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ORIGINAL RESEARCH ARTICLE

Direct and Indirect Costs of Immunoglobulin Replacement Therapy in Patients with Common Variable Immunodeficiency (CVID) and X-Linked Agammaglobulinemia (XLA) in Italy

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Abstract

Background In Italy, there is scarce evidence on the epidemiological and economic burden induced by primary antibody deficiencies.

Objective The aim of this study was to elaborate the available epidemiological and cost data in order to estimate the annual expenditure induced by the management of patients affected by the common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA) requiring immunoglobulin (Ig) replacement therapy.

Methods A probabilistic cost-of-illness model was developed to estimate the number of patients with CVID and XLA, and the economic burden associated with their therapy in terms of direct or indirect costs. A systematic literature review was carried out to reveal both epidemiological and economic data. Furthermore, a probabilistic sensitivity analysis with 5000 Monte Carlo simulations was performed.

Results The epidemiological model allowed us to estimate the number of prevalent patients affected by XLA and CVID in Italy in 2017, corresponding to 1885 (95% confidence interval [CI] 944–3145) and 133 (95% CI 115–152) patients, respectively. The estimated total expenditure for the treatment and management of patients with CVID and XLA requiring Ig replacement therapy amounts to €42.68 million (95% CI €14.38–€86.1 million).

Conclusions This information provides a comprehensive perspective of the economic issues, and facilitates better-informed public health decision making, in the management of CVID and XLA in Italy.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40261-018-0688-3) contains supplementary material, which is available to authorized users.

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Key Points

In 2017, the number of patients with CVID and XLA in Italy was 1885 and 133, respectively.

Direct costs were estimated at €41.22 million, with 94% being attributable to CVID (€38.7 million).

Indirect costs accounted for €1.5 million, representing 3.4% of total spending.

1 Introduction

Immunoglobulin (Ig) replacement therapy is the foremost treatment of primary immunodeficiency disorders (PIDs) with an antibody deficiency, a rare group of disorders representing failure of the immune system to produce sufficient antibodies in the bloodstream to combat infections [1].

Two major antibody deficiencies requiring Ig replacement therapy are the common variable immunodeficiency (CVID) and the X-linked agammaglobulinemia (XLA) [2]. For these conditions, Ig replacement therapy is effective in avoiding infections, as well as adverse effects induced by repeated infectious events. Consequently, Ig replacement can significantly improve survival rates and patients' quality of life [3]. Furthermore, different studies show that effective therapy can significantly reduce absenteeism from work or school due to illness [3].

In Ig replacement therapy, a recommended dose range of between 400 and 600 mg/kg body weight per month is commonly administered either intravenously (IVIG) every 3 or 4 weeks, or subcutaneously (SCIG) every 1 or 2 weeks [4, 5]. Several studies have pointed out the administration of SCIG in a home setting is associated with an improvement of patients' quality of life [6–8] when compared with IVIG administered in hospital. Additionally, intravenous administration can induce the onset of systemic adverse events during or after the infusion [9]. In comparison with IVIG, subcutaneous administration induces mild adverse effects that occur at the local level [10].

In Italy, evidence on the epidemiological and economic burden induced by primary antibody deficiencies is scarce. From an economic perspective, in 2008 Matucci et al. [11] published a cost minimization analysis that provided a thorough estimate of the mean cost per patient with CVID and treated with either IVIG or SCIG. As a result, the less costly alternative was SCIG (€15,192 per patient), corresponding to a 12.7% lower cost than the alternative IVIG (€17,409 per patient). This was mainly due to higher consumption of resources (medical, nursing and ambulatory) associated with intravenous administration.

From an epidemiological point of view, the prevalence of PIDs in Italy is, on average, the same as other European countries [12]. In May 2014, 1120 Italian patients with PIDs were recorded in the Italian Primary Immunodeficiencies Network (IPINET) and Italian Association of Pediatric Hematology Oncology (AIEOP) registries. However, this is not an accurate reflection of the total number of Italians affected by PIDs as not all patients with PIDs are included in the current registers, especially those with primitive immunodeficiencies affecting the adult population, such as CVID [2, 9].

The development of new technologies that improve diagnostic and treatment accuracy for people with rare diseases is increasing. However, to ensure the best quality of evidence-based care and treatment is offered to patients, the collection of reliable health data is compulsory. Although they seem to be associated with a considerable economic burden [13], cost-of-illness information on rare diseases is very limited, especially in Italy [14]. This kind of information is of primary importance for public health decision makers to provide proper healthcare services, to establish whether a new technology deserves to be introduced, and, finally, to allocate adequate funds. With a cost-of-illness procedure, a systematic evaluation of economic consequences of a given disease in the health system is performed.

The objective of this study was to estimate the annual economic burden related to the management of patients requiring Ig replacement therapy (specifically patients affected by CVID and XLA) from a societal perspective (i.e. direct and indirect healthcare costs).

