, including hematopoietic stem cell transplantation (HSCT), gene therapy, and Ig therapy (brand, dose, route of administration, side effects).

Level 2 requires the inclusion of laboratory values, in-depth clinical features, and additional information regarding treatments, in addition to covering Ig replacement, immune modifying treatment, and HSCT. Level 3 is specifically dedicated to the conduction of clinical studies within a specified time period.

As countries healthcare development situations within the EU are very different from one another, it can be difficult to analyse the gathered data and to compare the different countries. The creation of online tools can be instrumental to quickly build this kind of knowledge in the EU countries. This kind of initiative has been put in place for PID: in 2020, the International Patient Organisation for Primary Immunodeficiencies (IPOPI) has created the PID Life Index.[69] This Index offers a comprehensive and interactive framework to evaluate the status of the PID healthcare environment within a country, facilitating a better understanding of strengths and areas for improvement.

This interactive tool is based on six key principles of care and provides insights into the quality of care provided to PID patients.

These principles encompass the following parameters:

- PID Diagnosis: The tool evaluates the effectiveness of PID diagnosis within a country, considering factors such as early detection and accurate identification of patients.
- National Patient Organisations: The involvement and support of national patient organisations are taken into account to assess the level of awareness, advocacy, and patient empowerment within the country.
- Registries: The presence and use of registries for PID patients are evaluated, recognising their significance in collecting and analysing crucial data for research and patient management.
- Specialised Centres: The tool considers the presence and accessibility of specialised PID referral centres, which are instrumental in providing comprehensive care and expertise to patients.
- Treatments: The evaluation includes an assessment of the availability and accessibility of treatments for PID patients, considering both conventional and innovative approaches.
- Universal Health Coverage: The tool examines the extent to which PID healthcare services are covered by universal health coverage, ensuring equitable access to necessary care for all individuals affected by PID.

Table 3.4.3.1: Comparison of EMA guidelines to other European countries for replacement therapy

	Condition of prescription for PID	**Dosage for PID**	**Condition of prescription for SID**	**Dosage for SID**
European guidelines (EMA, 2019)[23,24]	PID with impaired antibody production	Recommended starting dose: 0.4-0.8 g/kg followed by at least 0.2g/kg every 3/4 weeks.	SID in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/L.	0.2-0.4 g/kg every 3/4 weeks.
French guidelines (ANSM, 2018)[31]	PID	0.4-g/kg every 3/4 weeks.	Myeloma, CLL, NHL or other SID with impaired antibody production (serum IgG level of <4 g/L) and recurrent infections requiring hospitalisation	0.2-0.4 g/kg every 3/4 weeks.
UK guidelines (NHS, 2021)[19]	A specific PID diagnosis must be established by a clinical immunologist In newly diagnosed patients with PID with no significant burden of infection, the decision to start Ig replacement should be based on a MDT discussion	Initiate at 0.4–0.6 g/kg/month; Dose requirements may increase and should be based on clinical outcome	Underlying cause of hypogammaglobinaemia cannot be reversed or reversal is contraindicated. OR Hypogammaglobinaemia and Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for six months, IgG <4 g/L (excluding paraprotein), Documented failure of serum antibody response to vaccine challenge Depending on the underlying cause of the SID, additional conditions of prescription may be added.	0.4 – 0.6 g/kg/month modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range

	Condition of prescription for PID	Dosage for PID	Condition of prescription for SID	Dosage for SID
Spanish guidelines * (For PID: Consensus Document of the SEIMC, the SEI, the SEIP-AEP and the SEICAP-AEP, 2020)[42] (For SID: Quirónsalud Madrid University Hospital, 2020)[38]	PID	Starting doses between 0,4 to 0,6 g/kg/3-4 weeks Maintenance doses: For patients without pulmonary abnormalities: trough IgG levels above 600 mg/dL For patients with chronic lung damage: trough IgG levels above 800 mg/dL	Ig replacement therapy is recommended: - If the underlying cause of hypogammaglobulinemia cannot be reversed or if its reversal is contraindicated, or also if it is associated with a malignant B-lymphocyte process with severe infections caused by persistent encapsulated bacteria despite prophylactic antibiotic therapy. - In case of CART cell therapy - After CLL or MM: In patients with SEVERE recurrent infections (that have required iv antibiotic treatment and hospitalisation) In those with hypogammaglobulinemia < 500 mg/dl, AND do not achieve adequate antibody levels after immunisation by vaccines	0.4 g/kg For CLL and MM: no dosage specified. Only the duration: every 3-4 weeks For MM: during 6-12 months
German guidelines (“Bundesärztekammer “, the German Medical Association, 2020)[45]	PID	0.4 to 0.8 g/kg bw as initial dose Maintenance therapy with 0.2 to 0.8 g/kg bw	When elimination of the cause is not an option, B-cell function does not improve due to therapy, serious or life-threatening infections occur despite antibiotic administration, or IgG levels are below 0.4 to 0.5 g/l	0.2 to 0.4 g/kg at intervals of 3 to 4 weeks

	Condition of prescription for PID	Dosage for PID	Condition of prescription for SID	Dosage for SID
		depending on serum concentration and clinic at 3- to 4-week intervals.		
Italian guidelines (AIFA website)[70]	Patients with congenital impaired antibody production (immunodeficiency syndromes primary)	Starting dose: 0.4 – 0.8 g/kg Maintenance dose: 0.2 – 0.8 g/kg bw depending on serum concentration	SID in patients with severe or recurrent infections, ineffective antimicrobial treatment and have demonstrated inability to produce specific antibodies (PSAF)* or serum IgG levels < 4 g/l. *PSAF = failure to produce at least a 2-fold increase in IgG antibody titre to vaccines pneumococcal polysaccharide and containing polypeptide antigen	The recommended dose is 0.2 – 0.4 g/kg every 3 – 4 weeks, depending on serum concentration and clinic data.

**These guidelines have been chosen for this country despite being local guidelines from the Quirónsalud Madrid University Hospital, which is part of the largest hospital group in Spain. Moreover, these guidelines are a recent update from those previously available in Spain that were outdated. The former guidelines were a translation performed by the Spanish Society of Hospital Pharmacy (SEFH) of the Clinical guidelines for Immunoglobulin Use, 2nd Edition Update, 2011, published by the British Department of Health.[1] For the establishment of the new guidelines, a representative of each of the hospital services reviewed the pathologies corresponding to their specialty contained in the previous version. Using this document as a starting point, the available evidence has then been reviewed and updated.*

3.5 Case study – Ig usage in France

For a detailed description of the background and healthcare consumption databases in France, please see Appendix VIII.

3.5.1 Study population

The study population included people who had received Ig from the liste en sus or retrocession between 2013 and 2022 (see Table 3.5.1). Over the ten-year period from 2013 to 2022, the number of patients treated rose by 23% as between 28,000 and 35,000 patients are treated with Ig each year.

Table 3.5.1 Study population

Number of patients treated with Ig in France per year

Year		2013		2014		2015		2016		2017		2018		2019		2020		2021		2022	
Total		**28 217**	*100%*	**29 719**	*100%*	**31 980**	*100%*	**34 402**	*100%*	**36 336**	*100%*	**35 809**	*100%*	**36 492**	*100%*	**36 391**	*100%*	**34 006**	*100%*	**35 877**	*100%*
	M	14 794	*52%*	15 388	*52%*	16 504	*52%*	17 850	*52%*	18 699	*51%*	18 289	*51%*	18 451	*51%*	18 578	*51%*	17 549	*52%*	18 452	*51%*
	F	13 423	*48%*	14 331	*48%*	15 476	*48%*	16 552	*48%*	17 637	*49%*	17 520	*49%*	18 041	*49%*	17 813	*49%*	16 457	*48%*	17 425	*49%*
Mean age		52,1		52,9		53,5		53,6		54,4		54,7		55,0		55,1		53,6		53,5	
Median age		58,0		59,0		60,0		60,0		61,0		61,0		62,0		62,0		61,0		61,0	
SD		*24,1*		*23,8*		*23,6*		*23,7*		*23,6*		*23,5*		*23,4*		*23,4*		*24,4*		*24,4*	
Age group		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	0-9	2 542	*9%*	2 515	*8%*	2 541	*8%*	2 801	*8%*	2 812	*8%*	2 672	*7%*	2 641	*7%*	2 596	*7%*	2 929	*9%*	3 188	*9%*
	10-19	1 599	*6%*	1 589	*5%*	1 681	*5%*	1 835	*5%*	1 882	*5%*	1 845	*5%*	1 840	*5%*	1 981	*5%*	2 088	*6%*	2 095	*6%*
	20-29	1 556	*6%*	1 603	*5%*	1 623	*5%*	1 662	*5%*	1 652	*5%*	1 609	*4%*	1 649	*5%*	1 641	*5%*	1 621	*5%*	1 675	*5%*
	30-39	1 914	*7%*	2 003	*7%*	2 199	*7%*	2 386	*7%*	2 361	*6%*	2 351	*7%*	2 410	*7%*	2 320	*6%*	2 186	*6%*	2 386	*7%*
	40-49	2 789	*10%*	2 907	*10%*	3 035	*9%*	3 144	*9%*	3 206	*9%*	3 101	*9%*	3 188	*9%*	3 041	*8%*	2 902	*9%*	2 997	*8%*
	50-59	4 274	*15%*	4 436	*15%*	4 785	*15%*	4 953	*14%*	5 378	*15%*	5 153	*14%*	5 124	*14%*	5 176	*14%*	4 682	*14%*	4 886	*14%*
	60-69	6 001	*21%*	6 552	*22%*	7 225	*23%*	7 830	*23%*	8 231	*23%*	8 040	*22%*	8 046	*22%*	7 734	*21%*	6 932	*20%*	7 284	*20%*
	70-79	4 769	*17%*	5 113	*17%*	5 553	*17%*	6 205	*18%*	6 797	*19%*	7 064	*20%*	7 550	*21%*	7 929	*22%*	7 208	*21%*	7 844	*22%*
	>=80	2 772	*10%*	2 999	*10%*	3 337	*10%*	3 583	*10%*	4 015	*11%*	3 973	*11%*	4 043	*11%*	3 967	*11%*	3 458	*10%*	3 520	*10%*
	MD	*1*		*2*		*1*		*3*		*2*		*1*		*1*		*6*		*0*		*2*	

MD = Missing Data

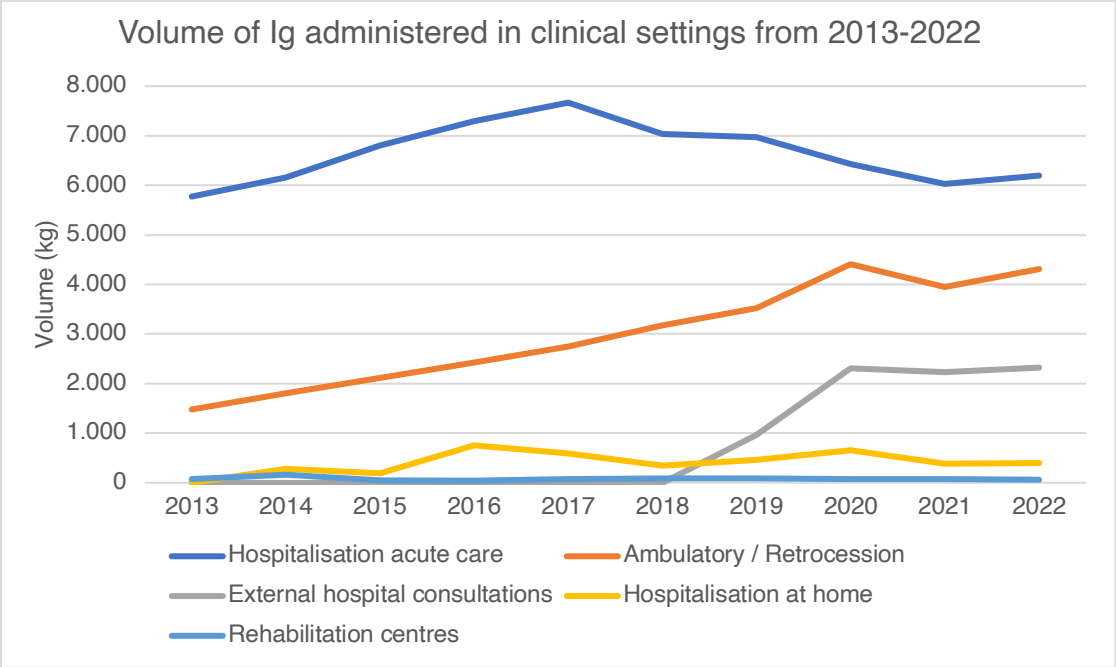
In 2021, between 60% and 70% of patients were administered Ig in the acute hospital setting. As explained in the Methodology section, there are different pathways for the distribution of Ig based on whether the Ig is administered to a patient in the hospital (inpatient or outpatient), or in ambulatory care irrespective of the IV or SC route:

- Hospitalised patients: Ig are delivered by the hospital pharmacy, and administered by hospital nurses,
- Ambulatory care/retrocession: Ig are delivered by the hospital pharmacy and administered in ambulatory care or at home. They are in the SNDS database but are not attached to a diagnosis unless the link with a full inpatient admission can be made.

A particularity of the French system is the coding of outpatient consultations in the hospital setting where the patient does not spend a night. These consultations can be coded as a DRG with a length of stay of zero days. However, they can also be considered as ambulatory consultations in which case the ambulatory care tariffication is used. In general, this latter type of outpatient consultation would engender less use of resources than those associated with a DRG.

Figure 3.5.1 shows the evolution of the use of different settings over the ten years studied. Since 2019, there has been a rise in the number of Ig administrations that take place at outpatient (external) consultations, possibly due to an increase in the tariff that can be charged.[71] During the period studied, there is also an almost constant progression in the number of Ig administered in the ambulatory setting, contrasting with the drop in administration in hospitalisation acute care since 2017. This evolution is certainly due to a change in practice, with a shift from part of the Ig consumption in the hospital setting toward the ambulatory ones.

Figure 3.5.1: Trends in Ig volumes administered in five clinical settings



Our preliminary results from the SNDS estimate the national Ig expenditure in 2021 in the acute hospital sector and ambulatory sector to be 434 million euros with 58% spent in the acute care hospital sector and 42% in ambulatory care (See Table 3.5.2). Over the ten-year period 2013 to 2022, 92% of hospital prescriptions were made in the public hospital setting and 8% in the private and private not-for-profit sector.

In comparison to these first SNDS results, in 2021, it was estimated that in France the national expenditure on Ig was 431 million euros by the OMEDIT survey (see Appendix

IX) that was described in the grey literature review. Whilst the figures vary slightly between the OMEDIT estimation and our estimation from the SNDS database, OMEDIT also report that 58% is spent in the acute care hospital sector and 42% in ambulatory care. The methodology used by OMEDIT is different to our study; for example, the usage in the ambulatory sector was estimated using aggregated data available in the public domain rather than at the patient level.

Table 3.5.2: Annual total expenditure in ambulatory and acute hospitalisation settings per year

Annual Total Expenditure (M€)	**2013**	**2014**	**2015**	**2016**	**2017**	**20188**	**2019**	**2020**	**2021**
Ambulatory	67	82	93	104	118	136	151	189	181
Hospitalisation (acute private)	7	9	10	11	12	12	12	12	11
Hospitalisation (acute public)	208	212	233	249	261	239	239	231	242
Total	282	303	337	364	390	386	402	432	434
Increase from previous year		7%	11%	8%	7%	-1%	4%	7%	1%

Total Ig consumption has a continuous increase until 2017 with a relative stabilisation between 2017 and 2020. A decrease is then observed in 2021. These evolutions could be explained by several factors, such as supply tensions exacerbated during the COVID years, and the implementation of the recommendations of ANSM in 2018 and updated in 2019.[72]

Table 3.5.3: Total volume of Ig in all settings (ambulatory, hospital (acute, home and rehabilitation)

	2013	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
Total volume (Kg)	**7 250**	**7 960**	**8 921**	**9 719**	**10 418**	**10 212**	**10 489**	**10 841**	**9 979**
Evolution from previous year		*10%*	*12%*	*9%*	*7%*	*-2%*	*3%*	*3%*	*-8%*
Nb prescriptions per year (1000s)	**878**	**939**	**1 000**	**1 048**	**1 096**	**1 095**	**1 094**	**1 141**	**995**
Evolution from previous year		7%	6%	5%	5%	0%	0%	4%	-13%

Over the five-year period the SNDS data estimated that 51,939 kg of Ig were prescribed so 10,388 kg on average per year. The OMEDIT survey reported an average of 10,453 kg per year.

3.5.2 Comparison of France with five other countries

To put this use in context, a comparison of France with five other countries over a five-year period regarding total kg used and kg per capita is shown in Figures 3.6.1A and 3.6.1B.

