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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 and Objective: In Italy, there is scarce evidence on the epidemiological and economic burden induced by the primary antibody deficiencies. 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 an Ig replacement therapy.

Methods: A probabilistic cost of illness model was developed to estimate the number of patients suffering from 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 5,000 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, corresponds to 1,885 (95% CI: 944-3,145) and 133 (95% CI: 115-152), respectively. The estimated total expenditure for the treatment and management of patients with CVID and XLA requiring an Ig replacement therapy amounts to € 42.68 million (95% CI €14.38-€86.1 million).

Conclusions: This set of information is supposed to provide a comprehensive perspective of the economic issues and facilitate better-informed public health decision-making in the management of CVID and XLA in Italy.

Key Points:

- In 2017, patients suffering from CVID and XLA in Italy were 1,885 and 133 respectively**.**
- Direct costs were estimated at € 41.22 million, 94% attributable to CVID (€ 38.7 million).
- Indirect costs accounted for € 1.5 million representing the 3.4% of total spending**.**

INTRODUCTION

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

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

In the Ig replacement therapy, a recommended range of dose between 400-600 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 pointed out that 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, the intravenous administration can induce the onset of systemic adverse events during or after the infusion [9]. In comparison to IVIG, subcutaneous administration induces mild side effects that occur at the local level [10].

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

From the epidemiological point of view, the prevalence of PIDs in Italy is on average the same as other European countries [12]. In May 2014, 1,120 Italian patients with PIDs were recorded, considering the Italian registry IPINET (Italian Primary Immunodeficiencies Network) and the registry AIEOP (Italian Association of Pediatric Hematology Oncology). However, this is not the real amount of Italian people affected by PIDs, as not all patients with PIDs are included in current registers, especially for those primitive immunodeficiencies affecting the adult population, such as the common variable immunodeficiency (CVID) [2, 9].

The development of new technologies that improve the diagnostic and treatment accuracy for people with rare diseases is living a bright moment. However, to assure that 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]. These kinds of information are 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 the study is to estimate the annual economic burden related to the management of patients requiring an Ig replacement therapy (specifically patients affected by CVID and XLA) from the societal perspective (i.e. direct and indirect health care costs).

1. **METHODS**

2.1 Design of the study

In order to estimate the annual costs caused by patients with PIDs requiring Ig replacement therapy, a probabilistic cost of illness model capable of estimating the number and distribution of patients suffering from 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 with data obtained from a systematic literature review. A Bottom-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 with 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 concerning CVID, XLA and Ig replacement therapy in Italy.

The systematic literature review was conducted using the following scientific search databases: MEDLINE (PubMed), Cochrane Library, Health Technology Assessment on the Net, Clinical trial. 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 web site dedicated to public health)], ResearchGate, National and International associations of physicians and patients (ESID, AIEOP, AIP). Moreover, the following Italian journals of health economics were examined: PharmacoEconomics Italian Research Article (Springer), Farmeconomia e Percorsi Terapeutici (JournalSeek), Global and Regional Health Technology Assessment (Wichtig), Quaderni dell'Italian Journal of Public Health. Peer-reviewed journals, conferences, congresses

and other available Internet sources were monitored up to June 2017 for presentations or communications of further information.

The research focused on papers published between 2007 and 2017 in Italian or English. The research was organized in two macro subjects: the epidemiological issues concerning XLA and CVID and the economic aspects related to the costs incurred by NHS as well as the society.

The systematic literature review process was organized in four steps: identification, screening, eligibility and inclusion (consistently with the recommended guidelines for the systematic analysis of scientific literature [18, 19]. The key words used for the scientific literature-scanning were as follows: 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, Prevalence. See Supplementary Material for details.

For the inclusion, two researchers independently reviewed the studies looking at the title, the abstract or the full text. Results have been compared afterword; any disagreement and risk of bias were solved through a discussion between the authors. The differences were discussed and solved through analyses and a confrontation with other experts. All the studies used to determine the epidemiological and economic parameters had 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 concerning the patterns of treatment for CVID and XLA;

3. refer to economic evaluations, and Health Technology Assessments including the cost of the Ig replacement therapy in patients with CVID or XLA;

4. refer to relevant studies concerning adverse events due to the Ig replacement therapy.

All other economic or epidemiological studies which were not meeting the above mentioned inclusion criteria were excluded. At the end of the systematic literature review process, 8 epidemiological/clinical (table 1 and 2) and 3 economic (table 3) papers were selected, respectively (figure 1).

