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ORIGINAL ARTICLE

Cost-effectiveness of newborn screening for severe combined immunodeficiency

Catharina P. B. Van der Ploeg[1] · Maartje Blom[2] · Robbert G. M. Bredius[2] · Mirjam van der Burg[2] · Peter C. J. I. Schielen[3] · Paul H. Verkerk[1] · M. Elske Van den Akker-van Marle[4]

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Abstract

Severe combined immunodeficiency (SCID) is a condition that often results in severe infections and death at young age. Early detection shortly after birth, followed by treatment before infections occur, largely increases the chances of survival. As the incidence of SCID is low, assessing cost-effectiveness of adding screening for SCID to the newborn screening program is relevant for decision making. Lifetime costs and effects of newborn screening for SCID were compared to a situation without screening in the Netherlands in a decision analysis model. Model parameters were based on literature and expert opinions. Sensitivity analyses were performed. Due to earlier detection, the number of deaths due to SCID per 100,000 children was assessed to decrease from 0.57 to 0.23 and a number of 11.7 quality adjusted life-years (QALYs) gained was expected. Total yearly healthcare costs, including costs of screening, diagnostics, and treatment, were €390,800 higher in a situation with screening compared to a situation without screening, resulting in a cost-utility ratio of €33,400 per QALY gained.

Conclusion: Newborn screening for SCID might be cost-effective. However, there is still a lot of uncertainty around the cost-effectiveness estimate. Pilot screening projects are warranted to obtain more accurate estimates for the European situation.

What is Known:

- *Severe combined immunodeficiency (SCID) is a condition that often results in severe infections and death at a young age.*
- *As the incidence of SCID is low, assessing cost-effectiveness of adding screening for SCID to the newborn screening program is needed.*

What is New:

- *Newborn screening for SCID is expected to reduce mortality from 0.57 to 0.23 per 100,000 children at additional healthcare costs of €390,800. The cost-utility ratio is €33,400 per QALY gained.*
- *Due to large uncertainty around cost-effectiveness estimates, pilot screening projects are warranted for Europe.*

Keywords Newborn screening · Severe combined immunodeficiency · Cost-effectiveness analysis · Decision analysis model

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✉ Catharina P. B. Van der Ploeg
Kitty.vanderPloeg@tno.nl

Maartje Blom
Maartje.Blom@rivm.nl

Robbert G. M. Bredius
R.G.M.Bredius@lumc.nl

Mirjam van der Burg
M.van_der_Burg@lumc.nl

Peter C. J. I. Schielen
Peter.Schielen@rivm.nl

Paul H. Verkerk
Paul.Verkerk@tno.nl

M. Elske Van den Akker-van Marle
M.E.van_den_Akker-van_Marle@lumc.nl

[1] TNO - Child Health, PO box 3005, 2301 DA Leiden, The Netherlands

[2] Department of Pediatrics, Leiden University Medical Center, PO box 9600, 2300 RC Leiden, The Netherlands

[3] RIVM, Department Biologicals, Screening and Innovation, PO box 1, 3720 BA Bilthoven, The Netherlands

[4] Department of Medical Decision Making, Leiden University Medical Center, PO box 9600, 2300 RC Leiden, The Netherlands

Abbreviations

SCID	Severe combined immunodeficiency
HSCT	Hematopoietic stem cell transplantation
TREC	T cell receptor excision circle
QALY	Quality adjusted life-year
NBSSCID	Newborn screening for SCID
Ig	Immunoglobulin
GvHD	Graft versus host disease
IVIG	Intravenous immunoglobulin

Introduction

Severe combined immunodeficiency (SCID) is a condition that often results in severe infections and death at a young age [4, 12, 16, 23, 27]. Early detection shortly after birth, followed by treatment restoring the immune system (usually a hematopoietic stem cell transplantation (HSCT)) before infections occur, largely increases the chances of survival. Most children with SCID lack a positive family history for SCID [16, 22, 34]. For these reasons several countries have already included screening for SCID in their newborn screening (NBS) program, or—like in the Netherlands—consider to do so [20, 30]. The T cell receptor excision circle (TREC) assay can be used on a heel prick blood sample for this purpose. TREC screening has identified infants with most forms of SCID and also some infants with very low T lymphocytes due to other conditions [20]. As the incidence of SCID is low, and resources are scarce, assessing cost-effectiveness of adding screening for SCID to the newborn screening program is relevant for decision making.

In cost-effectiveness studies from the USA, cost-effectiveness ratios (CERs) ranged from $27,907 to $53,560 per quality of life-year (QALY) gained [7, 12, 21]. No reports of cost-effectiveness for the European situation were found. As costs and benefits of screening and treatment are likely to differ between countries and especially between continents, we studied cost-effectiveness of newborn screening for SCID (NBSSCID) for the Netherlands.

Materials and methods

We compared lifetime costs and effects of NBSSCID with a situation without screening in the Netherlands by extending a previously developed deterministic decision analysis model of Ding et al. [12]. A Markov model was not believed to be necessary because these are used to model processes in which outcomes occur stochastically over time, whereas outcomes for children with SCID can be adequately represented in a more deterministic model [21].