Figures 3.6.1A: Total volumes of Ig used in six countries between 2017 and 2021

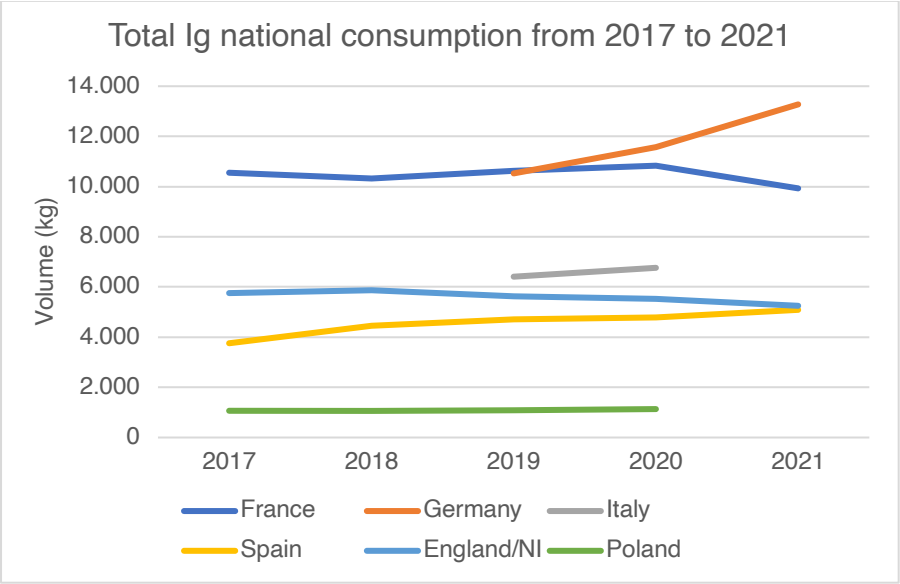
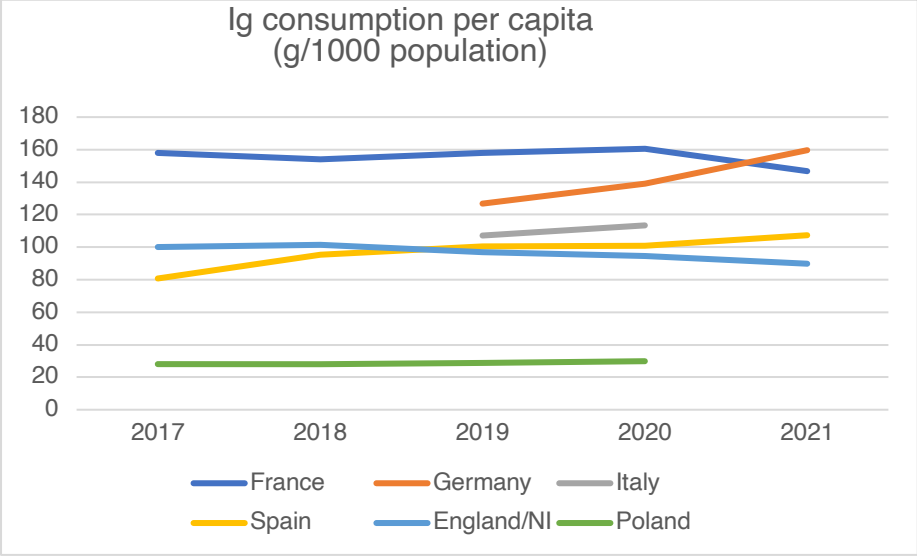


Figure 3.6.1B: Total Ig consumption per capita in six countries between 2017 and 2021



Sources:

- *France: SNDS database*
- *Italy: Demand for plasma-derived medicinal products in Italy. 2020 AIFA* [29]
- *Spain: (1): Sistema Nacional de Salud - Actividad de Centros y Servicios de Transfusión (2021)* [28] *; (2): Puig Rovira, Ll. (2019). PLASMA SELF-SUFFICIENCY IN SPAIN. Transfusion and Apheresis Science, 102700–. doi:10.1016/j.transci.2019.102700* [73] *and (3) Ministerio de Sanidad, Sistema de informacion del sistema nacional para la seguridad transfusional (SISNST)* [56]
- *Poland: Więsik-Szewczyk, E., Ziętkiewicz, M., Radziwilska-Muc, A. & Jahnz-Różyk, K. Increased Access to Immunoglobulin Replacement Therapy for Patients with Primary Immunodeficiency in Poland Based on Clinical Usage Data of Immunoglobulin G over a 5-Year Period. J. Clin. Med. 12, 2431 (2023). https://doi.org/10.3390/jcm12062431* [15]
- *Germany: Bericht für das Jahr Reports, Paul Ehrlich Institute* [47]
- *UK: National Immunoglobulin Data Update Reports, NHS* [54]

In Poland, there is a relatively low number of actual patients treated, which explains their total overall low usage as well as Ig per capita ratio as shown in Figures 3.6.1A and 3.6.1B. There was a diminution of the number of treated patients during the 2017/20 period, with only 8,547 treated in 2020, with a slight increase in the quantity **per patient** from 74.69 g in 2016 to 132.9 g in 2020. Conversely, Belgium only has eight indications for Ig reimbursement but the per capita the use per capita in this country was relatively high with 175 g per 1000 population in 2018. Further work must be done to compare usage by specialty with disease prevalence and guidelines at a country level since it may be that there is a treatment gap in some countries and perhaps inappropriate over-use in others.

Due to the inaccessibility of the SNDS database from 21st July to 28th July, the analysis by diagnostic code or EMA families as described in the European guidelines have not been completed and work will continue as the project moves forward after this deliverable; thus, these must be considered preliminary results. We will also work on the proportion of IVIg and SCIg prescriptions and their settings, whether hospital or ambulatory, as well as analysis at a regional or departmental level. Further work on the coding within the SNDS for pathology is also foreseen to enable comparison with disease prevalence and the guidelines.

The access to individual pseudonymised patient data in the SNDS database will have huge benefits in determining the usage of Ig in France in terms of number of patients, prescriptions, volume, and indication. However, the work is complex and the difficulties in identifying the indications from the ICD-10 to map to the EMA indication groups is a limitation of this intermediate analysis.

Chapter 4: Discussion

The results of this report show that the countries we assessed in Europe and the UK do not have a uniform policy on Ig use. Although the aim was to collect information of every EU MS, this was not feasible, due to several reasons, including the availability of resources and the short timeframe of this project. Nevertheless, by following the different approaches, such as a scoping review on published literature, next to a review on grey literature, dissemination of a survey towards prescribers, performing semi-structured interviews of hospital pharmacists and medical specialists, and analysing data on Ig use by the French national database as a case study, much information was gathered. We will discuss each approach separately and end with a proposal for a set of recommendations.

4.1 Scoping review and interview results

The limited scoping review results indicate the growing need for Ig in Europe and for harmonised evidence-based guidelines in the face of this continual demand. In the interviews, the respondents verified this demand particularly for SID patients. The respondents' various experiences regarding shortages during the pandemic illustrated the impacts felt within each country, and, more so, on a local level. The mitigating measures they described had some commonalities (e.g., decreasing dosages, using every drop of Ig, reviewing stable, chronic patients to see if regimes could be altered safely), but also differences, depending on the severity of the shortage and the pre-existing Ig protocols and procedures. Uniquely, Catalonia underwent a severe shortage and implemented internal and external changes that resulted in a 50% reduction of Ig usage for the clinician. Few respondents could speak of prioritisation documents. When respondents were asked of lessons learned and what recommendations they would advise on an EU-scale, the themes included multi-faceted communication for clinicians and donors, using evidence-based guidelines, "sticking to the evidence" for Ig use, and the need for a harmonised data collection method. These results aligned with what was also seen in the survey and grey literature results.

4.2. Survey results

The results of the doctor survey were not representative for all EU MS. The survey mainly included information from Italian prescribers (n=142) and from university and general hospitals, which reflected the personal network of our WP members. Overall, the most represented specialties were haematology (n=60), followed by paediatrics

(n=47; all specialties, not categorised) and neurology (n=45). In addition, among the respondents were also rheumatologists, dermatologists and nephrologists, which is in line with literature.[5] Ig prescription behaviour, as well as dosage strategy adherence, was also in line with literature for mainly primary and secondary immune deficiencies, and for its immunomodulatory effect in auto-immune diseases. Shortages were especially seen in Italy and Spain during the pandemic year 2021 and might be a consequence of the pandemic itself.

Overall, the survey results confirm adherence to some sort of guidelines (local, regional, national or EU guidelines), and when deviated, this was usually based on (new) evidence. Mitigation plans may differ per country and depend on whether there was an absolute or a relative shortage. In the latter, changing from IV to SC Ig, or changing brands could be an option. In case of absolute shortages, switching to a lowered dose, or using alternative therapies was the best used option. Prioritisation strategies were mostly performed according to any kind of guidelines, however, still a reasonable rate of clinicians (27.5%) make use of their own clinical judgement to prioritise.

4.3 Grey literature and French data case study

A process for Ig demand management across Europe should be adopted to ensure adequate supplies for all patients who require Ig treatment. This Ig management plan should cover all the difference in Ig use across Europe, but also offer comprehensive guidelines, a prioritisation system in case of shortages and a way to gather detailed Ig use by the patients across the EU. It should be supported by robust information on actual Ig use by indication, which requires nationwide collection of patient level data with diagnostic information.

Compared to the United States, Australia, and Canada,[74] Ig use is lower in European countries. This difference in usage is not linked to the number of on-label reimbursed indications. For example, Belgium recognised only eight indications for which Ig can be reimbursed. Nevertheless, the use per capita in this country was of 175 per 1000 population in 2018,[75] higher than some countries reimbursing more indications, such as England and Northern Ireland (101 g per 1000 population in 2018),[54] Italy (107 g per 1000 population in 2019),[29] or France (154 g per 1000 population in 2018, see Chapter 3.5 “Case study – Ig usage in France”). Moreover, the off-label use is important in this country.

Other factors may be linked to differences in Ig use, like the differences in diagnoses that have been observed between Australia and New-Zealand. But to correctly understand Ig use, there is a need to gather comprehensive data about prevalence of disease, diagnoses, but also dosages and clinical outcome data to evaluate the effectiveness of Ig prescriptions.

4.4 Proposal for a set of recommendations

4.4.1 Better data collection on Ig use on a patient level

To properly gather data about Ig use in all the European countries, the first question to answer is: “Is information on immunoglobulin use *at the patient level* collected in a national or regional database/registry?”

Such data collection is fundamental to evaluate their proper use and to deal with shortages. Each country should create a national database which collects and aggregates hospital discharge summaries, with the information on Ig use, at the patient level. This means to gather:

- Use of Ig consolidated at the patient level
- Discharge summary with the ICD-10 codes

Ideally, the data should be for both inpatient, outpatient and ambulatory use of Ig. But of course, data availability depends on lots of different parameters, like each country specific health systems, IT systems used, etc. Such a system has already been put in place in Denmark. Its national data registration register includes data on individuals admitted to somatic hospital departments since 1977, expanded to ambulatory, emergency, and psychiatric departments since 1995. It contains personal information, admission/discharge details, diagnosis (with ICD-10 codes), treatment records, accident information, and additional data on births. The UK has also a robust and successful National Immunoglobulin Database. All Ig use is recorded in a national registry since 2008 and offers a detailed view of current prescribing practice of Ig in England. Lastly, the ESID European online-PID registry launched in 2004, which has registered over 20,000 cases as of 2014, is an example of cooperation of European countries over the creation of a European database and allows a better insight on demand for this particular patient group.[68]

4.4.2 Regularly updated, harmonised guidelines

The Ig prescription practices are currently a challenge to evaluate, because of the diversity of the guidelines that are put in place in the different European countries, and

sometimes also within the same country. This diversity highlights the different strategies imagined and illustrates the need for globalised harmonised evidence-based guidelines in the EU, which would allow for a common action plan and a better coordination between the different countries in case of an important shortage.

The EMA has already provided evidence-based guidelines that are accessible to all Ig providers in the EU. They offer a prescription framework for major Ig indications, specifying dosages for each indication. However, the EMA guidelines do not cover all indications for Ig use in European countries, and their use is not consistent across all countries. Many EU countries prefer their own national guidelines, tailored to their healthcare system and written in their national language. They may also rely on guidelines from specialised scientific societies, which are often more specific and tailored to particular indications. The main issue is that it is mainly rare diseases that are treated with Ig and scientific evidence from large controlled clinical trials is lacking.

For better Ig management and better patient care, it could be interesting to create a set of harmonised guidelines, regularly updated. These harmonised guidelines need to be elaborated by international experts and must be usable by all (even non-expert clinicians) by the inclusion of precise scores or elements, as well as conditions of prescriptions and goals to achieve. But one must keep in mind that sometimes guidelines may not be strictly applied because they must be adapted to the specific healthcare system and constraints of each country, so they are more to be used as guides in the different European countries. Such guidelines have already been created in 2021 for haematology and published under the title of ”Treating secondary antibody deficiency in patients with haematological malignancy: European expert consensus.”[76]

In parallel to more standardised guidelines, for a variety of rare disease, large international clinical trials could help to determine the optimal doses to use and to prove the utility of Ig when used as immunomodulatory agents and in emerging SID situations.

4.4.3 Optimising Ig use

Some EU countries have taken measures to optimise their Ig use in a context of supply tension and/or increased costs burden for the health care systems.

The optimisation of Ig use is a vast and delicate subject because it must conciliate the wills of legislators, Ig manufacturers and clinicians, as well as ensuring optimal patient care. Nevertheless, as the Ig market is global, access to Ig is not guaranteed in case of shortages. An Ig management plan at the European level, listing ranking of conditions, with contingency plans for possible supply shortages could help the

different countries coordinate between each other in shortages situations, to ensure access to all the patients.[3] Outside of those shortage situations, the creation of expert groups that may guide prescribers with the creation of easy-to-use prescription tools (like scores) could be part of the solution to enforce the good use of Ig.

To be able to maintain a good care of Ig users, it is necessary to develop the management of Ig use across the EU with:

- The development of the flexibility of Ig use: with protocols detailing the switch from IVIg to SCIg, and the switch from one Ig brand to another, when available. To achieve this goal, it is necessary to promote large-scale clinical studies evaluating the equivalence between the brands and investigating clinical outcomes. Additionally, it is advisable to maximise the utilisation of pharmacovigilance registries and engage in post marketing surveillance to guarantee the safety of these protocols.[3]
- Matching plasma supply and demand within the EU;
- The promotion of the use of alternative treatments. It can be promoted through guidelines and evaluated with clinical trials;
- Best practices: use of the lowest dose possible for the shortest duration, personalisation of treatments (dosage adjusted with patient's BMI when possible), control of the prescription of new Ig treatments, limiting off-label use.

While there are several possibilities to limit Ig use, it is still a challenge to implement them. It may not be well received by clinicians, as they may fear a loss of treatment modalities for their patients. Educating non-expert clinicians and encouraging them to work in networks with expert centres may be as helpful to increase the good use of Ig.

4.4.4 Prioritisation plans

Maintaining Ig supply has been a challenge for European countries during the COVID-19 crisis. Thus, it is important to create strategies to face future shortages and to ensure a correct treatment to Ig users.

In case of important shortages or potential stock ruptures, some countries have put in place prioritisation systems. However, ranking of the indications is different from one country to another. These differences may reflect the lack of evidence for Ig use in some diseases, but also some political decisions: some countries preferring to focus on diseases for which Ig use is historic and constitute the only therapy available, like PID (France, Spain), and other focusing more on short-term Ig treatments in case of life-threatening condition (UK). Nevertheless, it should be possible to create a

European prioritisation plan, certainly for countries who currently have no plans of this type in place which could be adjusted to the country's resources and organisation.

4.4.5 Shortages awareness and collaboration between countries

Supply issues are more important in some countries or even regions within the same country, than in others. It is nevertheless very important to ensure a continuity of supply to all patients by improving shortage awareness of the different stakeholders as well as by creating a cooperation network between the different European countries.

Many European countries are not self-sufficient in plasma, nor in Ig products, even countries which authorise paid donors because the plasma is exported and not used to treat local patients. For example, Czech Republic currently produces three-times more plasma than needed for self-sufficiency. Nevertheless, Ig shortages were reported during the COVID-19 pandemic, because private fractionators distributing Ig in the country were acting independently from the national plasma collection.[77] In Germany, another country with paid donors, Octapharma, the manufacturer of SCIg Cutaquig®, imposed a supply stop for Germany in June 2022, impacting patients in the process. This decision was caused by a dispute with the GKV - *Spitzenverband der Gesetzlichen Krankenkassen* in connections with discounts under the 2010 statutory price moratorium, which freezes prices for most medicines at 2009 levels.[78]
Because no European country is safe from Ig shortages, it is very important to improve cooperation between them regarding supply issues with the different European countries.

Italy has effectively established a collaborative system among its regions, leading to successful interregional compensation. In a 2020 report, it was evaluated that notable beneficiaries of this system were Umbria, achieving 98% effective self-sufficiency compared to the potential 45%, Basilicata with 68% (compared to 45%), Sardinia with 72% (compared to 39%), Calabria with 63% (compared to 43%), and Sicily with 85% (compared to 58%).[29] This kind of collaboration (between regions, but also between whole countries) must be extended to all of EU.

For European countries to cooperate efficiently, it is necessary to create European mitigation plans to improve communication and awareness. It can be achieved for example by the creation of indicators about the availability of Ig and plasma stock levels, thus allowing an early detection of supply problems. To collect the information needed, it is possible to involve a network of sentinel pharmacy services as well as Ig distributors and manufacturers.

Linked to these indicators, to share efficiently the information, it is necessary to create and optimise sharing information systems such as:

- Online public information on national medicine agencies websites;
- Active communication services to facilitate access to the information by professionals and patients' organisations;
- Systems providing active information through community pharmacies to patients who request medicines with supply problems.[50]

There are efficient examples already put in place by some European countries, such as letters and leaflets provided by the NHS in England to inform Ig providers, healthcare structures, and patient associations about shortages, while also encouraging plasma donations. The Spanish Agency for Medicines publishes reports and utilises journal communications to raise patient awareness and promote plasma donations. The Italian Medicines Agency offers accessible guidance on shortages and import procedures on its website. In France, OMEDIT serves as regional information points during health crises, while real-time shortage information is available on the ANSM website. Overall, efforts to raise awareness and optimise information sharing are observed globally, but improving timeliness and specificity of supply information remains a goal for all countries.