2.3 Epidemiological and Clinical Parameters

Despite the lack of information and the underlying uncertainty concerning the epidemiology of PIDs, in the present study, we attempted to estimate the actual number of patients suffering from XLA and CVID in Italy. The summary of clinical and epidemiological information drawn from the scanned databases is shown in table 1 and table 2. Additional information was provided by a panel of expert clinicians (Expert opinion). The expert panel also validated inputs 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 the Italian registry for XLA (AIEOP) were not reported in a publication, prevalence values calculated in France [20] and the UK [21] were taken into account. The choice was made in accordance with the opinion of ESID regarding the validity of French registries and due to the socio-demographic similarities between UK and Italy.

As registries did not contain reliable estimations of diagnosed patients, the number of individuals suffering from 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 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 the Ig consumption, patient characteristics such as age, weight, dosage, frequency of treatment, and the utilization of Ig derived by contract manufacturing were considered.

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

The ISTISAN report [24] indicates that 81% of patients receiving IVIG at 5% dosage is treated with plasma-derived products. These patients were excluded from the computation because actually the cost of this treatment is not known.

2.4 Cost Parameters

Direct cost data associated with each Ig replacement therapy were identified. The costs were actualized to 2017 and parametrised 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: Immunoglobulins, 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. The details concerning the parameters and probabilistic ranges used in the model are indicated in table 3. Most of the cost parameters were derived from the paper published by Matucci [11], with the exception of the cost of Ig and adverse events occurring with subcutaneous therapy. As far as prices are concerned, those 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 grams of the most frequently used drugs in these circumstances (i.e. betamethasone dipropionate and dexchlorpheniramine maleate) [28] for an average duration therapy of two days [29].

2.5 Indirect costs

At the moment, there is no information about the loss of productivity caused by XLA or CVID. Therefore, some information was collected by the AIP (table 3), counting: percentage of patients who loses work hours due to infusion (SCIG), work hours lost per patient (SCIG), work days lost per patient (IVIG). This information was interpolated with hourly labour cost corresponding to €21.4 (estimation by EUROSTAT) [30]. Starting from these data, the value of a daily work amounts to €154 corresponding on average to 7 hours worked per day (36 hours worked per week in 5 days). The minimum value corresponded to 6 hours worked per day on average, while the maximum value to 8 hours worked per day on average. To estimate indirect costs and those associated with mortality, it was conservatively assumed that only a proportion of patients (57.7%) is employed and in productive age.

2.6 Statistical Analysis

In order to consider the variability of data used to inform the model, a Probabilistic Sensitivity Analysis (PSA) was performed. The analysis consists in using the differences found 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, distinguishing between costs (gamma distribution) and epidemiological parameters (beta distribution) [31]. Furthermore, the distribution of each parameter was used to perform 5.000 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 1,885 (95% CI: 944-3,145) and 133 (95% CI: 115-152) patients suffering from CVID and XLA, respectively. On a total of 2,017 patients (95% CI: 1,065-3,369), 86.2% commonly receive an Ig replacement therapy. The estimated patients were categorized by route of administration (SCIG and IVIG) and dosage (figure 2). The mean annual direct cost incurred by the Italian NHS for patient (with XLA and CVID) treated with SCIG and IVIG is equal to € 21,649 (95% CI: €7,812-€42,757) and € 25,801 (95% CI: €11,134 - €43,403), respectively. The difference of approximately €4,000 is mainly associated with the acquisition cost of Immunoglobulins. This is also confirmed when the distribution cost by disease (XLA and CVID) is analysed (figure 3). On average, about 80% of the total expense is absorbed by the acquisition cost of drugs.

The total direct cost incurred by the Italian NHS for patients affected by CVID and XLA is shown in table 4. The probabilistic model estimates an economic annual burden for direct costs corresponding approximately to € 41.22 million (95% CI: €13.54 - €84.06 million): 6% is pertaining 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)]. Tables 4 and 5 describe in detail either direct or indirect costs associated with the route of administration and dosage. As regards total indirect costs, they account for about € 1.5 million (95% CI: €0.47-€2.99 million), representing the 3.4% of total spending. The estimated total expenditure for the treatment and management of patients with CVID and XLA requiring an Ig replacement therapy amounts to € 42.68 million (95% CI: €14.38-€86.1 million). Large majority of this expense (94%) is attributable to patients with CVID, which is the most common condition that requires the most expensive therapy.