2 Methods

2.1 Design of the Study

In order to estimate the annual costs associated with patients with PIDs requiring Ig replacement therapy, a probabilistic cost-of-illness model capable of estimating the number and distribution of patients with CVID and XLA was developed. According to the purpose of the study, direct and indirect costs were estimated. To assess direct medical costs, the model was informed by data obtained from a systematic literature review. A 'bottoms-up' approach was implemented [15–17], multiplying the average cost per patient by the disease prevalence to estimate direct costs associated with the patient's management. The average direct medical cost of administration of Ig (both IVIG and SCIG) was quantified according to the different management practices used in the two diseases considered. Indirect costs were assessed using the human capital approach on the basis of data provided by the Italian Association for Primary Immunodeficiency (AIP). This method appraises costs in terms of loss

of productivity, taking into account the expected future earnings lost due to the disease [15–17].

2.2 Systematic Literature Review

A systematic literature review was carried out to identify the main parameters required to model the natural history of the diseases, looking at epidemiological and/or economic evaluation studies regarding CVID, XLA and Ig replacement therapy in Italy.

The systematic literature review was conducted using the following scientific electronic databases: MEDLINE (PubMed), Cochrane Library, Health Technology Assessment on the Net, ClinicalTrials.gov, European Medicines Agency (EMA), Italian Medicines Agency (AIFA), Italian National Agency for Regional Health Services (Age.Na.S), Italian National Institute of Statistics (ISTAT), Italian National Institute of Health (EpiCentro, the epidemiological website dedicated to public health), ResearchGate, and national and international associations of physicians and patients (European Society for Immunodeficiencies [ESID], Associazione Italiana di Ematologia e Oncologia Pediatrica [AIEOP], and AIP). Moreover, the following Italian health economics journals were examined: PharmacoEconomics Italian Research Article (Springer), Farmeconomia e Percorsi Terapeutici (JournalSeek), Global and Regional Health Technology Assessment (Wichtig), and Quaderni dell'Italian Journal of Public Health. Peer-reviewed journals, conferences, congresses and other available internet sources were monitored to June 2017 for presentations or communications providing further information.

Our research focused on papers published between 2007 and 2017 in Italian or English. The research was organized in two main topics: the epidemiological issues concerning XLA and CVID, and the economic aspects related to the costs incurred by the National Health Service (NHS), as well as society.

The systematic literature review process was organized in four steps: identification, screening, eligibility and inclusion (consistent with the recommended guidelines for systematic analysis of scientific literature [18, 19]. The keywords used for the scientific literature search were primary immunodeficiency, primary antibody deficiencies, common variable immunodeficiency, CVID, agammaglobulinemia, XLA, cost of illness, cost–benefit analysis, health technology assessment (HTA), cost-effectiveness analysis, cost-utility analysis, economic evaluation, epidemiology, and prevalence (see the Electronic Supplementary Material for details).

For study inclusion, two researchers independently reviewed the studies, looking at the title, abstract or full text. Results were compared and any disagreement and risk of bias was resolved through discussion between the authors. The differences were discussed and settled through analyses and consultation with other experts. All studies used to determine the epidemiological and economic parameters were required to meet at least one of the following inclusion criteria:

1. Refer to epidemiological data (with particular attention to the prevalence and distribution of treated patients) searched in population databases, national surveys or registries.
2. Refer to clinical studies regarding the patterns of treatment for CVID and XLA.
3. Refer to economic evaluations and health technology assessments, including the cost of Ig replacement therapy in patients with CVID or XLA.
4. Refer to relevant studies regarding adverse events due to Ig replacement therapy.

All other economic or epidemiological studies that did not meet the abovementioned inclusion criteria were excluded. At the end of the systematic literature review process, eight epidemiological/clinical (Tables 1 and 2) and three economic (Table 3) papers were selected (Fig. 1).

2.3 Epidemiological and Clinical Parameters

Despite the lack of information and the underlying uncertainty regarding the epidemiology of PIDs, in the present study we attempted to estimate the actual number of patients with XLA and CVID in Italy. The summary of clinical and epidemiological information drawn from the scanned databases is shown in Tables 1 and 2. Additional information was provided by a panel of expert clinicians (expert opinion), who also validated input to inform the model.

To overcome the lack of published data, the number of patients with XLA was estimated using an average prevalence value drawn from European registries. In particular, since data included in an Italian registry for XLA (AIEOP) have not been previously published, prevalence values calculated in France [20] and the UK [21] were taken into account. The choice was made in accordance with the opinion of the ESID in respect to the validity of French registries and due to the sociodemographic similarities between UK and Italy.