Chapter 5: Next steps

5.1 Workshop planning

The feasibility of our proposed recommendations will be discussed during a workshop with all relevant European stakeholders, including the competent health authorities, the patient organisations, and the medical specialties. This workshop will take place on September 6, 2023, and will be held virtually to optimise participation as much as possible. During this workshop several statements will be discussed and final recommendations will be developed.

5.2 Possible impact of the proposed SoHO regulation

On July 18, 2023, the European Parliament Committee on the Environment, Public Health, and Food Safety (ENVI) voted to adopt the amended report on regulating substances of human origin (SoHO), such as blood, plasma, organs, and tissues. This move is a significant step towards enhancing the safety and quality of these substances. It aims to safeguard the continuity and quality of supplies and improve the well-being of those donating and receiving SoHO-derived products. A key goal of the proposed regulation is to establish sustainable plasma supplies in Europe. By sharing data on supply and demand, stakeholders help ensure a stable source of plasma. Additionally, the proposed regulation seeks to prioritise the well-being of donors and recipients, to prevent any financial gains from such practices, and incorporates the expertise of the European Directorate for the Quality of Medicines & Healthcare (EDQM), which includes limits on the frequency of blood and plasma donations. The next step is the plenary vote in parliament on 12 September.[79,80]

Chapter 6: Conclusions and points to consider

Ig consumption is expected to increase due to a variety of factors; however, scarce scientific evidence is available to support this. Therefore, it is of vital importance to start benchmarking patients' Ig use on a national level, for better insight and to be able to give guidance to possible inappropriate Ig use and shortages. In addition, harmonisation of Ig indications, mitigation and prioritisation strategies are deemed necessary.

Although we collected a vast amount of interesting information regarding Ig use from several EU MS, there are several **urgent** points to consider:

- We believe off-label use is not desirable since guidelines are not followed and there may not be sufficient clinical evidence to support the use. However, it should be emphasised that countries, regions, and/or hospitals may also have a list of approved and reimbursed indications, which can be considered off-label, but may be approved by clinical societies or committees. Based on our findings, one should focus more on up-to-date guidelines as well as more detailed guidance, following the process of developing evidence-based guidelines and recommendations that entail approval from scientific groups/experts and supported by the relevant stakeholders.[81–83]
- A pan-EU collaboration to exchange best practices, collect data for joint registries, and initiate joint initiatives for projects and clinical studies was recommended by the authors of a green paper on appropriate use of Ig.[84] One example is the ESID PID registry, where Ig use is being registered for these patients, including follow up and clinical outcomes.
- Patients and patient advocacy groups are essential and should be involved in all discussions regarding the therapeutic value of current and future Ig use.
- Harmonisation of Ig indications, data collection and prioritisation for all EU member states can be a huge challenge, resulting in the lack of implementation. Therefore, flexibility for a tailor-made approach per MS, next to a fixed backbone would be preferable to reach optimal implementation.
- Clinical efficacy of Ig use is an important outcome, and must be incorporated in Ig data registries, next to other data on a patient level.

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Appendices

Appendix I – Search Strategy for Scoping Review

Three-part search strategy based on “future demand,” “plasma,” and “supply”[5]
(((("Pharmaceutical Preparations/economics"[Mesh] OR "Pharmaceutical Preparations/supply and distribution"[Mesh] OR "Immunologic Factors/economics"[Mesh] OR "Immunologic Factors/supply and distribution"[Mesh] OR "Immunoglobulins, Intravenous/economics"[majr] OR "Legislation, Drug"[Mesh:NoExp]) AND ("plasma-derived"[tw] OR "plasma derived medical products"[tw] OR "plasma derived medicinal products"[tw] OR "plasma derived medicines"[tw] OR "plasma derived preparations"[tw] OR "plasma derived product"[tw] OR "plasma derived products"[tw] OR "plasma derived drug"[tw] OR "plasma derived components"[tw] OR "plasma derived concentrate"[tw] OR "plasma derived concentrates"[tw] OR "plasma derived biological medicines"[tw] OR "plasma derived blood products"[tw] OR "plasma derived protein"[tw] OR "plasma derived proteins"[tw] OR "plasma derived therapeutic products"[tw] OR "plasma derived therapeutic proteins"[tw] OR "plasma derived therapeutics"[tw] OR "plasma derived therapies"[tw] OR "plasma derived drugs" [tw] OR (("PDMP"[tw] OR "PDMPs"[tw]) AND "plasma"[tw]) OR "Plasma Products"[tw] OR "Plasma Product"[tw] OR **(("Pharmaceutical Preparations"[mesh] OR "Biological Products"[mesh] OR "Biopharmaceutics"[mesh]) AND ("Plasma"[mesh] OR "plasma"[ti]))** OR "Immunoglobulins, Intravenous"[Mesh] OR "Intravenous Immunoglobulin"[tw] OR "Intravenous Immunoglobulins"[tw] OR "Intravenous IG"[tw] OR "IVIG"[tw] OR "IVIGs"[tw] OR "Intravenous Immune Globulin"[tw] OR "IV Immunoglobulins"[tw] OR "Flebogamma DIF"[tw] OR "Gamunex"[tw] OR "Globulin-N"[tw] OR "Globulin N"[tw] OR "Intraglobin"[tw] OR "Intraglobin F"[tw] OR "Gammagard"[tw] OR "Gamimune"[tw] OR "Gamimmune"[tw] OR "Modified Immune Globulin"[tw] OR "Privigen"[tw] OR "Sandoglobulin"[tw] OR "Venoglobulin"[tw] OR "Venoglobulin-I"[tw] OR "Venoglobulin I"[tw] OR "Iveegam"[tw] OR "Alphaglobin"[tw] OR "Endobulin"[tw] OR "Gamimune N"[tw] OR "Gamimmune N"[tw] OR "Gammonativ"[tw])**) OR (("current practice"[tw] OR "current clinical practice"[tw] OR "practice"[ti] OR "usage"[ti] OR "daily practice"[tw] OR "current usage"[tw] OR "current use"[tw] OR "common practice"[tw])** AND ("plasma-derived"[tw] OR "plasma derived medical products"[tw] OR "plasma derived medicinal products"[tw] OR "plasma derived medicines"[tw] OR "plasma derived preparations"[tw] OR "plasma derived product"[tw] OR "plasma derived products"[tw] OR "plasma derived drug"[tw] OR "plasma derived components"[tw] OR "plasma derived concentrate"[tw] OR "plasma derived concentrates"[tw] OR "plasma derived biological medicines"[tw] OR "plasma derived blood products"[tw] OR "plasma derived protein"[tw] OR "plasma derived proteins"[tw] OR "plasma derived therapeutic products"[tw] OR "plasma derived therapeutic proteins"[tw] OR "plasma derived therapeutics"[tw] OR "plasma derived therapies"[tw] OR "plasma derived drugs" [tw] OR (("PDMP"[tw] OR "PDMPs"[tw]) AND "plasma"[tw]) OR "Plasma Products"[tw] OR "Plasma Product"[tw] OR **(("Pharmaceutical Preparations"[mesh] OR "Biological Products"[mesh] OR "Biopharmaceutics"[mesh]) AND ("Plasma"[mesh] OR "plasma"[ti]))** OR "Immunoglobulins, Intravenous"[Mesh] OR "Intravenous Immunoglobulin"[tw] OR "Intravenous Immunoglobulins"[tw] OR "Intravenous IG"[tw] OR "IVIG"[tw] OR "IVIGs"[tw] OR "Intravenous Immune Globulin"[tw] OR "IV Immunoglobulins"[tw] OR "Flebogamma DIF"[tw] OR "Gamunex"[tw] OR "Globulin-N"[tw] OR "Globulin N"[tw] OR "Intraglobin"[tw] OR "Intraglobin F"[tw] OR "Gammagard"[tw] OR "Gamimune"[tw] OR "Gamimmune"[tw] OR "Modified Immune Globulin"[tw] OR "Privigen"[tw] OR "Sandoglobulin"[tw] OR "Venoglobulin"[tw] OR "Venoglobulin-I"[tw] OR

"Venoglobulin I"[tw] OR "Iveegam"[tw] OR "Alphaglobin"[tw] OR "Endobulin"[tw] OR "Gamimune N"[tw] OR "Gamimmune N"[tw] OR "Gammonativ"[tw])) **OR** (((demand*[ti] NOT "on-demand"[ti]) OR "demands"[ti] OR "supply"[ti] OR "supplies"[ti] OR "supplied"[ti] OR "future demand"[tw] OR "future demands"[tw] OR "demand change"[tw] OR "demand changes"[tw] OR "demand characteristics"[tw] OR "demand prediction"[tw] OR "future supplies"[tw] OR "future supply"[tw] OR "supply and distribution"[subheading] OR "Resource Allocation"[mesh] OR (("demand"[tw] OR "demands"[tw]) AND ("future"[tw] OR predict*[tw] OR "change"[tw] OR "changes"[tw] OR "changing"[tw]))) AND ("plasma-derived"[tw] OR "plasma derived medical products"[tw] OR "plasma derived medicinal products"[tw] OR "plasma derived medicines"[tw] OR "plasma derived preparations"[tw] OR "plasma derived product"[tw] OR "plasma derived products"[tw] OR "plasma derived drug"[tw] OR "plasma derived components"[tw] OR "plasma derived concentrate"[tw] OR "plasma derived concentrates"[tw] OR "plasma derived biological medicines"[tw] OR "plasma derived blood products"[tw] OR "plasma derived protein"[tw] OR "plasma derived proteins"[tw] OR "plasma derived therapeutic products"[tw] OR "plasma derived therapeutic proteins"[tw] OR "plasma derived therapeutics"[tw] OR "plasma derived therapies"[tw] OR "plasma derived drugs" [tw] OR (("PDMP"[tw] OR "PDMPs"[tw]) AND "plasma"[tw]) OR "Plasma Products"[tw] OR "Plasma Product"[tw] OR **(("Pharmaceutical Preparations"[mesh] OR "Biological Products"[mesh] OR "Biopharmaceutics"[mesh]) AND ("Plasma"[mesh] OR "plasma"[ti]))** OR "Immunoglobulins, Intravenous"[Mesh] OR "Intravenous Immunoglobulin"[tw] OR "Intravenous Immunoglobulins"[tw] OR "Intravenous IG"[tw] OR "IVIG"[tw] OR "IVIGs"[tw] OR "Intravenous Immune Globulin"[tw] OR "IV Immunoglobulins"[tw] OR "Flebogamma DIF"[tw] OR "Gamunex"[tw] OR "Globulin-N"[tw] OR "Globulin N"[tw] OR "Intraglobin"[tw] OR "Intraglobin F"[tw] OR "Gammagard"[tw] OR "Gamimune"[tw] OR "Gamimmune"[tw] OR "Modified Immune Globulin"[tw] OR "Privigen"[tw] OR "Sandoglobulin"[tw] OR "Venoglobulin"[tw] OR "Venoglobulin-I"[tw] OR "Venoglobulin I"[tw] OR "Iveegam"[tw] OR "Alphaglobin"[tw] OR "Endobulin"[tw] OR "Gamimune N"[tw] OR "Gamimmune N"[tw] OR "Gammonativ"[tw]))) NOT ("Animals"[mesh] NOT "Humans"[mesh]) AND ("2008/01/01"[PDAT] : "3000/12/31"[PDAT])

Appendix II – Interview Guide

I. Introductions
1. Myself and SUPPLY's background and objectives
2. Verbal consent for recording, how to address expert (title or first name)
3. Summary of pharmacist/clinician's role/background

II. Context
1. Hospital context pharmacist or clinician works in
2. What is the overall situation of Ig usage in the hospital? Has there been any trends/changes in usage in certain indications in recent years?
3. For what indications does the dr treat for? (Specify any off-label indications)
4. How do you determine dosages?
5. How many patients do you treat with Ig?

III. Guidance Documents
1. Are any guidance documents used? Please specify (Includes various guidelines, priority protocols, scientific evidence/RCTs, etc)
2. How long has/have these documents been used?
3. What is/are the impact of the document(s)? (Be as specific as possible)
4. Is it possible to get a copy of these docs?

IV. Non-crisis scenario
1. What is the process for ordering and approving Ig?
2. Who are key persons involved? Internal or external groups (e.g., regional IG panel)?
3. Do you need specific approval for off-label indications based on the clinical need of the patient according to your judgement?

V. Crisis scenario
1. Did you have Ig shortages due to COVID or because of another reason?
2. If yes, do you know why these shortages occurred? (E.g., brands or sizes out of stock or hospital couldn't afford to buy)
3. Mitigating measures: how did you manage? (Were you able to switch another brand, or did you have to adjust dosing/frequency, or did you have to find alternative treatments to IgG?)
4. Were there differences in the ordering process from above?
5. Were prioritization protocols or other documents used?
6. Overall, what were lessons learned during COVID regarding Ig? (Provide with examples)

VI. Decreasing usage

1. Due to global scenario of high Ig demand/low supply, have you ever tried to curb/decrease Ig demand in your hospital? Provide examples (can include internal/external organizational mitigating measures)
2. From your experience, do you think the yearly increase in Ig consumption is justified or is it possible to use a different approach to curb or decrease demand in daily practice?

VII. EU recommendations

1. Do you have any recommendations on improving the appropriate use of Ig at baseline?
2. Any recommendations on how to prioritize Ig in times of crisis/shortages?

VIII. Obtaining Ig data

1. Is there a national / regional database/registry which collects and aggregates hospital discharge summaries with the information on immunoglobulin use at the patient level?
   (This means use of Ig for a given patient linked with all hospitalisation data at the patient level (for example in France this is called a discharge summary) with the ICD9 or ICD-10)

IX. Clarifications and thanks

Appendix III – Doctors' survey

Introduction

Dear hospital doctor,

We would like to gain your insights into the status of human normal immunoglobulin (Ig) usage, shortages and the decision-making process regarding Ig utilization within your hospital, which is part of the "**SUPPLY project," a EU4Health Programme** funded project that aims to increase and strengthen the resilience of plasma collection (Ig being the main driver) in the EU to enable a stable and adequate supply of medicines in Europe, also in times of crisis.

With the results of this project, the European Hematology Association (EHA), together with the European Blood Alliance (EBA) and other stakeholders aim to develop a set of recommendations and guidance for medical societies, blood establishments, competent authorities, and other professional stakeholders to support them in being able to increase plasma collection in the EU by the public health sector and providing guidance for IG usage.

We have created a short survey that will take approximately 15-20 minutes to complete. This survey will involve a time period before the pandemic (until 2019) and during the pandemic (2020 and 2021) to know whether the pandemic has affected Ig usage as well. Also, we would like to know your opinion on future usage.

Your participation is completely voluntary, and your responses will be kept confidential and anonymous. If you agree, please click 'yes' below. Thank you in advance.

Yes/No (if no, skip to the thank you screen at the end of the survey)

1. Could you identify your primary area of clinical expertise?

a. Adult neurology

b. Adult immunology

c. Adult haematology

d. Adult infectious diseases

e. Adult rheumatology

f. Adult dermatology

g. Adult nephrology (including kidney transplant surgery)

h. Adult general medicine

i. Paediatrics (including all sub-specialties related to paediatrics)

j. Other

2. How many patients per year do you treat with immunoglobulin (Ig) therapy?

a. I do not treat patients with immunoglobulins (**end of survey)**

b. Up to 20

c. 21 to 50

d. 51 to 100

e. More than 100

3. In your practice, please indicate for whom Ig is prescribed for:

a. Inpatients only (100%)

b. Inpatients and outpatients (day care or at home)

c. Outpatients only (100%)?