4 DISCUSSION

This is the first study in which direct and indirect costs (incurred by either the NHS or the society) were taken into account to estimate the overall burden of some of the most frequently reported PIDs requiring an 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 an Ig replacement therapy in 2017 was estimated at a value just over € 42.7 million. Most of this expense (94%) is attributable to patients with CVID, which is the most widespread condition with the most expensive therapy. The higher cost of treatment is associated mainly with adult patients suffering from CVID, with a higher body weight and therefore with a greater consumption of Ig.

The developed model shows that indirect costs exceed € 1.5 million, corresponding to about 3.4% of total costs. However, it should be borne in mind that these indirect costs do not take into account the presenteeism and the 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 3-10 times 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 2,017 patients are supposed to be currently affected by CVID and XLA. In 2014, 1,020 Italian patients affected by PIDs with antibody deficiency were recorded in the ESID registry, whereas the patients estimated by our model is about twice, considering only CVID and XLA. This could be caused by several factors, including incomplete recordings, failure to update and missing patients. Our estimates however, are consistent with the inputs used in another important registry [12, 35].

The Ig intravenously administered are more expensive than SCIG, with a difference of about €4,000 per patient, due to a higher cost for administration as well as indirect costs. These figures are consistent with data recently published in a nationwide study [11]. In spite of a greater cost, the preponderance of patients in Italy is treated with IVIG regardless the disease type.

The SCIG therapy for PIDs has an equal efficacy compared to 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, as immunoglobulins facilitated with rHuPH20 (recombinant human hyaluronidase) 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 the administration, the management of adverse events, the cost of wasting, and also an improvement of patients' quality of life.

This study has some limitations. Firstly, 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 to identify a unique national body in charge of recording costs and epidemiological data concerning these diseases. At present, a specific prevalence study conducted on 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 to identify the most recent, accurate, and homogenous data sources that are well-acknowledged by the scientific community. The same very well-validated methodological sequence has already been implemented to measure the clinical and economic burden of different pathological conditions such as HPV- and HCV-induced diseases in Italy [37, 38]. Furthermore, probabilistic sensitivity analysis was purposely carried out to obtain solid interval estimations, considering the heterogeneity of the available data and the overall uncertainty of the sources used.

Secondly, 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 suffering from 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 the presenteeism, the loss of productivity of caregivers and finally early retirements induced by the diseases. There is another motivation that surely contributed to underestimate current results. According to a rigorous implementation of methodological procedures, expenses related to the treatment of patients receiving IVIG 5% [i.e. 144 (95% CI: 73-246 patients)] 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 unrevealed or just partially declared. This condition is expected to change soon; but at this moment in time these costs were basically omitted since they were unidentified.

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

5 CONCLUSION:

In conclusion, the present study aimed at filling the information gap concerning the epidemiological and economic burden associated with patients affected by CVID and XLA. This set of information is supposed to provide a comprehensive perspective for an enhanced understanding of the most relevant economic issues and facilitate better-informed public health decision-making in the management of these PIDs in Italy.

Declaration of Funding and conflict of interest

This analysis was funded by Baxalta SpA. The authors confirm that the paper is an accurate representation of the study results. All the authors declare that there is no conflict of interest regarding the publication of this paper.