For the base case analysis we used a health care perspective. All costs were discounted at a rate of 3% [13, 25] to convert future costs and effects to their present value. The price level of 2016 was used (€2016). Calculations were made for a cohort of 100,000 newborns.

Model definition

In the model of Ding et al. [12], effectiveness was expressed in life-years gained. We added the possibility to express effectiveness in QALYs gained. In addition, the time horizon for calculations was extended to lifetime, and the model was adapted to the planned screening strategy for a pilot study on newborn screening for SCID in the Netherlands.

In this pilot study, the TREC assay will be used as a screening test [24]. This test measures the number of TRECs, which are stable circular fragments of DNA formed as by-products during the T cell development. In children with SCID, T cell development is disrupted, which results in the absence of circulating TRECs in blood. If the TREC value is below the cutoff value of the assay, a retest in duplicate is performed on the same sample. If this retest on TREC is again below cutoff, while β-actin (test control) is measurable, the test result is positive. Children are then referred to a medical specialist for further evaluation, including diagnostic tests like flow cytometry and sometimes gene sequencing. In premature children with TREC values below cutoff a second blood sample is taken and analyzed before a referral to the hospital is given. A second blood sample is also taken when TREC values are below cutoff and the amount of β-actin is low. If the number of TRECs per microliter of blood is above the cutoff value, the result is negative/normal, without need of further steps.

Model parameters

Model parameters related to (1) the epidemiology of SCID and other disorders that might be detected with the TREC test (non-SCID), (2) screening results, and (3) costs (Table 1). Quantifications were based on literature and expert opinions. In case of uncertainty on a parameter, a minimum and maximum estimate was explored in a sensitivity analysis.

Epidemiological parameters

In the model, incidence of SCID and non-SCID disorders detectable with the TREC test were included, as well as the recognition that part of the SCID patients were detected early even without screening, because of a positive family history for SCID. Part of the children with SCID might die already before treatment, but also shortly after treatment. The chances of survival of SCID patients before and after treatment were estimated separately for early detection (higher odds) and for late detection (lower odds). The values found in literature for the probability of survival multiply to a basic survival probability of 86% after early detection of SCID [4, 16, 20] and to

Table 1 Model parameters and their values for the base case analysis and sensitivity analysis

Parameter	Value (base case)	Range for sensitivity analysis	Source (base case/sensitivity analysis)
1. Epidemiological parameters			
Incidence of SCID	1.72/100,000 (=1/58,000 newborns)	1.3–2.2/100,000 (=1/46,000–1/80,000)	Kwan et al. [20] (screening in USA) Screening in Taiwan (1.9/100,000) was within the 95% confidence interval (CI) [9]. Only special populations, like Navajo, Amish, have higher incidences than this range. In the Netherlands 43 SCID patients were detected in 15 years without screening: this is within the range [11]
% SCID patients early detected without neonatal screening	20%	15–30%	Myers et al., Chan et al., and Yee et al. [7, 22, 34]
Incidence of non-SCID	7.1/100,000 (=1/14,000 newborns)	6.1–12.2/100,000 (=1/8200–1/16,400)	Kwan et al. [20] Lower boundary: 95% CI Kwan et al. [20] Upper boundary: Chien et al. [9]
% non-SCID patients detected without neonatal screening	100%	0%	Most extreme possibilities
Probability to survive until treatment when SCID is detected early	94%	92–98%	Kwan et al. [20] Lower boundary: own estimate Upper boundary: Brown et al. [4]
Probability to survive after treatment when SCID is detected early	92%	90–98%	Brown et al., Kwan et al. and Heimall et al. [4, 16, 20] Boundaries: own estimate, 92–95% in other studies from USA [5, 16, 22, 23] and 100% in Chan et al. [8]
Probability to survive until treatment when SCID is detected late	78%	65–80%	Ding et al. [12] Lower boundary: Brown et al. and Pai et al. [4, 23] Upper boundary: own estimate
Probability to survive after treatment when SCID is detected late	80%	61–90%	USA: 66–90% [5, 16, 22, 23] UK: 61% [4]
Health status after transplantation (early/late detection)	Good: 80%/50% Moderate: 15%/30% Poor: 5%/20%	Good: 70%/50% Moderate: 20%/30% Poor: 10%/20%	Expert opinion
Life expectancy after transplantation (dependent on health status)	Good: 65 years (discounted: 40.8 years) Moderate: 40 years (30.3 years) Poor: 25 years (21.4 years)		Expert opinion Good: on average 65 years Moderate: on average 40 years Poor: on average 25 years
Quality of life (utility)	Good: 0.95 Moderate: 0.75 Poor: 0.5	0.75–1.0 0.5–0.95 0.3–0.7	Own estimates based on McGhee et al. [21]
Number of children without SCID who get flow cytometry (plus visit to clinic) because of suspected SCID	10 per child with SCID without screening in place		Expert opinion
2. Screening parameters			
% < cutoff TREC at first screen, i.e., retest on same sample	0.39% at < 25 TREC/μl	0.1–0.6%	UK: Adams et al. [1] and Netherlands: Blom et al. [3] Boundaries: own estimate for cutoff value of 25 TREC/μl
% second heel prick	0.25%	0.08–0.41%	Kwan et al. [19] (lower boundary), Verbsky et al. [31] (0.14%), Vogel et al. [33] (0.27%), and Chien et al. [9] (upper boundary)
% children with flow cytometry in total screened population	0.08%	0.01–0.14%	Own estimate, based on 16 studies with TREC only in Van der Spek et al. [30] Boundaries: minimum and maximum in Van der Spek et al. [30]
Sensitivity total screening program (SCID)	100%	99%	Van der Spek et al. and Kwan et al. [20, 30] (these report data from other studies) Lower boundary: own estimate
Sensitivity screening program (non-SCID)	100%		Assumption: all children with non-SCID as given by "incidence" are detected by screening