4. *In case answer 3 is b or c:* what percentage of the outpatients receive Ig at home?

a. 0%

b. Up to 10%

c. 10% to 25%

d. 26% to 50%

e. 51% to 75%

f. 76% to 99%

g. 100%

5. In your medical practice, do you use:

a. Only intravenous immunoglobulin therapy (IVIg)

b. Only subcutaneous immunoglobulin therapy (SCIg)

c. Both intravenous and subcutaneous immunoglobulin therapies

Immunoglobulin Use

If they choose options a or c at Q5

Below are the EMA guidelines for the main uses of intravenous immunoglobulin therapy (IVIg):

Replacement therapy in adults, and children and adolescents (0-18 years) in:

· Primary immunodeficiency syndromes (PID) with impaired antibody production

· Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF) or serum IgG level of <4 g/l

* PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Immunomodulation in adults, and children and adolescents (0-18 years) in:

· Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count

· Guillain Barré syndrome

· Kawasaki disease (in conjunction with acetylsalicylic acid)

· Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

· Multifocal motor neuropathy (MMN)

6. Please specify for which indication(s) you prescribe IVIg (multiple answers possible):

a. replacement therapy in PID

b. replacement therapy in SID

c. immunomodulation, Primary immune thrombocytopenia

d. immunomodulation, Guillain Barré Syndrome

e. immunomodulation, Kawasaki's disease

f. immunomodulation, Chronic inflammatory demyelinating polyneuropathy

g. immunomodulation, Multifocal Motor Neuropathy

h. Other (Off-label use, please precise)

7. When the answer is replacement therapy in SID: What are the main causes of secondary immunodeficiency? (Multiple answers possible)

a. B cell depletion therapy, such as rituximab

b. CAR-T cell therapy

c. Other immunosuppressive therapy

d. Due to the underlying disease: Multiple myeloma

e. Due to the underlying disease: Malignant Lymphoma

f. Due to the underlying disease: Chronic Lymphocytic Leukaemia

g. Due to another underlying disease

h. Other

8. What proportion of your IVIg prescriptions is outside the EMA indications?

a. None, all are prescribed according to the guidelines

b. Up to 20%

c. 21to 40%

d. 41% to 60%

e. >60%

9. When answers are b-e: what are the reasons for prescribing outside these indications?

a. New scientific evidence, not (yet) stated in local, national or international guidelines

b. Expert opinions/meetings.

c. Lack of information in existing local, national or international guidelines

d. Participation in a clinical trial

e. Based on my own clinical expertise.

f. Other

10. What is the usual dose that you give for: (the options proposed will depend on the answers in question 5)

a. Replacement therapy A (PID)

· Less than 200 mg/kg every 3-4 week

· Between 200 and 400mg/kg every 3-4 week

· Between 400 and 600mg/kg every 3-4 week

· Between 600 and 800mg/kg every 3-4 week

· More than 800mg/kg every 3-4 week

· Other (specify)

b. Replacement therapy B (SID)

· There is a great variability in Ig doses used, depending on the underlying disease

· Less than 200 mg/kg every 3-4 week

· Between 200 and 400mg/kg every 3-4 week

· Between 400 and 600mg/kg every 3-4 week

· Between 600 and 800mg/kg every 3-4 week

· More than 800mg/kg every 3-4 week

· Other (please specify the frequency of treatment)

c. Immunomodulation, disease 1 (Primary immune thrombocytopenia)

· Day one: 0.8-1g/kg

· For the following 2 to 5 days: 0.4 g/kg given daily (possible repeat of dosing in case of relapse)

· Day one: another dose (please specify)

· For the following days: another dose (please specify the number of days)

· 0.4–1 gr/kg, total maximal dose of 2 gr/kg, no difference in dosage between first and last day

· Other (please specify number of days of treatment)

d. Immunomodulation, disease 2 (Guillain Barré Syndrome)

· 0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).

· Other (please specify the number of days)

e. Immunomodulation, disease 3 (Kawasaki disease)

· 2g/kg as a single dose

· 400 mg/kg/day over 4 days

· Other (please specify the number of days)

· A second dose can be administrated (please specify the dose)

f. Immunomodulation, disease 4 (Chronic inflammatory demyelinating polyneuropathy)

· Starting dose: 2 g/kg divided over 2 -5 consecutive days

· Maintenance doses: 1 g/kg over 1-2 consecutive days every 3-4 weeks

· Starting dose: Other (specify)

· Maintenance dose: Other (please specify the number of days)

· Other schedule (please specify)

g. Immunomodulation, disease 5 (Multifocal Motor Neuropathy)

· Starting dose: 2 g/kg given over 2-5 consecutive days.

· Maintenance dose: 1 g/kg every 2 to 4 weeks

· Maintenance dose: 2 g/kg every 4 to 8 weeks

· Starting dose: Other (specify)

· Maintenance dose: Other (please specify the number of days)

· Other schedule (please specify)

If they choose options a or b at Q6

11. a. How do you determine the dosage given to your patients with IVIg used as a replacement therapy? (Asked separately for each answer to question 5)

a. Based on product label/package insert instructions

b. Based on international guidelines (EMA)

c. Based on local hospital guidelines

d. Based on new scientific evidence, not (yet) stated in guidelines

e. Based on expert opinions/meetings.

f. Based on my clinical expertise.

g. Based on the dosage given in similar diseases.

h. Based on participation in a clinical study

i. Other

If they choose options c to g at Q6

11. b. How do you determine the dosage given to your patients with IVIg used in immunomodulation? (Asked separately for each answer to question 5)

a. Based on product label/package insert instructions

b. Based on international guidelines (EMA)

c. Based on local hospital guidelines

d. Based on new scientific evidence, not (yet) stated in guidelines

e. Based on expert opinions/meetings.

f. Based on my clinical expertise.

g. Based on the dosage given in similar diseases.

h. Based on participation in a clinical study

i. Other

If they choose options b or c at Q5

Below are EMA guidelines for main usage of subcutaneous immunoglobulin therapy (SCIg):

Indications for subcutaneous administration (SCIg)

Replacement therapy in adults, children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes with impaired antibody production (see section 4.4).

- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated.

- Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients

- Hypogammaglobulinaemia in patients pre- and post- allogeneic haematopoietic stem cell transplantation (HSCT)

Ref: Guideline EMA/CHMP/BPWP/143744/2011 rev. 1

12. Please specify for which indication you prescribe SCIg (multiple answers possible):

a. Replacement therapy in Primary immunodeficiency syndromes

b. Replacement therapy in Chronic lymphocytic leukaemia

c. Replacement therapy in Multiple Myeloma

d. Replacement therapy in Haematopoietic stem cell transplantation

e. Other (Off-label use, please precise)

13. What proportion of your SCIg prescriptions is outside the EMA indications?

a. None, all are prescribed according to the guidelines

b. Up to 20%

c. 21to 40%

d. 41% to 60%

e. >60%

14. When answers are b-e: what are the reasons for prescribing outside these indications?

a. New scientific evidence, not (yet) stated in guidelines

b. Expert opinions/meetings.

c. Lack of information in existing guidelines

d. Participation in a clinical trial

e. Based on my own clinical expertise.

f. Other

15. What is the usual dose that you give for: (the options proposed will depend on the answers in question 11)

a. Replacement therapy in Primary immunodeficiency syndromes

· Loading dose of at least 200 to 500mg/kg with a maximal daily dose of 100 to 150 mg/kg

· Monthly dose of the order of 400-800mg/kg

· Loading dose: Other (specify)

· Monthly dose: Other (specify)

· Other schedule (please specify)

b. Replacement therapy in Chronic lymphocytic leukaemia

· Loading dose of at least 200 to 500mg/kg with a maximal daily dose of 100 to 150 mg/kg

· Monthly dose of the order of 400-800mg/kg

· Loading dose: Other (specify)

· Monthly dose: Other (specify)

· Other schedule (please specify)

c. Replacement therapy in Multiple Myeloma

· Loading dose of at least 200 to 500mg/kg with a maximal daily dose of 100 to 150 mg/kg

· Monthly dose of the order of 400-800mg/kg

· Loading dose: Other (specify)

· Monthly dose: Other (specify)

· Other schedule (please specify)

d. Replacement therapy in Haematopoietic stem cell transplantation

· Loading dose of at least 200 to 500mg/kg with a maximal daily dose of 100 to 150 mg/kg

· Monthly dose of the order of 400-800mg/kg

· Loading dose: Other (specify)

· Monthly dose: Other (specify)

· Other schedule (please specify)

If they choose option c at Q5

16. A. Do you determine differently the dosage given to your patients with SCIG than with IVIg?

a. Yes

b. No

c. I don't know

16. B. How do you determine the dosage given to your patients with SCIg? (if yes to precedent answer)

a. Based on product label/package insert instructions

b. Based on international guidelines (EMA)

c. Based on local hospital guidelines

d. Based on new scientific evidence, not (yet) stated in guidelines

e. Based on expert opinions/meetings.

f. Based on my clinical expertise.

g. Based on the dosage given in similar diseases.

h. Based on participation in a clinical study

i. Other

17. Do you adjust the dosage to each patient individually?

a. Yes, always

b. Yes, sometimes (if it is chosen, new question asking when do they adjust the dosage)

c. No

If they answered that they use IVIg for immunomodulation:

18. Do you use alternative therapies as immunomodulatory agents?

a. Yes

b. No

19. Do you use alternative therapies before or after trying Ig?

a. Before

b. After

Why?

Free textbox entry

If they answered that they use Ig as replacement therapy for immunodeficiency (both for IVIg and SC Ig):

20. For patients treated for secondary immunodeficiency, when are immunoglobulin levels measured or tested to prove specific antibody failure?

a. Before the initiation of B-cell depleting therapy for any condition,

b. Before a hematopoietic or solid organ transplantation,

c. Before the initiation of immunosuppressive treatment for blood cancer,

d. At the time of investigation for possible leukaemia, lymphoma, or multiple myeloma.

e. Immunoglobulin levels are not measured or tested to prove specific antibody failure

f. Other

21. For patients treated for secondary immunodeficiency, is a reassessment of the Ig treatment done?

a. Yes

b. No

22. If a reassessment is done, when is it done?

a. Six months after the beginning of the treatment

b. Every year after the beginning of the treatment

c. Every 2-5 years after the beginning of the treatment

d. At the end of a cycle of immunosuppressive treatment or B-cell depleting therapy

e. When the patient is free from infection for 6 months

f. When the patient is free from infection for 12 months

g. Other (specify)

Q23 only if they answered that they use IVIg for PID and/or SID AND for immunomodulation:

23. Can you estimate the proportion of Ig use for immunodeficiencies versus immunomodulation (in %, total must be 100%)?

24. Compared to 2019, how did COVID-19 impact Ig usage in your specialty? Please indicate in the table below)

a. Yes, in both 2020 and 2021 decreased

b. Yes, in both 2020 and 2021 increased

c. Yes, only in 2020 decreased

d. Yes, only in 2021 decreased

e. Yes, only in 2020 increased

f. Yes, only in 2021 increased

g. No, stable in both years

h. Only stable in 2020

i. Only stable in 2021

j. Not known

If "increased" has been selected in 2020 or 2021:

25. a. Why do you think there was an increase in Ig usage during the COVID crisis?

a. Experimental usage as an adjuvant therapy to treat COVID-19 patients

b. Increased use in primary immunodeficiencies

c. Increased use in secondary immunodeficiencies

d. Increased use for immunomodulation

e. Exploratory use in clinical trials

f. Off-label use

g. Use in solid organ transplantations

h. Use in neurological conditions

i. Other

If "decreased" has been selected in 2020 or 2021:

25. b. Why do you think there was a decrease in Ig usage during the COVID crisis?

a. Ig shortages

b. Growing use of protocols and guidelines

c. Concerns about the safety of use

d. Use of alternative therapies for immunomodulatory indications instead of an Ig treatment

e. Cost of treatment

f. Other

26. In your opinion, what are, in general, the main factors that contribute to an increased use of Ig?

a. Use for immunomodulation

b. Use as replacement therapy in primary immunodeficiencies

c. Use as replacement therapy in secondary immunodeficiencies

d. Exploratory use in clinical trials

e. Off-label use

f. Use in solid organ transplantations

g. Use in neurological conditions

h. Other

27. In your opinion, what are, in general, the main factors that could limit the use of Ig in the near future?

a. Ig shortages

b. Growing adherence to protocols and guidelines

c. Concerns about the safety of use

d. Use of alternative therapies for immunomodulatory indications instead of IgG treatment

e. Cost of treatment or reimbursement policies

f. Other (specify)

If they choose option c at Q5

28. Please estimate what proportion of each application route for Ig was prescribed for your patients in 2019 (It should total 100%)

a. Intravenous immunoglobulins (IVIg) …%

b. Subcutaneous immunoglobulins (SCIg) …%

29. Please estimate what proportion of each application route for Ig was prescribed for your patients in 2020 (It should total 100%)

a. Intravenous immunoglobulins (IVIg) …%

b. Subcutaneous immunoglobulins (SCIg) …%

30. Please estimate what proportion of each application route for Ig was prescribed for your patients in 2021 (It should total 100%)

a. Intravenous immunoglobulins (IVIg) ____%

b. Subcutaneous immunoglobulins (SCIg) ___%

31. From January 2017- December 2021 (5 calendar years), did you change your prescribing policy for Ig usage in your practice?

a. Yes

b. No

c. I don't know

(If 'yes' go to #30. If 'no' or 'I don't know,' go to #31

32. Do you know why a change in usage occurred? (Please indicate all that apply)

a. Due to a change in cost or reimbursement

b. Due to a change in indications (for example new incoming scientific evidence/RCT), if yes: please state the main indication type and subgroup (defined group) as stated in the table-drop down menu

c. Due to a change in hospital/regional/national policies

d. Due to a change in application route to subcutaneous (SC) instead of IV route from IV to SC, if yes: dosage increase? Same? Decrease? Do you use a conversion factor (for example: FDA recommendation)

e. Due to a change in dosage. If yes, ask why this change.

f. Due to the COVID-19 pandemic

g. Other

Other

33. Who are the key individuals who approve Ig orders for non-standard (off-label) indications? (Please indicate all that apply)

a. Pharmacists alone

b. Dual clinician-pharmacist

c. The requesting department /clinician

d. Immunologists

e. The blood bank/transfusion medicine dept

34. In general, what are factors taken into consideration when approving Ig use in your hospital? (Please indicate all that apply)

a. Guidelines (if yes drop down menu for: international EMA guidelines, national, local??.....)

b. Expert opinion/multidisciplinary meetings

c. Your own clinical input

d. Cost/reimbursement to your hospital

e. Contextual circumstances (i.e., whether there is sufficient supply or not)

f. Other

35. Between 2019-2021, did your hospital experience Ig shortages? (By 'shortages,' we mean insufficient supply/stock overall, from brand and/or administration route shortages which restricted prescribing, and there was a need to decline or deny Ig requests as orders are reviewed more than usual)

a. Yes

b. No

c. I don't know

If they answered "yes" at Q35

Did COVID-19 worsen shortages?

a. Yes

b. No

c. I don't know

36. In case of an Ig shortage, what are your own mitigating measures as the clinician? (multiple options possible)

a. Referral to another hospital

b. Switching to a lower dose/increase the time between two doses

c. Substitution with other drugs/products/treatments

d. Delay of Ig treatment

e. Importing products from another country

f. Change of brand

g. Switching to another administration route

h. Other

37. How do you prioritize which patients receive Ig?

a. Use of hospital-based priority protocols

b. Use of national-based priority protocols

c. Use of European-based priority protocols

d. My own clinical judgement

e. Other (specify)

38. Do you expect future shortages?

a. Yes

b. No

c. I don't know

Descriptives

39. Where is your hospital located?

40. What type of hospital do you work in? (DROP DOWN MENU: general, teaching, university, specialty for example cancer, childrens, other)

41. How is Ig paid for in your hospital? (Multiple options possible; perhaps use %s)

a. Health insurance

b. Government

c. Hospital budget, not reimbursed

d. Other

Future involvement

42. Would you be willing to participate in interviews? If yes, please leave your name and email address where we can contact you. This will NOT be linked with your answers.

a. Yes , name and email-address:……

b. No

43. Is there anything else you would like to share? Please write it in the text box.

Thank you message (shown at the end of the survey or when respondent does not consent)

Thank you for your participation.

If you have questions or comments, please contact the EHA Office

S.badreh@ehaweb.org

Appendix IV - Tables from the doctors' survey

Table 3.3.2A – Indications for which Ig is prescribed for (multiple answers could be chosen)

Please specify for which indications you prescribe immunoglobulins.	Italy	Spain	NL	Other	Total (n=193) N (%)*
Replacement therapy in primary immunodeficiency syndromes	55	9	3	10	77 (40)
Replacement therapy in secondary immunodeficiency syndromes	57	8	5	19	89 (46)
Immunomodulation in ITP	66	8	7	21	102 (53)
Immunomodulation in GBS	51	3	5	1	60 (31)
Immumodulation in Kawasaki	31	-	-	1	32 (17)
Immunomodulation in CIDP	38	2	3	3	46 (24)
Immunomodulation in MMN	30	3	2	-	35 (18)

*Percentages are calculated from total number of respondents, n=193

Table 3.3.2B – Main causes for SID (multiple answers could be chosen)

What are the main causes of secondary immunodeficiency?	Italy	Spain	NL	Other	Total (n=89) N (%)*
B-cell depletion therapy, e.g., Rituximab	45	7	3	19	74 (83)
Other immunosuppressive therapy	38	5	-	9	52 (58)
Due to underlying CLL	20	6	4	11	41 (46)
CAR-T cell therapy	18	-	1	3	22 (12)
Due to underlying ML	16	4	2	8	30 (34)
Due to underlying MM	14	5	3	9	31 (35)

**Percentages are calculated from total number of respondents, n=89*

Table 3.3.3 – Proportion of prescriptions outside of EMA guidelines

What proportion of your IVIG prescription is outside the EMA indications?	Italy (n=134)	Spain (n=15)	NL (n=11)	Other (n=23)	Total N (%)
None, all are prescribed according to guidelines	74	8	5	14	101 (55)
Up to 20%	44	4	3	8	59 (33)
21% - 40%	3	1	-	1	5 (3)
41% - 60%	3	1	2	-	6 (3)
More than 60%	10	1	1	-	12 (7)
Total responses	126	15	11	23	183 (100)

Table 3.3.3A – Reasons for prescribing outside guidelines (multiple answers could be chosen)

What are reasons for prescribing outside these indications?	Italy	Spain	NL	Other	Total N (%)
A. New scientific evidence, not yet stated in local, national, or international guidelines	43	2	3	5	53 (56)
B. Lack of information in existing local, national, or international guidelines	15	4	1	7	27 (28)
C. Participation in a clinical trial	3	1	1	-	5 (5)
D. Other[a]	5	2	2	1	10 (11)
Total responses	66	9	7	13	95 (100)

[a] *Includes absence of valid alternatives with class III/IV efficacy; clinical experience; new scientific evidence stated in national or international guidelines; not included in EMA, but in standard of care; several publications about efficacy in inflammatory diseases; 60% of paediatric medication is off-label use because children are rarely involved in clinical trials. We solve this in the NL by publishing our expert consensus on www.kinderformularium.nl*