As registries did not contain reliable estimations of diagnosed patients, the number of individuals with CVID was calculated as follows:

1. The minimum value was derived from the prevalence of CVID reported in the UK registry [21].
2. The maximum value was estimated considering the overall prevalence of PIDs [22] multiplied by the frequency of CVID observed among the PIDs [23], and multiplied

Table 1 Epidemiological parameters related to patients with XLA and CVID requiring Ig replacement therapy

Parameter	Base-case	Minimum	Maximum	Source	Distribution	Alpha	Beta
Epidemiological parameters, CVID							
Prevalence (per 100,000)	3.17	1.27	5.07	[21, 22]	Beta	8.91	700.366
Treated with Ig	85.0%	78.0%	92.0%	[2]	Beta	84.97	13.99
IVIG	69.5%	60.0%	79.0%	[2]	Beta	62.71	26.52
IVIG 5%	62%			Expert opinion			
IVIG 10%	38%			Expert opinion			
SCIG	30.5%	21.0%	40.0%	[2]	Beta	27.52	61.71
SCIG 16%	34.0%			Expert opinion			
SCIG 16.5%	13.0%			Expert opinion			
SCIG 20%	53.0%			Expert opinion			
Contract manufacturing	81.0%			[24]			
Epidemiological parameters, XLA							
Prevalence (per 100,000)	0.22	0.19	0.25	[20, 21]	Beta	0.71	378.673
Treated with Ig	91.5%	88.9%	94.0%	[2]	Beta	422.44	38.50
IVIG	66.5%	60.0%	73.0%	[2]	Beta	134.70	66.86
IVIG 5%	62%			Expert opinion			
IVIG 10%	38%			Expert opinion			
SCIG	33.5%	27.0%	40.0%	[2]	Beta	67.86	133.70
SCIG 16%	34.0%			Expert opinion			
SCIG 16.5%	13.0%			Expert opinion			
SCIG 20%	53.0%			Expert opinion			
Contract manufacturing	81.0%			[24]			

XLA X-linked agammaglobulinemia, *CVID* common variable immunodeficiency, *Ig* immunoglobulin, *IVIG* intravenous immunoglobulin, *SCIG* subcutaneous immunoglobulin

by the rate of patients diagnosed in Italy (expert opinion).

3. The central value of distribution was calculated on the basis of the two extremes.

In order to assess Ig consumption, patient characteristics such as age, weight, dosage, frequency of treatment, and utilization of Ig derived by contract manufacturing were considered.

Five regimens of Ig replacement therapy were individualized: 5% and 10% dose of IVIG, and 16%, 16.5% and 20% dose of SCIG [24, 25].

The ISTISAN report [24] indicates that 81% of patients receiving a 5% dose of IVIG were treated with plasma-derived products. These patients were excluded from the computation because the cost of this treatment is unknown.

2.4 Cost Parameters

Direct cost data associated with each Ig replacement therapy were identified. The costs were actualized to 2017 and parameterized for comparison with the price index for monetary revaluation by ISTAT [26]. Data were related to the annual management of XLA and CVID, including the cost of Igs, premedication, adverse events, administration, and diagnostic procedures. To reflect the variability between different regional health services, a range for each parameter (corresponding to 15%) was built. Details regarding the parameters and probabilistic ranges used in the model are reported in Table 3. Most of the cost parameters were derived from the paper published by Matucci et al. [11], with the exception of the cost of Ig and adverse events occurring with subcutaneous therapy. As far as prices are concerned, those prices commonly charged to the Italian NHS, including net discount rates specified by law [27], were considered.

The cost of adverse events was calculated on the basis of the utilization of 2 g of the most frequently used drugs in these circumstances (i.e. betamethasone dipropionate and dexchlorpheniramine maleate) [28] for an average duration therapy of 2 days [29].

2.5 Indirect costs

No information regarding the loss of productivity caused by XLA or CVID is currently available. Therefore, some information was collected by the AIP (Table 3), including percentage of patients who lost work hours due to infusion (SCIG), work hours lost per patient (SCIG) and work

Table 2 Clinical parameters related to patients with XLA and CVID requiring Ig replacement therapy