Reference

1. Driessen, G. and M. van der Burg, *Educational paper: primary antibody deficiencies.* Eur J Pediatr, 2011. **170**(6): p. 693-702.
2. Stonebraker, J.S., et al., *Modeling primary immunodeficiency disease epidemiology and its treatment to estimate latent therapeutic demand for immunoglobulin.* J Clin Immunol, 2014. **34**(2): p. 233-44.
3. Shehata, N., et al., *The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline.* Transfus Med Rev, 2010. **24 Suppl 1**: p. S28-50.
4. Quinti, I.B., G., *Le immunoglobuline per uso endovenoso: efficacia, tollerabilità e consumo.* Rivista di Immunologia e Allergologia Pediatrica, 2013: p. 28-36.
5. Kerr, J., et al., *Is dosing of therapeutic immunoglobulins optimal? A review of a three-decade long debate in europe.* Front Immunol, 2014. **5**: p. 629.
6. European Primary Immunodeficiencies Consensus Conference, *Consensus Report and Recommendations*, in *European Primary Immunodeficiencies Consensus Conference*. 19-20 June 2006: Paul-Ehrlich-Institut, Langen, Germany.
7. Berger, M., *Subcutaneous immunoglobulin replacement in primary immunodeficiencies.* Clin Immunol, 2004. **112**(1): p. 1-7.
8. Berger, M., *Subcutaneous administration of IgG.* Immunol Allergy Clin North Am, 2008. **28**(4): p. 779-802, viii.
9. Bonilla, F.A., *Intravenous immunoglobulin: adverse reactions and management.* J Allergy Clin Immunol, 2008. **122**(6): p. 1238-9.
10. Wasserman, R.L., *Subcutaneous immunoglobulin: facilitated infusion and advances in administration.* Clin Exp Immunol, 2014. **178 Suppl 1**: p. 75-7.
11. Matucci, A., et al., *Analisi di minimizzazione dei costi della terapia con Immunoglobuline (Ig) per il trattamento di pazienti con immunodeficienza primaria: confronto tra terapia con Ig sottocute vs endovena.* Giornale Italiano di Health Technology Assessment, 2008. **1**(1): p. 31-37.
12. Grimbacher, B. and E.R.W. Party, *The European Society for Immunodeficiencies (ESID) registry 2014.* Clin Exp Immunol, 2014. **178 Suppl 1**: p. 18-20.
13. Angelis, A., D. Tordrup, and P. Kanavos, *Socio-economic burden of rare diseases: A systematic review of cost of illness evidence.* Health Policy, 2015. **119**(7): p. 964-79.
14. Mazzucato, M., et al., *A population-based registry as a source of health indicators for rare diseases: the ten-year experience of the Veneto Region's rare diseases registry.* Orphanet J Rare Dis, 2014. **9**: p. 37.
15. Hodgson TA, M.M., *Cost of Illness Methodology: A Guide to Current Practice and Procedures.* Milbank Memorial Fund Quarterly, 1982. **60**(3): p. 429-462.
16. Berger ML, et al., *Cost of Illness Study*, in *Health care cost, quality, and outcomes*, ISPOR, Editor. 2003: USA. p. 43-44.
17. Joel E, S.B., *Cost-of-Illness Studies - A Primer*. 2006, RTI-UNC Center of Excellence in Health Promotion Economics.
18. Green, S. and J. Higgins. *Cochrane handbook for systematic reviews of interventions 4.2.5. The Cochrane Collaboration.* 2005 19 May 2009]; Available from: http://www.cochrane.org/resources/glossary.htm.
19. Moher D, L.A., Tetzlaff J, Altman DG, The PRISMA Group., *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Medicine 2009. **6**(6).

20. group, C.T.F.P.s., *The French national registry of primary immunodeficiency diseases.* Clin Immunol, 2010. **135**(2): p. 264-72.
21. Edgar, J.D., et al., *The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008-2012.* Clin Exp Immunol, 2014. **175**(1): p. 68-78.
22. Kobrynski, L., R.W. Powell, and S. Bowen, *Prevalence and morbidity of primary immunodeficiency diseases, United States 2001-2007.* J Clin Immunol, 2014. **34**(8): p. 954-61.
23. Gathmann, B., et al., *The European internet-based patient and research database for primary immunodeficiencies: results 2006-2008.* Clin Exp Immunol, 2009. **157 Suppl 1**: p. 3-11.
24. Calizzani, G., et al., *Analisi della domanda dei principali medicinali plasmaderivati in Italia. Anni 2007-2011.*, in *Rapporto ISTISAN* 2012, Isituto Superiore di Sanità. p. 167.
25. Quinti, I., et al., *Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study.* J Clin Immunol, 2011. **31**(3): p. 315-22.
26. Istituto Nazionale di Statistica. *Rivalutazione e documentazione su prezzi, costi e retribuzioni contrattuali. Indice dei prezzi al consumo per famiglie operai e impiegati.* Novembre 2013]; Available from: http://rivaluta.istat.it/.
27. Gazzetta Ufficiale della Repubblica Italiana. *Regime di rimborsabilità e prezzo di vendita di nuove confezioni dei medicinali*. 2015; Available from: http://www.gazzettaufficiale.it.
28. Farmadati Italia. *Banca Dati Online*. [cited 2016 Maggio]; Available from: http://www.farmadati.it/default.aspx.
29. Berger, M., *Adverse effects of IgG therapy.* J Allergy Clin Immunol Pract, 2013. **1**(6): p. 558-66.
30. EUROSTAT, *Hourly labour costs* 2016.
31. Briggs, A., K. Claxton, and M. Sculpher, *Decision Modelling for Health Economic Evaluation*, ed. O.U.P. Inc. 2007, New York.
32. Stewart, W.F., et al., *Cost of lost productive work time among US workers with depression.* JAMA, 2003. **289**(23): p. 3135-44.
33. Hemp, P., *Presenteeism: at work--but out of it.* Harv Bus Rev, 2004. **82**(10): p. 49-58, 155.
34. Capone, A., et al., *Health Data Entanglement and artificial intelligence-based analysis: a brand new methodology to improve the effectiveness of healthcare services.* Clin Ter, 2016. **167**(5): p. e102-e111.
35. Mahlaoui, N., et al., *The European Society for Immunodeficiencies (ESID) Registry: recent advancements in the epidemiology of Primary Immunodeficiencies and how does that translate in clinical care.* RARE DISEASES AND ORPHAN DRUGS, 2014. **1**(4): p. 25-27.
36. Wasserman, R.L., et al., *Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency.* J Allergy Clin Immunol, 2012. **130**(4): p. 951-7 e11.
37. Baio, G., et al., *Economic burden of human papillomavirus-related diseases in Italy.* PLoS One, 2012. **7**(11): p. e49699.
38. Marcellusi, A., et al., *The economic burden of HCV-induced diseases in Italy. A probabilistic cost of illness model.* Eur Rev Med Pharmacol Sci, 2015. **19**(9): p. 1610-20.
39. Stiehm, E.R., *Adverse effects of human immunoglobulin therapy.* Transfus Med Rev, 2013. **27**(3): p. 171-8.
40. Istituto Nazionale di Statistica. *ISTAT*. 2017 [cited 2017; Italian employment rate]. Available from: http://www.istat.it/it/.