Table 3.3.3B- Proportion of IVIG prescription outside guidelines

What proportion of your IVIG prescription is outside the EMA indications?	A. New scientific evidence not yet in guidelines	B. Lack of information in existing guidelines	C. Participation in clinical trial	D. Other[a]	Total N (%)
Up to 20%	38	19	2	6	65 (71)
21% - 40%	3	3	0	0	6 (7)
41% - 60%	4	1	1	1	7 (8)
More than 60%	6	3	1	3	13 (14)
Total responses	51	26	4	10	91 (100)

[a]*See note above in Table 3.3.3A*

Table 3.3.4A- Dosage adherence for replacement therapy (multiple answers could be chosen)

How to determine dosages for IVIG as *replacement therapy*	Italy	Spain	NL	Other	Total N (%)
Label/package insert	6	5	-	8	19 (11)
EMA guidelines	46	8	2	14	70 (41)
Local hospital guidelines	12	4	4	5	25 (15)
New scientific evidence not yet in guidelines	6	3	2	4	11 (6)
Expert meetings	4	1	2	5	11 (6)
My clinical expertise	16	1	-	1	22 (13)
Dosages given in similar diseases	2	-	1	24	4 (2)
Participation in clinical trial	3	15	12	2	3 (2)
Other	3	-	1	2	6 (4)
Total responses	98	37	24		171 (100)

Table 3.3.4B- Dosage adherence for immunomodulation (multiple answers could be chosen)

How to determine dosages for IVIG as *immunomodulation*	Italy	Spain	NL	Other	Total N (%)
Label/package insert	14	4	-	10	28 (11)
EMA guidelines	74	7	4	14	99 (39)
Local hospital guidelines	18	4	4	5	31 (12)
New scientific evidence not yet in guidelines	20	3	1	1	25 (10)
Expert meetings	15	3	3	4	25 (10)
My clinical expertise	18	2	1	3	24 (9.5)
Dosages given in similar diseases	7	2	1	-	10 (4)
Participation in clinical trial	4	-	1	-	5 (2)
Other	1	1	2	1	5 (2)
Total responses	171	26	17	38	252 (100)

Table 3.3.5 – Dosing strategies across specialties

Do you adjust Ig dosage to each patient individually?	Always	Sometimes	No	Total (n=168) N (%)
Specialty of respondents				
Neurology	22	17	5	44 (26)
Immunology	10	5	1	16 (9.5)
Haematology	24	16	10	50 (30)
Infectious diseases	2	-	1	3 (2)
Rheumatology	3	-	-	3 (2)
Dermatology	1	-	-	1 (1)
Nephrology	1	-	-	1 (1)
General medicine	3	-	1	4 (2)
Paediatrics (including all sub-specialities)	26	7	4	37 (22)
Other	8	-	1	9 (5)
Total respondents	100 (60)	45 (27)	23 (14)	168 (100)

Table 3.3.6 – Alternative therapies

Do you use alternative therapies before or after trying Ig?	Italy (n=76)	Spain (n=8)	NL (n=8)	Other (n=18)	Total (n=110) N (%)
Yes, before	25	8	5	12	50 (45)
Yes, after	51	-	3	6	60 (55)

Table 3.3.7- COVID-19 impact on usage

Compared to 2019, how did COVID-19 impact Ig usage in your specialty?	Italy		Spain		NL		Other		Total, N (%)	
	2020 (n=121)	2021 (n=119)	2020 (n=13)	2021 (n=13)	2020 (n=8)	2021 (n=8)	2020 (n=22)	2021 (n=22)	2020 (n=164)	2021 (n=162)
Increased usage	19	14	2	2	2	2	5	4	28 (15)	22 (11)
Stayed the same	63	65	4	6	5	5	8	10	80 (42)	86 (45)
Decreased usage	30	30	3	2	-	-	3	2	36 (19)	34 (18)
Unknown	9	10	4	3	1	1	6	6	20 (10)	20 (10)

Table 3.3.8 – Key individuals for off-label approval (multiple answers could be chosen)

Who are the key individuals who approve Ig orders for off-label indications?	Italy	Spain	NL	Other	Totals (n=197) N (%)
Pharmacists alone	16	-	1	2	19 (10)
Dual clinician-pharmacist	65	9	2	5	81 (42)
The requesting department/clinician	37	5	8	17	67 (35)
Immunologists	9	1	1	2	13 (7)
The blood bank/transfusion medicine department	15	1	-	1	17 (9)
Total responses	134	16	12	27	197 (100)

Table 3.3.8A – Factors considered for Ig approval (multiple answers could be chosen)

In general, what are factors taken into consideration when approving Ig use in your hospital?	Italy	Spain	NL	Other	Totals (n=193) N (%)*
Guidelines	101	10	7	18	136 (59)
Expert opinion/multidisciplinary meetings	57	6	7	12	82 (43)
My own clinical input	31	5	5	10	51 (26)
Cost / reimbursement to your hospital	24	5	2	12	43 (22)
Contextual circumstances (i.e., whether there is sufficient supply or not)	32	5	-	9	46 (24)

**Percentages are calculated from total number of respondents, n=193*

Table 3.3.8B- Guidelines used (multiple answers could be chosen)

What are the guidelines that you use?	Italy	Spain	NL	Other	Totals (n=193) N (%)
EMA guidelines	87	9	3	14	113 (59)
National guidelines	54	6	7	9	76 (39)
Local guidelines	12	2	6	3	23 (12)
Other guidelines[a]	4	2	1	1	8 (4)

[a]From scientific societies, ESID, AIEO, AAP, EAP, and guidelines on liver transplantation

**Percentages are calculated from total number of respondents, n=193*

Figure 3.3.9C - Ig shortages in Italy from 2019-2021

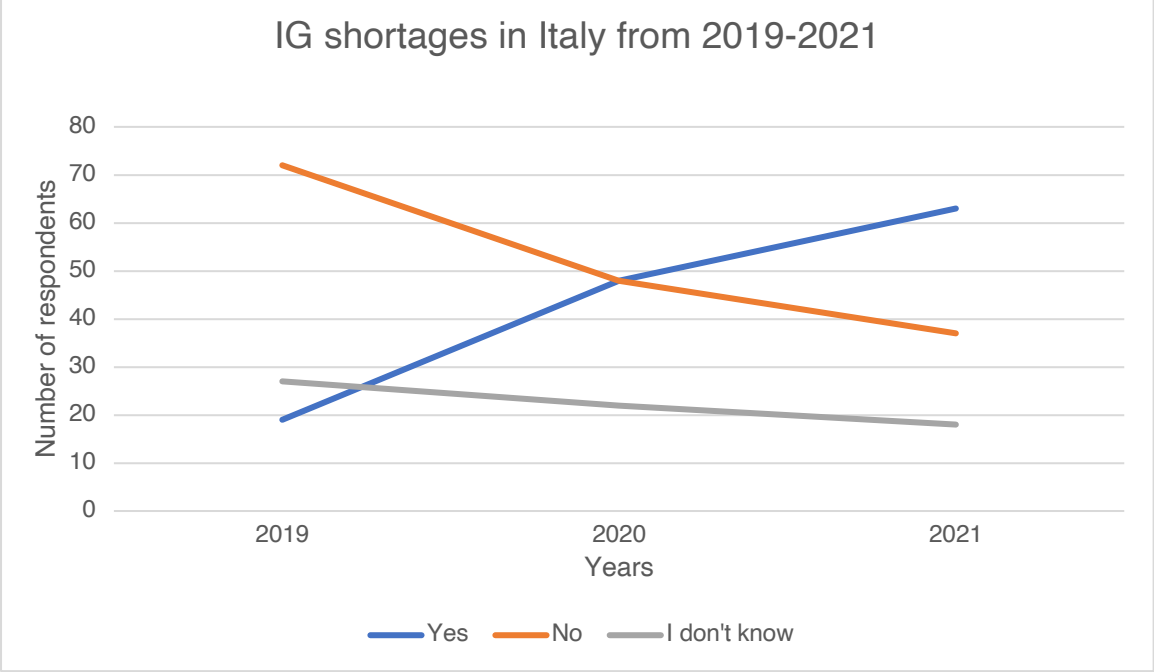

Figure 3.3.9D - Ig shortages in Spain from 2019-2021

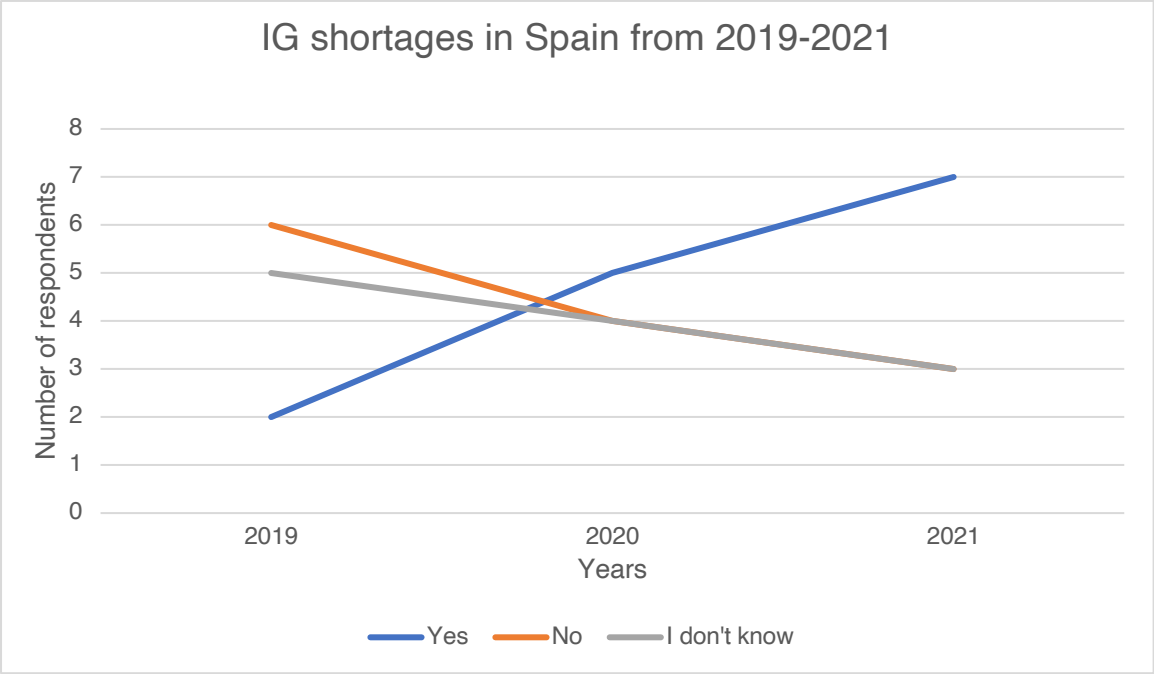

Figure 3.3.9E - Ig shortages in the Netherlands from 2019-2021

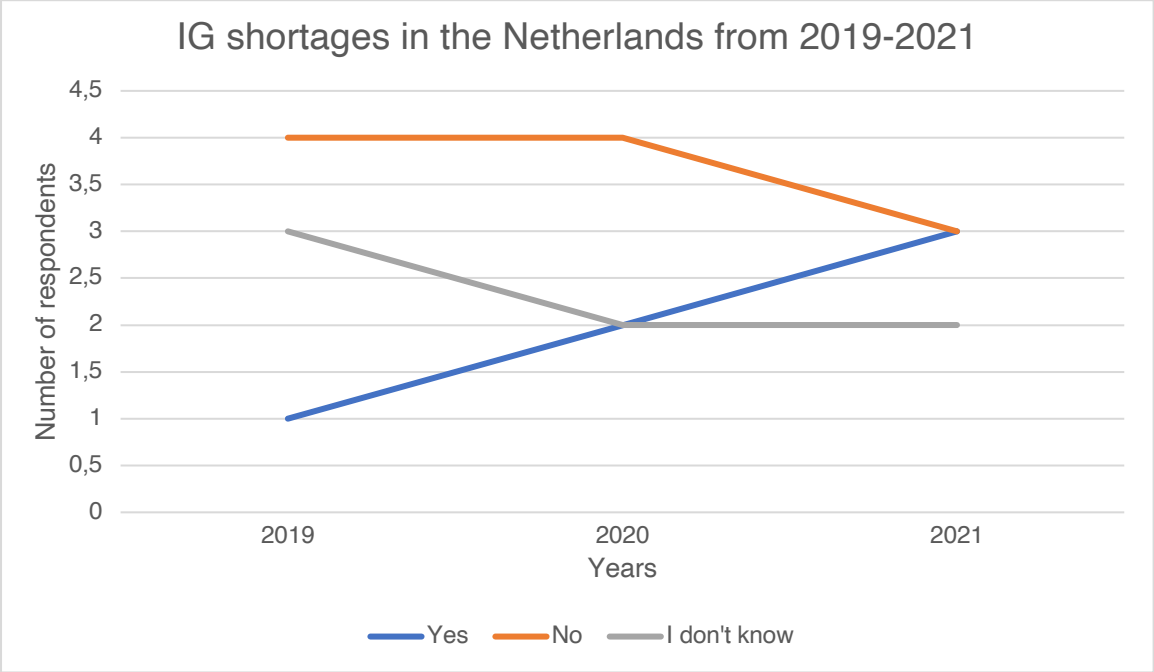

Table 3.3.9C – Prioritization of patients receiving Ig across specialties (multiple answers could be chosen)

How do you prioritise which patients receive Ig?	Neurology	Haematology	Immunology	General medicine	Paediatrics (all specialties)	Infectious diseases	Rheumatology	Dermatology	Nephrology	Other	Total N (%)
Use of hospital-based priority protocols	17	19	5	-	11	1	1	-	1	5	60 (25)
Use of national-based priority protocols	13	19	4	1	20	2	-	1	-	4	64 (27)
Use of European-based priority protocols	7	9	7	2	15	-	-	-	-	3	43 (18)
My clinical judgment	27	15	7	-	12	1	2	-	-	1	65 (28)
Other	-	-	1	1	-	1	-	-	-	1	4 (2)
Total responses	64	62	24	4	58	5	3	1	1	14	236 (100)

Appendix V – Survey question 17

Do you adjust Ig dosage to each patient individually? For those who chose "sometimes" and their reasons why

Neurology	Immunology	Haematology	Paediatrics
Clinical impairment	according to IgG serum levels and infection history	About not right level arrive	Following recommendations given by the hub centre
clinical response	age, comorbidities	according to BMI	In accordance to the weight
Good clinical response	based on clinical efficacy and sometimes on IgG levels (IgG target > 5-6)	after 5-6 months treatment then annually	Based on clinical conditions (e.g., on the basis of neurologist, immunologist advice)
good response: we try to reduce dosage	Enteropathy, bronchiectasis	Asymptomatic patients	Spendono review
If there are clinically problems		it depends on the age of patient	
In case of side effects		Obesity	
in paediatric patients and in the maintenance		Presence of infection justifying i. e. administration every 3 weeks instead of four	
Long efficacy		prophylaxis/treatment of infections	
Persistent clinical stability over time		SEVERE ITP	

Insufficient response to recommended dosage			
previous clinical response		to obtain serum level around 07g/L	
related to clinical follow up		To prevent infections due to low immunoglobulin levels	
TOLERANCE, EFFICACY		weight	
very old people, concomitant renal failure		When the calculated dose is not rounded	
When the patient is in remission and I want to "taper" the therapy		When there is risk of complications, namely, cardiac	
when the patient is not adherent with the treatment			

Appendix VI – Survey question 38

Please clarify why you do or do not expect future shortages

Yes, I expect shortages	**No, I do not**
News from National medicines agency	I don't think there can be any problems with IVIG as the healthcare industries are in the process of having the product.
The problem is always signalled by the pharmacy	I hope there will be an increase in the number of donors and an optimization of the use of immunoglobulins
Because already at the moment there are problems	In my experience the Ig shortage was mainly linked to the pandemic so I expect a return to previous Ig availability in the next future
Increased cost and off-label usage	We haven't received any warning yet.
blood supply has been reduced in general in our country	The COVID-19 emergency will probably end, and it will not be necessary to prefer immunoglobulins to other therapies
PERSISTING LACK OF IVIG	I hope for blood donors
Less blood donations, more IVIG needs, less use of other plasma derivates and no interest for private companies to increment IVIG production	Because of the scientific worth
Decrease blood donation	Because we can expect that clinical indications and number of cases remain the same
Reduction of income; costs	
I hope that in the next future people offer more plasma	
DECLINE IN DONORS	

Increasing number of patients requesting IgG therapy; decreasing availability of blood donors	
I expect future shortages due to increasing use of Ig for immunomodulating treatments and to commercial policies of the national health system and of the Ig producing companies, that might favour Ig availability in other countries rather than in Italy. This is a great concern for patients with PID and SID and partly due to the unawareness of the decision makers.	
Same situation persisting	
Due to increase in patients and decrease in donors	
Expensive	
Economic crisis	
there is a low number of donor	
Because now there is still shortage	
Increased request (worldwide) of Ig therapies, decrease blood donors	
The growing reduction of available donors	
Because clinical picture with low Ig levels will be more and more: consider CART and/or BiTe for lymphoma treatment.	
Demand exceeds supply	
Less people for blood donation and more therapeutic indication	
because I have not heard so far form my pharmacy that the problem of shortage is improving	
More use, less donors	
Our pharmacists expect shortages	

Because of increasing of the requests and the increasing of the use for other indications or off-label use	
Increasing usage for not approved and non-approved indications	
I cannot see how the shortage might end in such a chaotic situation	
paucity of voluntary donors	
Increase of the request of IVIg for newly diagnosed patients,	
High consumption and low production of IVIG in my region	
The reduction of number of blood donors	
Reduced production in Canada	
Reduction of donation	
As population is becoming older, it is increasingly difficult to recruit blood donors	
The global economic crisis	
Pharmacist communication	

Appendix VII – Grey literature country assessments

United Kingdom

I. Introduction: Overview of national Ig consumption

The United Kingdom (UK) is an exception in Western Europe regarding Ig use. For over twenty years, the British government prohibited the use of plasma sourced from the UK to produce immunoglobulins. This measure aimed to minimise the risk of transmitting variant Creutzfeldt-Jakob Disease (vCJD). Consequently, the country relied solely on imported plasma, predominantly from the US. It was not until February 2021 that the restriction on collecting and fractionating UK plasma was finally lifted.[30]

In April 2021, the Government instructed the NHS Blood and Transplant service to resume plasma donation. The objective was for domestically collected plasma to contribute 20% of England's future supply within the next two to three years. This strategy aims to safeguard patients from potential pressures on the international supply of plasma. As a result, the UK is currently collecting a little under 9,500 litres of plasma a month from UK donors.[8]

Regarding Ig consumption, the annual number of patients using Ig therapy in England and Northern Ireland has recently fallen, from a little under 18 000 during the year 2017-2018 to 15 330 during the year 2021-2022.[8] This decrease in the number of patients receiving immunoglobulin therapy is correlated with the decline in recorded Ig volumes used during the same period: from 5.8 million grams in 2017-2018 to almost 5.25 million grams in 2021-2022.[8] Reported to the population, it is a use of 90 grams per 1,000 inhabitants in England and Northern Ireland.