	Base-case	Minimum	Maximum	Source	Distribution	Alpha	Beta
Age of CVID patients (years)							
> 12	9.0%	27.0%	10.0%	[2]	Beta	283.16	2.862.11
13–17	8.0%	11.0%	8.0%	[2]	Beta	25.13	288.02
18–29	19.0%	15.0%	12.0%	[2]	Beta	70.21	298.31
30–44	21.0%	18.0%	16.0%	[2]	Beta	148.71	558.43
45–64	30.0%	25.0%	39.0%	[2]	Beta	29.88	68.72
< 65	13,0%	4,0%	15,0%	[2]	Beta	141,21	944,00
Age of XLA patients (years)							
> 12	35.0%	27.0%	10.0%	[2]	Beta	47.79	87.76
13–17	18.0%	11.0%	8.0%	[2]	Beta	20.83	93.89
18–29	30.0%	15.0%	12.0%	[2]	Beta	10.76	24.10
30–44	13.0%	18.0%	16.0%	[2]	Beta	22.59	150.20
45–64	4.0%	25.0%	39.0%	[2]	Beta	0.13	2.21
< 65	0.0%	4.0%	15.0%	[2]	Beta	0.00	1.20
Body weight by age (years)							
> 12	21.90	11.45	48.20	[2]	Gamma	2.66	8.22
13–17	61.95	43.95	91.15	[2]	Gamma	17.29	3.58
18–29	73.20	54.50	105.05	[2]	Gamma	20.29	3.61
30–44	78.05	60.60	110.30	[2]	Gamma	22.50	3.47
45–64	81.20	61.90	109.70	[2]	Gamma	31.18	2.60
< 65	76.05	57.60	97.85	[2]	Gamma	46.75	1.63
Ig dosage by administration (mg/kg)							
IVIG	382	187	546	[2]	Gamma	20.84	18.33
SCIG	105	48	179	[2]	Gamma	7.73	13.58
Treatment frequency (per year)							
IVIG	15	13	26	[2, 9]	Gamma	7.14	2.10
SCIG	54	24	104	[2, 9]	Gamma	12.45	4.34
Premedication/adverse events							
Patients receiving premedication (IVIG)	42%						
Incidence AEs (SCIG)	75%			[29, 39]			
Percentage of treated adverse events	25%			Expert opinion			

XLA X-linked agammaglobulinemia, *CVID* common variable immunodeficiency, *Ig* immunoglobulin, *IVIG* intravenous immunoglobulin, *SCIG* subcutaneous immunoglobulin, *AEs* adverse events

days lost per patient (IVIG). This information was interpolated with hourly labour costs corresponding to €21.4 (estimated by EUROSTAT) [30]. Starting with these data, the value of a day's work amounts to €154, corresponding to, on average, 7 h worked per day (36 h worked per week over 5 days). The minimum value corresponded to an average of 6 h worked per day, while the maximum value corresponded to an average of 8 h worked per day. To estimate indirect costs and those costs associated with mortality, it was conservatively assumed that only a proportion of patients (57.7%) were employed and were in the productive age group.

2.6 Statistical Analysis

In order to consider the variability of data used to inform the model, a probabilistic sensitivity analysis (PSA) was performed, consisting of using the differences identified in the examined sources, indicating a minimum and maximum value of the uncertainty distribution of each parameter.

The probabilistic distribution was attributed, applying what is generally reported for the development of economic evaluation models, and distinguishing between costs (gamma distribution) and epidemiological parameters (beta distribution) [31]. Furthermore, the distribution of each parameter

Table 3 Direct and indirect costs induced by patients with XLA and CVID requiring Ig replacement therapy

Parameter	Base-case (€)	Minimum (€)	Maximum (€)	Reference	Distribution	Alpha	Beta
Direct cost parameter per patient							
IVIG							
Cost of Ig 5% (€/g)	47.88			[27]			
Cost of Ig 10% (€/g)	49.80			[27]			
Cost for medical and nursing staff (per administration)	135.3	115.0	155.6	[11]	Gamma	179.73	0.79
Cost for ambulatory (per administration)	179.8	152.85	206.80	[11]	Gamma	170.74	1.05
Cost of premedication (per administration)	1.05	0.90	1.21	[11]	Gamma	170.74	0.01
Cost of diagnostic examination procedures (per year)	274.9	233.7	316.1	[11]	Gamma	170.74	1.61
SCIG							
Cost of Ig 16% (€/g)	47.88			[27]			
Cost of Ig 16.5% (€/g)	47.88			[27]			
Cost of Ig 20% (€/g)	50.40			[27]			
Cost for infusion pump[a] (per year)	348.10	295.89	400.32	[11]	Gamma	170.74	2.04
Cost of the materials for infusion (per administration)	16.82	14.30	19.35	[11]	Gamma	170.74	0.10
Cost of AEs (per administration)	0.76	0.73	0.80	Calculation	Gamma	1.386.82	0.001
Cost of diagnostic examination procedures (per year)	274.9	233.7	316.1	[11]	Gamma	170.74	1.61
Indirect cost parameter							
Daily labour cost per patient	€154	€128	€180	Calculation [30]	Gamma	138.30	1.11
Hourly labour cost per patient	€21.4	€16.0	€26.7	[30]	Gamma	61.47	0.35
Percentage of people who lost work hours for infusion (SCIG)	24%			AIP			
Lost hours per patient, SCIG	1.37	1.0	2.5	AIP	Gamma	5.59	0.24
Days lost per patient, IVIG	1.01	0.50	1.43	AIP	Gamma	21.77	0.046
Employment rate	58.1%			[40]			

XLA X-linked agammaglobulinemia, *CVID* common variable immunodeficiency, *Ig* immunoglobulin, *IVIG* intravenous immunoglobulin, *SCIG* subcutaneous immunoglobulin, *AEs* adverse events, *AIP* Association for Primary Immunodeficiency

[a]Cost of the main infusion pump (Crono S-PID®) used for SCIG administration in Italy

was used to perform 5000 Monte Carlo simulations in order to obtain interval estimates (95% confidence interval [CI]) of the main epidemiological and economic data.