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

Clinical parameter	Base-case	Minimum	Maximum	Source	DISTRIBUTION	ALPHA	BETA
Epidemiological parameters CVID							
Prevalence*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*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,

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

Age of CVID patients (2014)	Base-case	Minimum	Maximum	Source	DISTRIBUTION	ALPHA	BETA
>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 (2014)							
>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 (2014)							
>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 AE (SCIG)	75%			[29, 39]			
% treated adverse events	25%			Expert opinion			

XLA: X-linked agammaglobulinemia, CVID: Common variable immunodeficiency, Ig: Immunoglobulin, IVIG: Intravenous immunoglobulin, SCIG: Subcutaneous immunoglobulin, AE: adverse events,

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

Direct cost parameter per patient	Base-case	Minimum	Maximum	Reference	DISTRIBUTION	ALPHA	BETA
IVIG							
Cost of Ig 5% (€/g)	€ 47.88			[27]			
Cost of Ig 10% (€/g)	€ 49.80			[27]			
Cost for medical and nurse 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 AE (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	**Base-case**	**Min**	**Max**	Reference	**DISTRIBUTION**	**ALPHA**	**BETA**
Day labour cost per patient	€ 154	€ 128	€ 180	Calculation. [30]	GAMMA	138.30	1.11
Hourly labour costs per patient	€ 21.4	€ 16.0	€ 26.7	[30]	GAMMA	61.47	0.35
% of people who lose 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, AE: Adverse events

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

Table 4- Direct costs associated with the IG administration in € million (Minimum- Maximum)

XLA				
IVIG 5%	**IVIG 10%**	**SCIG 16%**	**SCIG 16.5%**	**SCIG 20%**
€ 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)				

XLA: X-linked agammaglobulinemia, CVID: Common variable immunodeficiency, Ig: Immunoglobulin, IVIG: Intravenous immunoglobulin, SCIG: Subcutaneous immunoglobulin

Table 5 - Indirect costs associated with the IG administration in € million (Minimum- Maximum)

XLA		CVID	
IVIG	SCIG	IVIG	SCIG
€ 0.05 (€0.02-€0.1)	€ 0.02 (€0.003-€0.04)	€ 1.07 (€0.28-€2.39)	€ 0.31 (€0.04-€0.86)
Total indirect cost XLA		Total indirect cost CVID	
€ 0.07 (€0.03-€0.13)		€ 1.38 (€0.43-€2.89)	
Total indirect cost			
€ 1.45 (€0.47-€2.99)			

XLA: X-linked agammaglobulinemia, CVID: Common variable immunodeficiency, Ig: Immunoglobulin, IVIG: Intravenous immunoglobulin, SCIG: Subcutaneous immunoglobulin

Figure 1 - PRISMA Flow diagram

Figure 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

Figure 3- Annual average cost per patient requiring an Ig replacement therapy

XLA: X-linked agammaglobulinemia, CVID: Common variable immunodeficiency, Ig: Immunoglobulin, IVIG: Intravenous immunoglobulin, SCIG: Subcutaneous immunoglobulin, AE: Adverse events, pts: patients