These declining trends are in sharp contrast with the previous recorded numbers in this database. Indeed, anterior to the year 2017, there was a continuous increase both in patient numbers as well as in Ig recorded volumes. This declining pattern could be linked to the supply shortages experienced by the country during the COVID crisis and the significant efforts undertaken to minimise inappropriate use, which will be described next.[26]

II. Guidelines

The UK has put in place detailed guidelines to monitor their Ig use. The most recent version from 2021 are national guidelines with updated commissioning criteria for the use of therapeutic Ig.[19] The indications listed in this guide are summarised by the selection and exclusion criteria, the position of Ig (place of Ig treatment vs. alternative therapies), the recommended dose, the outcome measures to be recorded on the national database, and the potential need of prior approval by a panel of experts.

There are also regional guidelines, such as those from the East of England Immunoglobulin Assessment Panel.[52] However, this guideline does not replace the national version, but instead reflects and adds to it (the chapter of indication classification for example). These panels, composed of experts, review every Ig use in their hospital groups called NHS Trusts, so Ig use is monitored and follows closely the national guidelines.

NHS Trusts, under the governance of the NHS, serve as legal entities responsible for delivering a wide range of healthcare services to patients. These services encompass hospital care, community services, and various aspects of patient well-being. Additionally, NHS Trusts can assume the role of commissioners by subcontracting patient care services when necessary.[85]

NHS refers to the publicly funded healthcare systems operating in the United Kingdom, encompassing NHS England, NHS Scotland, and NHS Wales. All of them are overseen by the NHS, which facilitates various aspects such as data collection, as well as the development and dissemination of national guidelines that are applicable across the entire UK.

III. National Ig management plan

In 2006, the UK Department for Health initiated a "National Demand Management Program" for Ig containing the following three elements:[6]

- The Demand Management Plan, outlining procedures to follow in times of IVIG shortages;
- The National Immunoglobulin Database, providing information for improving consistency in standards of care and to predict future use;
- The Clinical Guidelines for immunoglobulin use.

This programme is a prime example on how to address specific Ig supply issues by providing a clear plan to follow to be ready in case of shortages, such as:

- The establishment of a local Ig assessment panel, in order to monitor Ig use;
- The development of means of communication for patients to raise their awareness about the risk of shortages, the need to control Ig usage, or about the value of considering alternative therapies.

IV. Data collection on Ig use

The National Immunoglobulin Database has been developed under the National Demand Management Program to support long-term planning, and to provide data on the use of Ig.[54] Launched on 2nd June 2008, it provides analysis of Ig usage across England & Northern Ireland. The direct database access is reserved to the NHS

employees, but there are annual reports published and available for the public since 2008.
A substantial amount information and data is available in these reports, for example:

- The volume of recorded Ig and patients on Ig therapy by indication
- The monthly and annual number of patients treated by regime
- The monthly and annual number of patients treated by medical specialty
- The number of patients on Ig therapy by commissioning region
- The recorded volumes of Ig and patients on Ig therapy
- The monthly/annual recorded volume of IV and SC Ig
- The number of long-term patients on Ig therapy with Follow-Ups recorded
- The number of short-term patients on Ig therapy with outcomes recorded
- ITP dosage data 2015 - 2022

However, the data is not linked to a discharge summary which means that the follow-up of patients is difficult. The clinicians are required to enter the outcome measures for their patients in this database, but the percentage of patients with actual outcomes measured or follow-ups is decreasing every year. Indeed, the percentage of long-term patients on Ig therapy with recorded follow-ups has fallen from 78% in 2017-2018 to 51% in 2021-2022.[8]

Because the data collected is very thorough, this national database is also used to aid in commissioning and therapy initiatives for Ig. For example, it is currently used to investigate Ig dosages for Immune Thrombocytopenic Purpura (ITP). Ongoing efforts include evaluating if the doses used are in alignment with guidelines and validating financial reimbursement for Ig usage within Trusts. These efforts have led to a successful decrease in Ig consumption for this indication: from 56% of the patients using 2g/kg and over in 2015, to 19% in 2022. Most of the ITP patients are now on a 1g/kg and under dosage, thus reducing Ig annual demand.[54]

There is a second, more specialised database called the UK Primary Immunodeficiency (UKPID) registry. Set up in 2008, this registry covers 97% of UK PID centres.[86] Data on individual patients, including their diagnosis, treatment, investigations, infections, and complications, are gathered anonymously. The collection of data is ongoing, and entries are regularly updated on an annual basis.[87]

V. National prioritisation plan

In the Commissioning Criteria Policy for the use of therapeutic immunoglobulin guidelines, Ig indications are classed into two categories: routinely commissioned and non-routinely commissioned.[19]

- Indications “routinely commissioned” encompass the prioritised indications (conditions for which there is a risk to life without treatment), the conditions for

which there is a reasonable evidence base for the use of Ig but other treatment options are available, and indications with limited or little/no evidence of the utility of Ig.
- Indications "not routinely commissioned" must follow an extensive approbation process by expert panels.

Routinely commissioned indications are not as clearly hierarchised as in the French colour-coded prioritisation plan. Nevertheless, prioritised indications are sometimes elaborated in clinical guidelines released by the regional Immunoglobulin Assessment Panels. For example, in 2022, the East of England Immunoglobulin Assessment Panel (EOEIAP) clearly classified all of the Ig indications (routinely, not routinely commissioned as well as not recommended for use) into five different classes.[52] The first class regroups the conditions with high risk of mortality or morbidity, and clearly states that Ig are to be reserved for this class in case of shortages. For the other classes, it is simply specified that "use should be reviewed/ modified in times of national shortage", with the notable exception of class 5 indications for which Ig are not recommended for use at all.

VI. Communication methods for shortage awareness

Immunoglobulin providers are informed by communications from the NHS when there are supply shortages. In a letter sent to Ig providers the 10th November 2021 the NHS alerted about the providers about shortages causes by the COVID crisis, gave a list of the impacted products, and provided guidance on switching Ig products for existing patients on long term treatment.[60] From the interviews, respondents spoke about the "allocation system" implemented during the pandemic to avoid stockpiling of Ig products through monthly forecasting; furthermore, hospitals had a coordinated system of mutual aid in case any of them needed additional Ig.

The NHS also provides healthcare structures and patient associations with leaflets warning about Ig shortages and providing information on the scale of the shortage, and the potential repercussions for the patient. The potential switch of specialties was also the subject of a letter of information for patients from the NHS in November 2021.[61]

Spain

I. Introduction: Overview of national Ig consumption

Spain is divided into 17 autonomous communities that are coordinated by the Ministry of Health in Spain through the National Health System Interterritorial Board. These regions have plenty of autonomy with each one of them governing healthcare policy and delivery through their own departments.

Spain achieved close to 43% of Ig self-sufficiency in 2017. National data on usage is difficult to access, but a study evaluated the Ig use as 3.76 million grams in 2017, with a steady increase in consumption since 2012. However, there was a relative stagnation in consumption during the 2019-2020 period (from 4.72 million grams in 2019 to 4.77 million grams in 2020).[73]

In 2019, there was a drop in self-sufficiency to 34%,[51] which highlights a growing dependency to external sources of Ig. The annual Ig growth in consumption is continual, with the Ministry of Health evaluating the 2021 consumption at 5.09 million grams in 2021 and a use of 107.89 gram per 1,000 inhabitants.[28,88]

II. Guidelines

There are Spanish national clinical guidelines for the use of Ig called "Guía Clínica para el Uso de Inmunoglobulinas." [53] It is translated from the UK "Clinical Guidelines for Immunoglobulin Use", 2nd Edition Update,[6] and includes recommendations of Ig use, a list of approved and non-approved indications, and a prioritisation system and specific dosages for each disease listed. However, these guidelines are now outdated since the last version was published in 2011. There are also other national guidelines that are in use, more tailored to specific diseases such as immune thrombocytopenia, developed with the support of the Spanish Society of Haematology and Haemotherapy.[42]

Beside these guidelines, hospitals may have their own protocols on how to provide Ig at a local level. This multiplication of different guidelines creates a problem of harmonisation since different dosages can be recommended to treat the same disease. For example, for PID, the guidelines of La Mancha Centro hospital (2013) advise to use a loading dose between 0.4 and 0.8 g/kg/day and a maintenance dose between 0.2-0.8 g/kg/day every three weeks, whereas the guidelines from the University hospital of Reina Sofía (2010) recommend a loading dose between 0.4 and 0.6 g/kg/day until a through level of 600mg/dL and a maintenance dose between 0.4 and 0.6 g/kg/day every 21 to 28 days, to be adjusted to maintain a minimum Ig through levels superior to 600mg/dL.[39,41] Finally, in the regional protocol written by the Comunidad de Madrid for the rational use of Ig (Protocolo local para el uso racional de inmunoglobulinas en el hospital, the initial treatment 0.4 g/kg/day every 28 days, and in case of bronchiectasis, the dose increases to 0.6 g/kg/day every 28 days. It is stated in these guidelines that a loading dose may be necessary without any more precision.[38]

Interviews conducted with experts from this country have reported that hospital prefers to create their own guidelines for diseases for which there is little evidence linked to Ig use, such as for bone marrow transplants. These guidelines are adapted from their own clinical expertise and experiences and can follow international standards.

However, they are also tailored to the resources available to each region. As a result, Spain has guidelines which (slightly) vary from each other, which could cause a problem of harmonisation and of Ig resources management at the national level.

Regarding the off-label use, a retrospective observational study conducted over a period of six months in 2014 by the Pharmacy Service revealed that 47.1% of Ig were used for off-label indications, out of which 21% were prescribed for indications clearly not recommended or with very weak evidence of use.[89]

III. National Ig management plan

In Spain, the creation of the AEMPS Medicine Supply Guarantee Plan 2019-2022[50] was a strategy aiming to address global medicine supply problems, but it does not directly address Ig supply issues, even if it mentions blood products.

A programme more directly Ig focused is the "Spanish consensus for the sufficiency of plasma and its by-products" (Consenso español por la suficiencia de plasma y sus tratamientos derivados).[51] It is part of the initiative promoted in 2022 by the Spanish Association of Primary Immune Deficiency (AEDIP). This programme is the result of a joint effort by patient organisations, blood donors and scientific societies. It contains recommendations about better Ig management and aims for self-sufficiency of blood products in Spain. It also highlights the fact that:

- Spain does not have adequate planning to meets its future Ig needs and depends too much on external sources;
- There is no shared plan across the country for organising and overseeing treatments made from plasma;
- The ways the different regions work together are limited and not very effective: there are differences in how easily people can get these treatments in each region and the criteria for the use of treatments are not consistent.

By highlighting some deficiencies in Ig use and monitoring, and providing recommendations, this consensus document constitutes a first step toward national Ig management in Spain.

IV. Data collection on Ig use

Since 2012, Catalonia has been employing a specialised database known as the Registry of Treatments and Patients (RPT) to document comprehensive information regarding the indications and utilisation of hospital medications for outpatient purposes. Moreover, the RPT also gathers data on pragmatic evaluations relating to the effectiveness and safety of drugs, such as therapeutic indication, administration route, dates of start of treatment, patients' weight, expected length of treatment and monthly dose (g/Kg), and required follow-up.[55] This is a first step toward national data

gathering and good use of Ig. This useful information is beginning to be documented at a national level in the Spanish Registry of Primary Immunodeficiencies (REDIP) that has just been implemented within the Registry of Rare Disease Patients (REPER) of Instituto de Salud Carlos.[57]

Spain also created in 2005 the National System for Transfusion Safety in order to move towards self-sufficiency of blood and blood derivatives, including plasma and Ig, with data about general Ig use.[56] This system is constituted by the Scientific Committee for Transfusion Safety, the National Hemotherapy Commission, and, where applicable, the regional hemotherapy commissions and transfusion committees. It is fed by the activity records of Blood Transfusion Centres and Services and the Hemovigilance System. It is not directly accessible to the public but annual reports are published.[28]

V. National prioritisation plans

La Guía Clínica para el Uso de Inmunoglobulinas is a 2012 document written by the scientific society “Sociedad Española de Farmacia Hospitalaria” (SEFH). It was based upon the translation into Spanish of the work "Clinical guidelines for Immunoglobulin Use, 2nd Edition 2008", along with the 2nd Edition Update of 2011, published by the UK Department of Health.

Further, the shortage problem due to the COVID-19 pandemic has recently originated two new prioritisation documents, one at a national level led by the Agencia Española del Medicamento (AEMPS) and another at regional level led by the Comunidad de Madrid with the participation and consensus of multiple scientific associations. The AEMPS document ("PRIORIZACIÓN DEL USO DE INMUNOGLOBULINA HUMANA INESPECÍFICA”) is an internal document that is **only** used in times of shortages.[90]

Indications have been classified into three categories:

- Priority: Recommended therapy; high priority due to the life threat posed by the no treatment;
- Selective: Second treatment option: Reasonable evidence base, but available other therapeutic options. Reserved for vital and/or functional emergencies and/or in case of failure of therapeutic alternatives;
- Non-priority: Grey indications: evidence of the efficacy of treatment with immunoglobulin is weak or absent.

The Comunidad de Madrid (CAM) document, updated in 2020, has been elaborated using as a starting point the UK “Clinical guidelines for Ig Use, 2nd Edition 2008", along with the 2nd Edition Update of 2011.

Based on the updated available evidence for each indication, indications have been classified into three colour-coded categories:

- Green: solid evidence of use;
- Blue: weak evidence. A treatment with IVIg should be considered on an individual basis, considering other alternatives, especially in situations of shortage;
- Red: no evidence or not recommended.

These two prioritisation plans are coexisting, so a harmonisation (for example of the colours) between the two would prevent any confusion that could occur.

VI. Communication methods for shortage awareness

The Spanish agency for medicines and health products published semi-annual reports of medicines shortages. They inform Ig handlers about punctual availability problems for non-specific IgG medicines.[62] These reports are criticised for being very general, not tailored to the specific issue of Ig shortages and that their publication frequency does not allow for a quick reaction of the different stakeholders. However, reports of medication shortages are consistently documented and regularly updated on the AEMPS website, rendering it easily accessible to anyone through quick research.[91]

Nevertheless, patients have suffered from the major shortages experienced during the COVID crisis and experienced delays in therapeutic intervention, dose reduction and postponed treatments and even suspensions. A joint communication (Unidos por la suficiencia de plasma) has been made in journals aiming to raise awareness and to stimulate plasma donations from the general public during this period.[63] Medical associations and clinicians are aware of the Ig supply issues, and some initiatives are taken regionally to facilitate communication and coordinate the different hospitals between them, for example in the Catalonia region.

In 2000, the comprehensive public healthcare system called SISCAT was established in Catalonia. This system brought together various healthcare networks under a single public system. Some of the entities within this system are owned by the Department of Health or Catalan Health Services (CatSalut). CatSalut provided information to different SISCAT hospitals regarding the use of IgG, along with several recommendations that could be helpful in case of shortages.

These recommendations included:

- Assessing whether different presentations of IgG can be interchanged;
- Sharing lists of patients with indications that have low supporting evidence;
- Describing strategies for reducing dosage or temporarily discontinuing treatment for immunomodulatory indications when patients are in remission;
- Communicating available alternative treatments as substitutes for IgG.