3 Results

The epidemiological model allowed us to estimate the number of prevalent patients affected by XLA and CVID in Italy in 2017. This estimate corresponds to 1885 (95% CI 944–3145) and 133 (95% CI 115–152) patients with CVID and XLA, respectively. Of a total of 2018 patients (95% CI 1065–3369), 86.2% commonly received Ig replacement therapy. The estimated number of patients were categorized by route of administration (SCIG and IVIG) and dose (Fig. 2). The mean annual direct costs incurred by the Italian NHS for patients (with XLA and CVID) treated with SCIG and IVIG is equal to €21,649 (95% CI €7812–€42,757) and €25,801 (95% CI €11,134–€43,403), respectively. The difference of approximately €4000 is mainly associated with the acquisition cost of Igs; this is also confirmed when the distribution cost by disease (XLA and CVID) is analysed (Fig. 3). On average, approximately 80% of the total expense is absorbed by the acquisition cost of drugs.

The total direct costs incurred by the Italian NHS for patients affected by CVID and XLA are shown in Fig. 4. The probabilistic model estimates an economic annual burden for direct costs corresponding to approximately €41.22 million (95% CI €13.54–€84.06 million): 6% is due to to XLA (€2.5 million [95% CI €1.15–€4.34 million]), while the majority is due to CVID (€38.7 million [95% CI €11.59–€81.94 million]). Figures 4 and 5 describe in detail direct and indirect costs, respectively, associated with the route of administration and dose. Total indirect costs account for approximately €1.5 million (95% CI €0.47–€2.99 million), representing 3.4% of total spending.

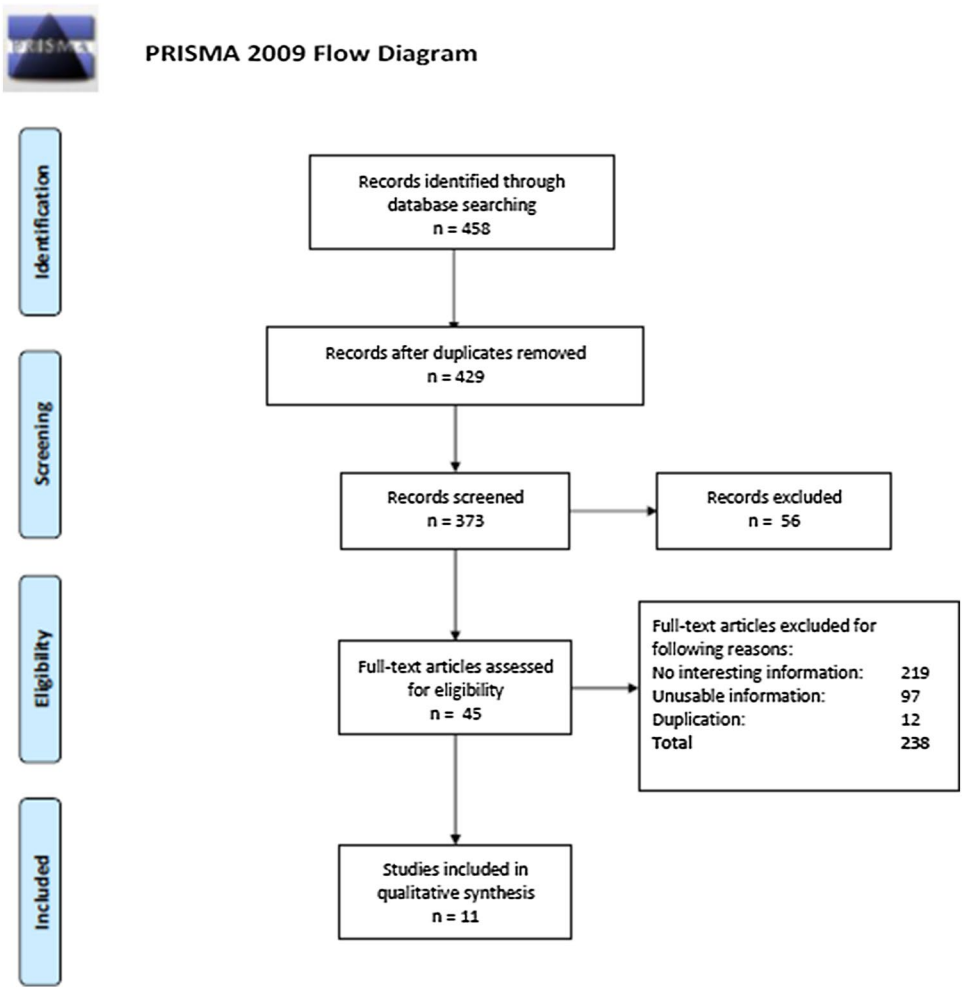

Fig. 1 PRISMA flow diagram. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

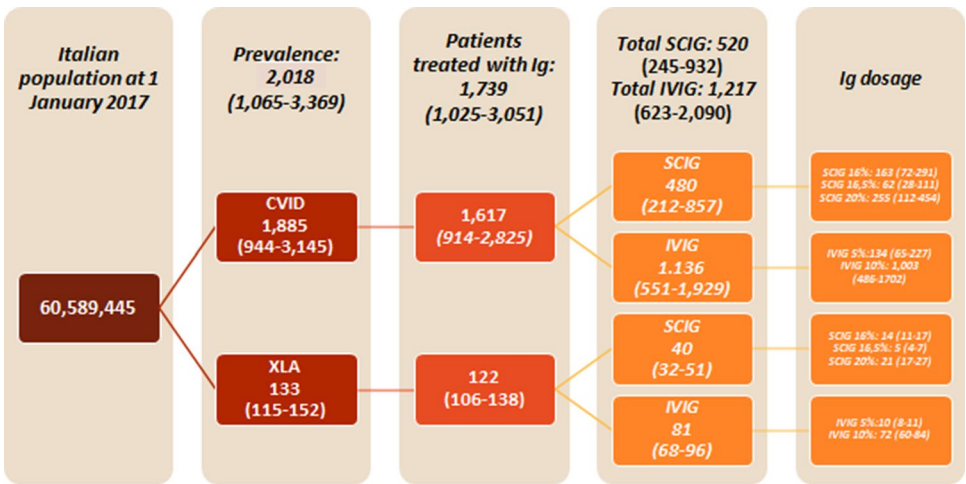

Fig. 2 Number of patients by disease (CVID and XLA), and route of administration per year (2017). *XLA* X-linked agammaglobulinemia, *CVID* common variable immunodeficiency, *Ig* immunoglobulin, *IVIG* intravenous immunoglobulin, *SCIG* subcutaneous immunoglobulin

The estimated total expenditure for the treatment and management of patients with CVID and XLA requiring Ig replacement therapy amounts to €42.68 million (95% CI €14.38–€86.1 million), with the large majority of this expense (94%) being attributable to patients with CVID, which is the most common condition requiring the most expensive therapy.