Germany

I. Introduction: Overview of national Ig consumption

The amount of human plasma collected in Germany each year remains constant at almost 3 million litres. Germany is one of the rare European countries to allow a remuneration for plasma donors, nevertheless the plasma collected is insufficient to meet the patients' needs for Ig. So, in addition to the fractionation plasma collected in Germany, a large amount, on average 6.0 million litres, is imported into Germany. However, an even larger quantity, on average 6.4 million litres, is exported again, so that less fractionation plasma is available in Germany per year than was collected.[27]

The demand for normal Ig continues to rise. In the last decade, annual consumption has more than doubled, increasing from 5,643 kg in 2012 to 13,276 kg in 2021. Standardised by inhabitants, the Ig use is of 159.6 gram per 1,000 inhabitants. However, local manufacturing capacities are insufficient to meet the increased demand but can only be met by importing the finished medicinal products. [27]

II. Guidelines

There are guidelines developed by scientific societies with an analysis of the recent literature. These guidelines are specific to one medical specialty. For example, there are the "Evidence-based Practice guidelines of the German Society for Neurology" written in 2018,[43] for neurological indications, or the "guideline for primary antibody deficiency diseases,"[44] from the Working Group of Scientific Medical Societies.
Moreover, cross-sectional guidelines for therapy with blood components and plasma derivatives are also available from the Executive Board of the German Medical Association dating from 2020. These guidelines include dosages for IVIg and SC/IMIg for approved indications as well as for off-label use in autoimmune diseases, and diseases of unknown organ transplants.[45]

III. National Ig management plan

The German Transfusion Act was put into place in 1998. The aim was to ensure self-sufficiency and a secured collection of blood and blood components, including plasma. Data is collected by the Paul-Ehrlich-Institute which then publish yearly reports on blood and plasma collection, blood components production (including plasma proteins), loss, expiry and market placement, as well as information about importations of blood products.[47] Nevertheless this act focuses on the supply of blood products and the quality control of the blood and blood-derived products produced, and not on the good use of the latter.[48]

IV. Data collection on Ig use

The data from healthcare facilities in Germany, blood and tissue establishments' blood products are collected by the Paul-Ehrlich-Institute. Reports are produced every year, under the name "Bericht des Paul-Ehrlich-Instituts über die nach § 21 Transfusionsgesetz gemeldeten Daten"[27] and a compilation of reports covering the last ten years is also available online.[47]

In these reports, it is possible to find information about:

- Collection of plasma for fractionation (in litres)
- Collection, import, export and processing of plasma for fractionation (in litres)
- Marketing and manufacture of normal Ig (IVIg/IMIg/SCIg) (in K of kg)
- Consumption (and decay) of Ig (in kg)

These reports allow us to have a general idea about Ig consumption and trends in Germany (data cover 100 % of manufacturers and more than 95 % of consuming facilities), but do not allow for a detailed analysis, for example at the specialty level, because the Ig use recorded is neither linked to specific patients, nor hospital discharge data.

The German National Registry of Primary Immunodeficiencies was created in 2009. This registry is affiliated with the European Society for Immunodeficiencies registry. The main objective of the German registry is to collect comprehensive data concerning the epidemiology, diagnostic delays, diagnoses, and treatments related to PIDs.[58] Unlike the annual reports of the Paul-Ehrlich-Institute, this registry allows the gathering of clinical and laboratory data, including data on Ig treatment.

V. National prioritisation plans

Our grey literature search did not find any prioritisation systems in Germany.

VI. Communication methods for shortage awareness

The Federal Institute for Drugs and Medical Devices (BfArM) oversees providing the public with information regarding reported supply shortages.
The reports are made by the pharmaceutical companies to the BfArM and are made available to the public in a database that contains a comprehensive overview of supply bottleneck reports for human medicinal products (excluding vaccines) in Germany.[64]

Italy

I. Introduction: Overview of national Ig consumption

The 2020 report of the Italian National Blood Centre (Centro Nazionale Sangue, CNS) and the AIFA, aims to offer guidance and strategic measures to attain and sustain self-sufficiency in plasma and plasma-derived medicinal products (PDMPs) at both regional

and national levels. It also provides useful insight on general Ig consumption in the country.[29] Since 2020, this report is issued every year, always updated according to trends. The total demand for Ig had a very small increase between 2019 and 2020, from 6.41 million gram to 6.76 million grams. At the population level, the Ig demand is of 113.4g per 1,000 population in 2020.

Considering the usage disparities between IVIg and SC/IMIg, the national demand for SC/IMIg accounted for 24% of the total demand for Ig in 2020.
There are important differences in Ig use between the different Italian regions. For example, SCIg use exhibited notable variations, with the regions of Tuscany, Umbria, Latium, and Liguria recording the highest values ranging from 38 to 56 grams per 1,000 population. Conversely, the regions of Friuli V. Giulia, Autonomous Province of Bolzano, and Sardinia reported the lowest values, amounting to 7 grams per 1,000 population.

After standardisation of these statistics of regional demand for intravenous Ig in 2020, the regions of Aosta Valley, Molise, and Tuscany exhibited the highest demand, with quantities ranging from 149 to 214 grams per 1,000 population. Conversely, the regions of Basilicata and Calabria had lower standardised demand, with recorded volumes ranging from 43 to 49 grams per 1,000 population.

II. Guidelines

In Italy, universal coverage is provided through Italy's National Health Service. However, the organisation and delivery of health services is decentralised. Primary, specialist and hospital care are all managed at a local level with 100 units in 19 regions and two autonomous provinces.[92]

The overall annual consumption of Ig is approximately 110g/1,000 inhabitants, well below the consumption of other developed countries.[17] For some years now, the use of plasma-derived medicines, and in particular Ig, has been examined by Italian scientific societies. The different regions and health units have created various guidelines, for example the Tuscany region guideline on the use of solutions of Ig and human albumin was translated and adapted from the NHS Scotland Clinical guidelines for Immunoglobulin use (2012).[34] However, there are also more specialised guidelines at a national level. For example, for primary immunodeficiency (PID) more than 60 Italian medical centres participate in a national network and registry called IPINet [35] that was created in 2000.

For diseases like CIDP, Italian experts have reported using international guidelines, such as those produced by the European Academy of Neurology and Peripheral Nerve Society.[36] In addition, in 2022, the National Blood Centre and the Italian Medicines

Agency (AIFA) issued a guideline document for the use of Ig in situations of shortage. This document has been distributed to all regional governments and hospitals. These guidelines are in part adapted from the "The National Plan of Management of Shortages of Immunoglobulin Products", elaborated by the Canadian Blood Services and National Advisory Committee on Blood and Blood Products, and are to be updated every year by the National Blood Centre.[17] The different chapters are:

- A list of authorised and reimbursed indications in Italy;
- Some data on national consumption and expenditure of Ig;
- General strategies to tackle shortages of Ig, adapted from the Canadian national Plan of Management of shortages.

III. National Ig management plan

Recently, the Italian Ministry of Health has established a national plasma and plasma-derived medicinal products programme for the 2016-2020 period,[49] along with the national self-sufficiency in blood and blood products programme issued in 2020. This programme establishes the reference principles as well as the strategic objectives to be pursued in this five-year period in order to achieve self-sufficiency.
During this programme, an annual report was published "Demand for plasma-derived medicinal products in Italy."[29] These reports included key information about plasma-derived products, including exhaustive information about Ig such as an overview of the brands available, quantification and characterisation of the demand for IVIg and SCIg during the previous year period, and the relative variations in percentage at national and regional levels.

IV. Data collection on Ig use

The analysis of the demand for plasma-derived medicinal products and recombinant therapies, including the assessment of self-sufficiency levels achieved and the costs sustained by the Italian National Health Service for the provision of these products is available in the public domain. In the "Demand for plasma-derived medicinal products in Italy" report of 2020, data are available about total demand (national and by region) and total standardised demand for Ig for intravenous and subcutaneous/ intramuscular use. Here again, this report allows us to have a general idea about Ig consumption, but does not allow for a detailed analysis, because Ig use data available is neither linked to specific patients, nor hospital discharges. Moreover, during interviews with Italian experts, we understood that it was not possible to use the delivery of Ig as an extraction criteria for a hospital discharge database.

Like the UK, Italy has created a national registry for PID: IPINet.[35] Established in 1999, it precedes the UK Primary Immunodeficiency (UKPID) registry. In 2020, the Italian registry covered 60 PID centres and gathered data from more than 3,300 PID patients. It collects clinical data such as blood examination results, imaging data, treatments,

and infectious episode, which provide valuable insights into the epidemiology, diagnosis, and progression of these disorders.

V. Prioritisation plan

The Italian Medicines Agency has published the “Guidelines on the use of Human Immunoglobulins in Case of Shortages.”[17] These guidelines were adapted in 2022 from the “Canadian Blood Services and National Advisory Committee on Blood and Blood Products” and elaborated during The National Plan of Management of Shortages of Immunoglobulin Products (Interim Guidance. 2020-7-27).
It is not a list of hierarchised indications but describes several inventory levels based on whether they meet the current Ig demands and linked to these supply levels, Ig allocation criteria. The goal is to create a “framework to guide clinical decisions and triage” in case of shortage. There are four inventory levels with corresponding Ig management criteria, based on their availability. The more severe the Ig shortage is, the greater the decrease of Ig use is advised, adapted for each condition.

In addition to these “Inventory phases”, there are criteria to be respected when Ig are prescribed for ensuring an appropriate and priority use of Ig. For some conditions, the criteria for Ig use can become more restrictive depending upon the severity of the shortage.

VI. Communication methods for shortage awareness

Information about medicine shortages and unavailability is accessible on the AIFA website[93] along with several useful other chapters like:

- What to do when a drug is missing, listing the actions needed in case a medicine is missing from the market;
- Import of medicines in case of shortage, giving indications on this complex procedure aimed to clinicians but also to patients.

France

I. Introduction: Overview of national Ig consumption

In France, regional structures for support and vigilance, evaluation, information and scientific expertise called OMEDIT are set up with the Regional Health Agencies (Observatories for Medicines, Medical Devices and Therapeutic Innovations).[59] They evaluate Ig national consumption using data from the hospital medical information system programme (PMSI) as well as the publicly available ambulatory care data (Retroced'AM website). Created by a decree on the 24th of August 2005, OMEDITs are also part of a systematic, organised, and continuous monitoring of proper use of health products.

The hospitalisation data analysed by OMEDIT is divided between different sectors:

- MCO: medicine, surgery, obstetrics
- HAD: hospitalisation at home
- SSR: follow-up and rehabilitation care

The MCO sector alone represents nearly all of Ig consumption in hospitals (almost 99% in 2021).

Over this period, overall Ig consumption increased until 2017 with a relative stabilisation between 2017 and 2020 (from 10,544 kg in 2017 to 10,833 kg in 2020). Nevertheless, during this period, part of the consumption of the hospital sector seems to have shifted to the ambulatory sector. A decrease in consumption was observed for the first time in 2021 (Table Appendix V.1). At the population level, the Ig use in 2021 is of 148.3 grams per 1,000 inhabitants.

Table Appendix V.1: Evolution of Ig consumption in France between 2017 to 2021 (2022 report of the IDF OMEDIT[59])

Year	Consumption (kg)		
	Ambulatory (retrocession)	MCO	Total
2017	2 826	7 718	10 544
2018	3 238	7 087	10 325
2019	3 602	7 030	10 632
2020	4 480	6 353	10 833
2021	4 007	5 922	9 929

These trends (relative stabilisation then decline) could be explained by several factors:

- Accentuation of supply tensions;
- Shift of certain dispensations toward the ambulatory sector (because of the COVID-19 crisis);
- Implementation of the recommendations of the ANSM.

IVIg consumption is heterogenous between the different French regions. In 2021, the Ile-de-France (IDF) region was in 6th place in regional consumption and represented 20% of the national consumption. In France, in 2021, the average Ig use was 85.7 grams/1,000 population, but in IDF, it was 94.8 grams/1,000 population.

II. Guidelines

National recommendations edited by the French Health Products Safety Agency (Agence nationale de sécurité du médicament et des produits de santé; ANSM) in 2018, updated in 2019, which includes prioritisation of indications, but also criteria to refocus their use on public health priorities, such as:

- The clinical and/or biological criteria justifying Ig treatment;
- The minimum effective dosage and/or, if applicable, the available references such as recommendations from the network of reference centres;
- The need for prior validation of the prescription by a specialist opinion or a rare diseases reference network.[31]

An information booklet about PDMPs derived from plasma and associated recombinants (*Les médicaments dérivés du plasma et les recombinants associés*) is updated every two years by the PERMEDES Committee (Platform for Exchange and Research on Blood-derived Medicines and their recombinant analogues). The PERMEDES is a working group of the French Society of Clinical Pharmacy (Société Française de Pharmacie Clinique; SFPC). This document aims to be a reference for the prescription of all plasma-derived drugs and recombinant analogues for all French healthcare professionals. In particular the document details the Ig specialties, their indications, good practices, and the recommended dosages.[94]

More detailed guides exist that cover rare diseases such as the National Diagnostic and Care Protocols (Protocoles nationaux de diagnostic et de soins; PNDS). The objective of a PNDS is to explain the optimal diagnostic and care pathway to the professionals concerned for a patient suffering from a given rare disease. They are developed by the competent centres of reference for rare diseases using a method proposed by the Haute Autorité de Santé (HAS).[33] These protocols provide non-specialist doctors with guidance in prescribing allowing them to benefit from the expertise of centres and specialists in rare diseases for which often there is very little accessible published data.

III. National Ig management plan

France has legislated on the subject of Ig supply as early as 2008 in order to manage Ig supplies and supply tensions (Circular DGS/PP/DHOS/E2/AFSSAPS No. 2008-92, 14 March 2008).[46] The goals of this circular were to establish:

- A regular collection of supply data, provided by the Ig manufacturers;
- A steering committee;
- A system to check the availability of IVIG/SCIg;
- A prioritisation table of IVIG/SCIg prescriptions.

The steering committee, equipped with data from the Ig manufacturers, has the mission to prevent and to manage shortages by:

- the definition of rules allowing a better distribution of IVIG/SCIg within the national territory;
- the evaluation of a minimum threshold of emergency stock in the internal use pharmacies;
- the need to establish a list of referrals contact points (a doctor and a pharmacist) in hospitals to support the steering committee;
- the definition of a shortage alert threshold (on a regional or national basis), which would allow for the immediate implementation of the necessary changes and adaptations of prescribing methods.

IV. Data collection on Ig use

French data were accessible from two main sources. First, by screening the OMEDIT websites, we accessed several surveys developed to evaluate French Ig use. OMEDIT consists of regional structures for support and vigilance, evaluation, information and scientific expertise set up in each French region in 2005. OMEDIT carry out a systematic, organised, and continuous monitoring of proper use of health products. For this purpose, OMEDIT had conducted various surveys on the consumption of health products and made an analysis of the collected data.

The following surveys are available on their website:

- Purchase and consumption of medicines in hospital (ATIH) survey (Enquête Achat et consommation de médicaments à l'hôpital) conducted in 2019;
- The regional Ig hospital pharmacists (PUI) survey, conducted for the "Ile-de-France" region in 2018 and 2022. The Ile-de-France region accounts for roughly 20% of national Ig consumption;
- The regional Ig PUI survey, had also been conducted among hospital pharmacists for the "Hauts de France" region in 2019;
- The National Ig PUI Survey, conducted in 2020. This survey covers seven regions and two overseas departments and regions of France (DROM), representing two-thirds of the national consumption of Ig. It is a retrospective survey conducted from October 2019 to October 2020;
- The national "buyers" survey, conducted in 2020. There were 11 participating regions representing 77% of total intra-hospital Ig consumption and 18 purchasing groupings allowing for an analysis of the hospital Ig market in France.

For this study, we also have access to a French national database: the SNDS (National Health Data System). This will be detailed more fully in the case study chapter. For SUPPLY, we will extract aggregated patient resource use data associated with the

delivery of Ig, retrospectively, and linked to ICD-10 discharge diagnoses, over seven years. These data will be used to assess the use of Ig in France, to establish a European strategy for better use of Ig (stock management, prioritisation of indications, better use of available resources).

V. National prioritisation plan

The indications are prioritised by the French National recommendations edited by the ANSM in 2018, updated in 2019 (Prioritisation of indications).[31] The indications are classified into three categories:

- Red: Indications considered a priority in case of shortage;
- Blue: Indication for which Ig use is to be reserved for vital and/or functional emergencies and/or functional emergencies and/or in case of failure of therapeutic alternatives;
- Black: Indications not considered a priority in case of shortage.

Not all the indications listed in the ANSM prioritisations document are included in the MA; Ig have a MA for a more restricted set of diseases, but their use is accepted in a wider variety of indications. Indications for Ig are prioritised by considering:

- clinical and/or biological criteria justifying treatment with Ig;
- the minimum effective dosage and, if applicable, the available guidelines and recommendations;
- the need for prior validation of the prescription by a specialist opinion.

VII. Data collection on Ig use

The OMEDITs are information points on supply tensions in times of health crisis, such as during the COVID crisis.[66] In the context of the COVID-19 pandemic, the IdF OMEDIT had reported that there were alarm points which may have aggravated the already delicate context of Ig supply, by increasing the consumption of SCIg. These alarms points were:

- The transfer of the use of IVIg to SCIg, particularly in the context of home treatment of certain patients to limit their trips to the hospital. Thus, the OMEDIT had advised that the postponement had to be reserved for cases where the use of the IV route was not possible and on justified medical indication (e.g., an impaired access route).
- The movement of several confined patients far from their main residence. To face the increase of Ig consumption following the lockdown in some areas, the OMEDIT had demanded an additional supply of certain PUIs to be administered in ambulatory care, with the aim of limiting as much as possible the arrival of patients and their families in hospitals.
- The shortages experienced at the beginning of the COVID crisis were likely to be aggravated in the upcoming months, due to the impact of the pandemic on the blood and plasma collection.