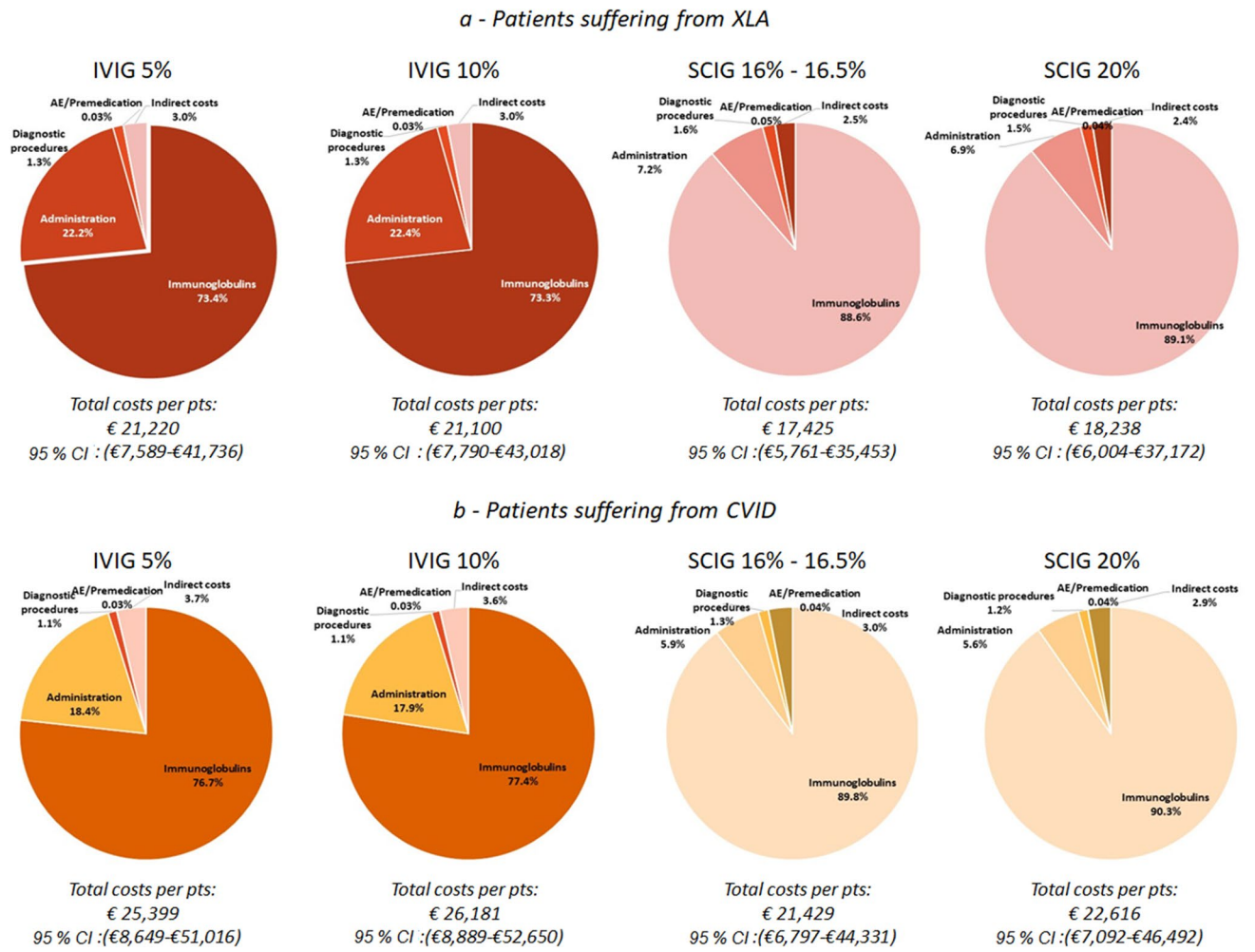

Fig. 3 Annual average cost per patient requiring Ig replacement therapy. *XLA* X-linked agammaglobulinemia, *CVID* common variable immunodeficiency, *Ig* immunoglobulin, *IVIG* intravenous immunoglobulin, *SCIG* subcutaneous immunoglobulin, *AE* adverse events, *pts* patients, *CI* confidence interval

Fig. 4 Direct costs associated with the Ig administration, € million (95% CI). *XLA* X-linked agammaglobulinemia, *CVID* common variable immunodeiciency, *Ig* immunoglobulin, *IVIG* intravenous immunoglobulin, *SCIG* subcutaneous immunoglobulin

IVIG 5%	IVIG 10%	SCIG 16%	SCIG 16.5%	SCIG 20%
XLA				
€ 0.20 (€0.07-€0.39)	€ 1.52 (€0.52-€3.04)	€ 0.23 (€0.07-€0.49)	€ 0.09 (€0.03-€0.19)	€ 0.38 (€0.12-€0.79)
Total cost XLA IVIG		Total cost XLA SCIG		
€ 1.77 (€0.61-€3.53)		€ 0.72 (€0.23-€1.48)		
Total cost XLA				
€ 2.49 (€1.15-€4.34)				
CVID				
IVIG 5%	**IVIG 10%**	**SCIG 16%**	**SCIG 16.5%**	**SCIG 20%**
€ 2.60 (€0.54-€6.28)	€ 25.26 (€5.74-€58.95)	€ 3.38 (€0.7-€8.14)	€ 1.29 (€0.27-€3.11)	€ 5.53 (€1.14-€13.32)
Total direct cost CVID IVIG		Total cost CVID SCIG		
€ 28.53 (€6.49-€66.57)		€ 10.21 (€2.11-€24.57)		
Total cost CVID				
€ 38.73 (€11.59-€81.94)				
Total direct cost				
€ 41.22 (€13.54-€84.06)				

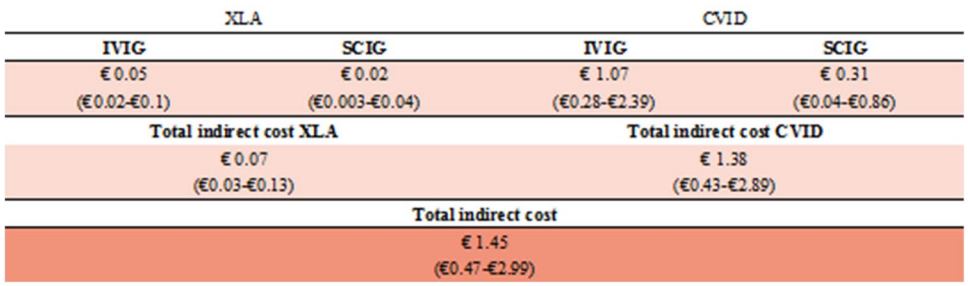

Fig. 5 Indirect costs associated with the Ig administration, € million (95% CI). *XLA* X-linked agammaglobulinemia, *CVID* common variable immunodeiciency, *Ig* immunoglobulin, *IVIG* intravenous immunoglobulin, *SCIG* subcutaneous immunoglobulin

4 Discussion

This is the first study in which direct and indirect costs (incurred by either the NHS or society) were taken into account to estimate the overall burden of some of the most frequently reported PIDs requiring Ig replacement therapy in our country. The results provide new insights for which there was scarce or fragmented evidence in the previous literature.

The economic yearly burden induced by patients requiring Ig replacement therapy in 2017 was estimated at just over €42.7 million. Most of this expense (94%) is attributable to patients with CVID, the most widespread condition with the most expensive therapy. The higher cost of treatment is mainly associated with adult patients with CVID, with a higher body weight and therefore a greater consumption of Ig.

The developed model shows that indirect costs exceed €1.5 million, corresponding to approximately 3.4% of total costs. However, it should be borne in mind that these indirect costs do not take into account the presenteeism and loss of productivity of caregivers. These two types of indirect costs express the extent of productivity losses, and the relative amount might be remarkable, especially for patients with XLA. It is also noteworthy to mention that presenteeism may actually be a much costlier problem than absenteeism (approximately three- to tenfold higher) [32, 33]. Furthermore, presenteeism is quite common in tough economic times, when employees may be extremely afraid of losing their job [34].

The epidemiological model estimates 2018 patients are currently affected by CVID and XLA. In 2014, 1020 Italian patients affected by PIDs with antibody deficiency were recorded in the ESID registry, whereas the number of patients estimated by our model is approximately twice that, considering only CVID and XLA. This could be caused by several factors, including incomplete recordings, failure to update, and missing patients. However, our estimates are consistent with the input used in another important registry [12, 35].

Intravenously administered Ig is more expensive than SCIG, with a difference of approximately €4000 per patient, due to higher administration costs as well as indirect costs. These figures are consistent with data recently published in a nationwide study [11]. In spite of the greater cost, the preponderance of patients in Italy are treated with IVIG regardless of disease type.

The SCIG therapy for PIDs has equal efficacy compared with IVIG, induces fewer systemic reactions, and may be self-infused, but, on the other hand, requires multiple infusion sites, more frequent infusions, and dose adjustment to achieve pharmacokinetic equivalence [36]. To solve these problems, new treatments might be useful, such as Igs facilitated with recombinant human hyaluronidase (rHuPH20) that increases tissue permeability and facilitates dispersion and absorption, enabling administration of monthly doses in one site with the option of home-based self-administration [36]. This type of Ig should generate the reduction of the overall costs associated with administration, management of adverse events, cost of wasting, and also an improvement in patients' quality of life.

This study has some limitations. First, the true prevalence of CVID and XLA is uncertain because the model was not informed with complete epidemiological Italian data. This is due to the impossibility of identifying a unique national body in charge of recording costs and epidemiological data regarding these diseases. At present, a specific prevalence study conducted on a representative sample of the Italian population is lacking and data drawn from local registries are unpublished. Therefore, it was necessary to calculate the estimates of the main epidemiological indicators using some of the European registries [21, 22].

However, the systematic literature review, performed according to rigorous international guidelines, allowed identification of the most recent, accurate, and homogenous data sources that are well-acknowledged by the scientific community. The same well-validated methodological sequence has already been implemented to measure the clinical and economic burden of different pathological conditions such as human papillomavirus- and hepatitis C virus-induced diseases in Italy [37, 38]. Furthermore, a PSA was purposely carried out to obtain solid interval estimations, considering the heterogeneity of the available data and the overall uncertainty of the sources used.

Second, due to scarce or missing information, it was not possible to estimate some expense items associated

with the diseases of interest. As a consequence, results tend to underestimate the overall economic burden. This is particularly significant in regard to indirect costs. Only the loss of productivity of patients with CVID and XLA was considered. However, a cost-of-illness evaluation should take into account the full range of indirect costs, including the loss of productivity and competitiveness associated with presenteeism, loss of productivity of caregivers, and, finally, early retirements induced by the diseases. Furthermore, there is another motivation that surely contributed to underestimation of the current results. According to rigorous implementation of methodological procedures, expenses related to the treatment of patients receiving IVIG 5% (i.e. 144 [95% CI 73–246]) were excluded from the computation of the economic burden. Indeed, the direct cost incurred by regions for plasma-derived products (due to contract manufacturing) is commonly not revealed, or just partially declared. This condition is expected to change soon, but currently these costs have basically been omitted since they were unidentified.

Finally, the direct health costs were calculated on the basis of data collaborated from Careggi's Immunoallergology Centre in Florence [11]. Although the results provided by this study are statistically robust, they cannot be considered fully representative of the national health context.

5 Conclusions

The present study aimed to fill the information gap regarding the epidemiological and economic burden associated with patients affected by CVID and XLA. This information provides a comprehensive perspective for an enhanced understanding of the most relevant economic issues and to facilitate better-informed public health decision making in the management of these PIDs in Italy.

Compliance with Ethical Standards

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Conflicts of interest Viti Raffaella, Marcellusi Andrea, Capone Alessandro, Matucci Andrea, Vultaggio Alessandra, Pignata Claudio, Spadaro Giuseppe, Vacca Angelo, Marasco Carolina, Agostini Carlo, and Mennini Francesco Saverio declare that there are no conflicts of interest regarding the publication of this paper.

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