To improve the sharing of information between healthcare professionals and to optimise patient care (e.g., avoiding delays in treatment for patients with priority indications), a patient recto-verso card has been developed by a collaborative group including members of the IDF OMEDIT. This card is offered to the patients receiving an Ig treatment.[32] It is presented in a triptych format, to be printed and completed. For optimal use of the card OMEDIT recommends that hospital pharmacists fill in the contact details before distributing it to Ig prescribers in their establishment. The hospital doctors should then distribute them to each patient treated with Ig after having completed the sections "My immunoglobulin treatment history", "Personal information" and "Prescribing hospital/Doctor". Patients are then advised to present it to each professional involved in their disease management by Ig. Nevertheless, it does not provide patients with information about potential Ig shortages.

The elaboration of cards and booklets providing information in case of shortages and optimising the sharing of information between healthcare professionals is a desirable and easily reachable goal for all EU countries to facilitate the continuity of patient care in normal situations and in case of Ig shortages.

Healthcare professionals can also be informed in real time about Ig shortages on the ANSM website. Pharmaceutical laboratories notify the ANSM of any risk of stock-outs or actual stock-outs, and a list of all drugs of major therapeutic interest currently experiencing supply difficulties is published and regularly updated.[67]

Other countries: Belgium

I. Indications

As stated in the 327th Report of the Belgian Health Care Knowledge Centre (KCE), in 2019, Belgium recognised only eight diseases giving rise to a reimbursement of Ig:[95]

1. PID:
   a) congenital defects in the production of antibodies resulting in low titres
   b) congenital Specific Polysaccharide Antibody Deficiency
   + recurrent clinically significant infections for which antibiotics were indicated
2. Secondary hypogammaglobulinemia due to
   a) B cell malignancy (cancer) such as Multiple Myeloma or Chronic lymphocytic leukaemia
   b) iatrogenic B cell deficiencies due to chemotherapy, or monoclonal antibodies
   c) allogenic or autologous hematopoietic stem cell transplantation
   + recurrent clinically significant infections for which antibiotics were indicated

3. Idiopathic thrombocytopenic purpura + serious bleeding or risk of bleeding
4. Kawasaki disease
5. Syndrome Guillain Barre or variants + progressive muscle weakness/symptomatology
6. Invasive streptococcal group A infection (streptococcal toxic shock syndrome) + when failing of other therapeutic options
7. MMN + distortion daily functioning
8. CIDP + distortion daily functioning + contra-indication or ineffectiveness of oral corticoid treatment

Exceptions are possible via special programmes in which a commission decides on possible reimbursement for individual cases (the following criteria must be met to be eligible: rare disease, threatening vital functions, no therapeutic alternative, and scientific effectiveness/value), but Belgium is one the European countries with the least authorised indication for Ig therapy.

II. Data collection on Ig use

At the time of the report in 2019, there is no national data collection specifically capturing the use of Ig for specific indications, whether they are reimbursed or used off-label. A Belgian study published in 2011 indicated that off-label use accounted for approximately 46% of all patients treated with IVIg in 2007, based on an analysis by IMS Health of a nationally representative sample of 47 Belgian hospitals.[96] However, the authors noted that this estimate may have been overestimated. Off-label use was observed in various fields such as unspecified conditions, surgery, orthopaedics, and oncology, while the use in Myasthenia Gravis was limited.

Given the high costs associated with Ig therapy, the Monitoring of Reimbursement Significant Expenses (MORSE) report, conducted by the National Institute for Health and Disability Insurance, regularly monitors the financial impact on the national insurance budget, but only for reimbursed products. The MORSE report serves the following purposes:

- Comments on the observed developments in the main drug classes.
- Assesses the financial impact of government measures.
- Attempts to make predictions for future expenditures.[97]

In Belgium, monitoring of Ig use is conducted through a monthly follow-up of the tender procedure, which covers approximately 50% of the reimbursed market for IVIg. In response to supply issues experienced since 2018, the three companies that sell Ig in the Belgian market were requested to provide sales data to the Federal Agency for Medicines and Health Products (FAGG) to facilitate monitoring. However, the current systems do not capture information on specific indications for Ig use.[95]

III. Recommendations

The FAGG provides recommendations for hospital pharmacists and specialist physicians within the hospitals: [98]

- Switch to SCIg when clinically possible;
- Prescribe rationally and only within the reimbursable indications. It is important to limit improper or off-label use as much as possible;
- No unnecessary stockpiling.

In addition to these recommendations, reimbursement criteria were harmonised (for some IVIg products) allowing a greater flexibility among the different brands for the eight defined reimbursed indications.

Denmark

I. Guidelines

The Medicines Council is an independent council established by the Danish regions in 2017. It aims to ensure fast adoption of new medicines, proven effectiveness, consistent use across hospitals and regions, and stringent requirements for documenting effectiveness by developing treatment guidelines for medicines used in the hospital sector. These guidelines provide assessments of which medications are the most appropriate for treating patients within a therapeutic area.
For example, guidelines for CIDP by the Medicines Council serve as the basis for the Medicines Council's drug recommendation to the regions for this disease.[99,100]

II. Data collection on Ig use

Denmark has a highly advanced and comprehensive data collection system. Various health data is recorded during visits to general practitioners (GPs), hospitals, medical specialists, pharmacy purchases, and receipt of healthcare services in municipalities. These data are systematically collected and stored in national health registers. These health registers contain a wide range of information, including diseases, treatments, financial aspects, and healthcare system employees. Each register serves a specific purpose, such as monitoring disease trends or evaluating treatment effectiveness.
The Danish Health Data Authority is responsible for maintaining these national health registers, which encompass data concerning the health of the entire Danish population and healthcare services. By using the data from the national health registers, the Danish Health Data Authority regularly publishes analyses and reports on the health of the population and the functioning of the Danish healthcare system.[101]

One notable register is the National Patient Register (NPR), established in 1977, which stores information on all examinations (in and outpatients) and treatments conducted

in Danish hospitals over the past 40 years. The private sector was mandated to communicate its data in 2003. The NPR initially served as a monitoring tool for hospital activities. However, starting from 2000, it has also become the foundation for both public and private hospitals' payment system, specifically through the Diagnostic Related Group (DRG) system.

The data recorded in the NPR can be classified into two categories: administrative data and clinical data. The administrative data includes patient identification and municipality, hospital ward identification, date and time of activity, and information regarding accidents leading to hospital contact. On the other hand, the clinical data comprises diagnoses (using ICD-10 codes) and surgical procedures.
While the NPR serves as a valuable tool for clinical purposes and is an important resource for epidemiological studies, it is a complex register that requires careful consideration of various potential errors to ensure accurate retrieval of the register data.[102]

Netherlands

I. Introductions

In the Netherlands, IVIG medication falls under the so-called “expensive medication” category and are therefore earmarked in the hospital’s database. This can be extracted by patient name, date, indication and diagnosis, and therefore very time consuming. The National Health Authority decides which medications fall under this “expensive medication” category. However, SCIg does **not** fall under this category, which means that the definition is not only about the costs, but other points are taken into account. When searching for medication names, these SCIg prescriptions can also be found in the hospital database.

Furthermore, outpatient prescriptions go through another desk called the “politheek”, who collects information on home prescriptions. It depends on the type of hospital how this is organised. In general, academic hospitals are organised in a holding, in which there is one database, whereas other hospitals may have collaborations with the regional pharmacies, which make data collection slightly more difficult.

I. Guidelines

The Dutch transfusion guidelines, also known as CBO guidelines, are evidence-based recommendations and protocols developed by the Dutch Institute for Healthcare Improvement (CBO) that govern blood transfusion practices in the Netherlands. These national guidelines provide healthcare professionals with guidance and best practices to ensure safe and effective blood transfusions. They encompass various aspects, such as indications for transfusion, appropriate selection of blood products, dosages, monitoring, and management of transfusion reactions. The CBO guidelines aim to

promote standardised and high-quality transfusion practices across healthcare institutions throughout the Netherlands.[103]

II. National Ig management plan

In the Netherlands, an initiative to change the way Ig are prescribed was proposed in 2021. Called the "*overheveling*" or "Transfer Act," it was proposed by the Ministry of Health in 2017 to reduce the demand for Ig by restricting its prescription and distribution exclusively to hospitals. In doing so, it aimed to eliminate distribution from local pharmacies, which provided reimbursement regardless of the indication, and, instead, patients and their treatment costs would be transferred to the hospital budget.[5] [104] However, this Transfer Act was postponed due to COVID-19.

III. Data collection on Ig use

There is no overarching national database where granular data can be found regarding the IG usage in relation to dosage, indication and diagnosis. Data on immunoglobulin use, by diagnosis, are findable, however, incomplete and time consuming and requires a search in different resources/databases. Diagnosis registrations are reported in an open database of the National Health Authority:
DIS open data (opendisdata.nl). However, some diseases are being categorised under one name, for example “neuromuscular diseases,” and therefore not named separately for indications such as MMN and CIDP, possibly due to its rare prevalence and therefore categorised under one ICD code (similar to France).

Most Ig are reimbursed by the health insurance companies, called *Stichting Farmaceutische Kengetallen (SFK)* and *Zorgverzekeraars Nederland (ZN)*. Some off-label medication will still be reimbursed when there is an agreement on those specific indications. Therefore, Ig information can be obtained for these indications on these websites. For those non-reimbursable indications, it comes out of the hospital budget. Therefore, this is not publicly accessible because it stays in the hospital records.[105]

Appendix VIII - Context of the French case study

Background

To understand the full picture of Ig use in Europe in terms of indications, volumes, dosages, off-label and on-label use, and time trends, exhaustive national data at a patient level is required. Assuming that the patient management systems in Europe are fully digitalised, not all EU countries systematically collect this data centrally/nationally or even at a geo-administrative level and the information remains lying in the hospital IT systems (be they public or private) or the ambulatory systems such as GP surgeries or specialists acting outside of the hospital setting.

If databases with the relevant information are available in each country, gaining access may be a problem in terms of developing search algorithms and data extraction programmes to extract the Ig use. In addition, there are strict data protection laws restricting access to personal medical data making this task difficult and cumbersome.

Using Ig dispensation as the method to identify patients is preferable in comparison to searching a database or registry on every possible diagnosis or indication for this product to identify patients prescribed Ig. This not possible in all EU countries but should be possible in France. Ideally, we need both inpatient, outpatient and ambulatory use of IG, but this will depend on country specific health systems and IT systems used.

Health care consumption databases

Every quarter, a systematic collection of administrative and standardised medical information from all public and private hospital information systems in acute care - medicine, surgery, obstetrics and odontology (MCO; *médecine, chirurgie, obstétrique et odo ntologie*) is carried out. This data collection is called the Medicalised information system program (PMSI; *Programme National de Médicalisation des Systèmes d'Information*).[106,107] The data transmitted every three months is the cumulation of all data from the 1st January of the current financial year. This collection has been mandatory for all French and French overseas territories' private and public hospitals since 1996 for acute care and has since been expanded for psychiatric care and the rehabilitation sector. The hospital activity data collected concerns hospitalisations with or without overnight stays (RSA files containing the DRG[108] tariffication information and other activity data relating to pregnancy terminations), ambulatory activity (other medical acts as part of external consultations) and emergency room activity. The French hospital data (PMSI) uses the ICD-10 codes for diagnostics.

Information Box 1
Production of anonymous discharge summary files in French hospitals

A medical unit summary (RUM; résumé d'unité médicale) is produced at the end of each patient's stay in a medical service/unit/ward providing MCO care, regardless of the mode of discharge from this unit. The RUM contains a limited amount of administrative and medical information, which must be systematically completed and coded according to standardized nomenclatures and classifications, in order to benefit from automated processing.
Digital standardized discharge summaries (RSS; résumés de sortie standardisés) are created from the RUMs and controlled by the doctors responsible for medical information systems within the hospital. Thus, the RSS contains all the RUMs relating to the same hospital stay of a patient in the MCO sector and includes as many RUMs as the patient has attended medical units during this stay. For example, a patient treated in intensive care and then transferred to a ward would have at least two RUMs that are then summarised into one RSS. All hospital stays in the field of MCO lead to this digital standardised discharge summary (RSS: résumé de sortie standardisé) that contains administrative, demographic, medical and treatment information about the patient stay.
Following the creation of the RSS, an anonymous exit summary (RSA) that is the result of pseudonymization is created by removing directly patient-identifying information. This operation to generate an RSA is carried out by the Genrsa software developed by the Hospital Information Technology Agency (ATIH; Agence technique de l'information sur l'hospitalisation).

Hospital admission – administration of Ig with or without overnight stays is recorded in the PMSI database. Use of healthcare that is not carried out within hospitals is managed in different systems attached to multiple Social Health Insurance schemes that are merged into a single national database (DCIR ; *données individuelles des bénéficiaires*) with individual beneficiary data on healthcare consumption that is part of the national health Insurance Information System (SNIRRAM; *Système National d'Information Inter Régimes de l'Assurance Maladie*).

Ig can be distributed by a hospital pharmacy to ambulatory patients to be administered outside of the hospital – these prescriptions are commonly known in France as *retrocession*. These products present particular constraints of distribution, dispensation or administration, have requirements related to security of supply or

require monitoring of the prescription or dispensing of the product. According to the Public Health Code (Article R 5126 -102), hospital retrocession is "the dispensing by a hospital pharmacy (PUI; *pharmacie à usage intérieur*) for use of drugs not available in a retail pharmacy to patients who are not hospitalised".
The French hospital and ambulatory data are deposited in the National Health Data System (SNDS; *Système National des Données de Santé*, https://www.snds.gouv.fr/SNDS). The SNDS, a merger of a number of databases, is managed by the National Health Insurance Fund (CNAM; *Caisse Nationale de l'Assurance Maladie*). The SNDS enables linkage between the SNIIRAM database, the PMSI database and national mortality data from the Epidemiological Centre for Mortality by Medical Causes (CépiDC; *Centre d'épidémiologie sur les causes médicales de Décès*).

Information Box 2
Medicines on the French retrocession list

The drugs on this list have particular distribution, dispensing or administration constraints or require monitoring of the prescription or dispensing. This list includes drugs derived from blood, antiretrovirals, drugs for chronic hepatitis B or C, certain antibiotics, antifungals, orphan drugs, and anticancer drugs.
These medicinal products must meet the following conditions:
- *be intended for non-hospitalised patients,*
- *not be reserved for hospital use,*
- *present particular constraints of distribution, dispensation or administration,*
- *have requirements related to security of supply,*
- *require monitoring of the prescription or dispensing.*

The SNDS is possibly unique in Europe, as a national, comprehensive, consolidated, and exhaustive claims database which collects and makes available pseudonymised health information collected by public bodies. The SNDS is constantly being developed to include other sources of French health data. SNDS data are kept for a period of nineteen years and after this period, these data are archived for a period of ten years.

Accessing health care consumption databases in France

Since the SNDS is mainly made up of personal health data, access is strictly supervised in order to protect the fundamental rights and freedoms of individuals and any data processing is subject to the provisions of the French Data Protection Act, the European Data Protection Regulation (as of May 25, 2018) and the French public health code. The French national agency regulating data protection (CNIL; *Commission Nationale de l'Informatique et des Libertés*) is responsible for monitoring the application of these texts: https://www.cnil.fr/en/home.

Certain organisations with a public service mission, listed by decree, have permanent access to SNDS data. Each of these state departments, public establishments, or bodies responsible for a public service mission with permanent access to SNDS data is required to keep up to date in standardised documents the following information:

- Transparency of permanent access and their uses,
- The list of individual SNDS data processing and its characteristics,
- The list of persons authorised within it to access SNDS data and the authorisation procedures put in place – the authorisation for an individual to access SNDS can only be given for personnel of these organisations with permanent access who have successfully completed specific SNIIRAM/SNDS training courses.

Also of note is open access to certain aggregated data, statistics and reports that are made available by the CNAM (https://assurance-maladie.ameli.fr/etudes-et-donnees).

Appendix IX – OMEDIT surveys

I. Purchase and consumption 2019
   A. This is an annual retrospective survey of all public and private sector health facilities, including hospitals of the armed forces health service
   B. Link: https://www.atih.sante.fr/enquete-achat-et-consommation-de-medicaments-l-hopital-2020-0 (in French)

II. Restitution Ig PUI Survey in Ile-de-France, survey of hospital pharmacists
   A. The regional Ig PUI survey has been conducted among hospital pharmacists for the Ile-de-France region
   B. Link: https://www.omedit-idf.fr/wp-content/uploads/2019/08/Rapport-IGHN-2018VF.doc.pdf (in French)

III. Restitution of Ig PUI Survey in Ile-de-France, survey of hospital pharmacists, October 2022
   A. Assessment of consumption in health care institutions in Ile-de-France and positioning in relation to national data
   B. Link: https://www.omedit-idf.fr/wp-content/uploads/Synthese-donnees-quantitatives_12octobre-2022.pdf (in French)

IV. Restitution Ig PUI Survey: Hauts de France Regional Data, 2020
   A. Following the increase in supply tensions (TA) on immunoglobulins, particularly subcutaneous, a retrospective survey was conducted from October 2019 to October 2020
   B. Link: http://www.omedit-hdf.arshdf.fr/wp-content/uploads/2021/05/Enquete-Ig-PUI_25.03.21-point-Regional-HDF-et-resultats-nationaux.pdf (in French)

V. Restitution Ig PUI Survey: National Data - Survey of hospital pharmacists, 2020
   A. Seven regions and two DROM representing two-thirds of the national consumption of IgHN have relayed the survey to the most consuming ones. It is a retrospective survey that was conducted from October 2019 to October 2020
   B. Link: https://www.omedit-idf.fr/wp-content/uploads/Enquete-nationale-IgHN-PUI-Synthese-RESOMEDIT-2021.pdf (in French)