Table 1 (continued)

Parameter	Value (base case)	Range for sensitivity analysis	Source (base case/sensitivity analysis)
Distribution non-SCID into % transient, % idiopathic, and % other non-SCID	7.1% transient 2.9% idiopathic 90.0% other non-SCID		Kwan et al. [20]
3. Cost parameters (€2016)			
Costs of screening test (TREC within NBS program)	TREC: € 4.71 (€4.36 + devices €0.35)	€ 3.50–5.50	Expert opinion
Costs of retest (duplo)	TREC: € 9.42	€ 7–11	Expert opinion
Costs of second heel prick	€ 29.01 (blood collection €20.30 + postage €1.60 + processing €2.40 + TREC test)		Expert opinion
Costs of diagnostics for referred children	€ 1598 (pediatrician €102), flow cytometry (€498 including clinic visit), repeat flow cytometry for 2/3 of screen positives, genetic tests of €2000 for 1/3		Dutch tariff NZA 2017 (https://puc.overheid.nl/nza/doc/PUC_13010_22/1/), Kanters et al. [17], expert opinion
Costs of diagnostics in situation without screening for children with SCID or non-SCID	€ 2600 per child with SCID or non-SCID (pediatrician €102), flow cytometry (€498 including clinic visit), genetic tests (€2000)		Dutch tariff NZa 2017 (https://puc.overheid.nl/nza/doc/PUC_13010_22/1/), Kanters et al. [17], expert opinion
Costs of transplantation SCID when detected early	€ 90,000	€75,000–125,000	Clement et al. [10]; lower and upper boundary own estimate
Costs of transplantation SCID when detected late	€ 205,000	€150,000–450,000	Clement et al. [10]; lower boundary own estimate, upper boundary Buckley [5]
Costs of treatment non-SCID per type	Transient: € 2200 Idiopathic: € 6200 Other: € 6200	€1500–3000 €4000–8000 €4000–8000	Resource use based on Ding et al. [12] and Dutch prices from [17]; lower and upper boundary own estimate
Costs of treatment for child with SCID which dies before transplantation	€ 135,000	€75,000–225,000	Own estimate (conservative compared to Ding et al. [12], see text): 1.5 times costs of transplantation at early detection; lower and upper boundary own estimate
Costs of treatment in remaining lifetime, dependent on health status (per year)	Good: € 26 Moderate: € 18,148 Poor: € 9713		Expert opinion and SCETIDE database: Good: once per 5 years immunologist + lab Moderate: once per 3 years immunologist + lab and 68% Ig Poor: yearly immunologist + lab and 36% Ig
Costs at end of life (per year, during last 5 years)	Good: € 0 Moderate or poor: € 6314 because of lung disease/malignant		Expert opinion; www.kostenvanziekten.nl and www.volksgezondheidenzorg.info
Productivity costs (additional sickness leave for SCID in comparison to general population)	Good: € 0 Moderate: €4208 × 25% Poor: € 0		Expert opinion: Good: no additional sick leave Moderate: 25% had a job, yearly sick leave 4 weeks of 30 h Poor: does not have paid work

62% after late detection of SCID [5, 12, 16]. Only one treatment possibility was included into the model, i.e., hematopoietic stem cell transplantation. Gene therapy is still in the experimental phase and not yet performed in the Netherlands, and Dutch children are seldomly referred abroad for this indication. Enzyme replacement therapy was excluded as a potential therapy as Dutch ADA-SCID patients receive HSCT to the same extent as other SCID patient types [11]. The outcome in terms of health after transplantation can differ. In consultation with clinical experts, three possibilities were defined: a good health status, in which an average age of 65 years is reached in a good quality of life (utility of 0.95); a moderate health status, in which an average age of 40 years is reached in moderate quality of life (utility of 0.75); and a poor health status, in which an average age of 25 years is reached in a lesser quality of life (utility of 0.5). Patients with a good health status were alive and well with no need for further surgery or immunoglobulin (Ig) treatment. Patients with a moderate health status were either alive and well with Ig therapy (42% within moderate group), alive with clinical symptoms without Ig therapy (32% within moderate group), or alive with clinical symptoms with Ig therapy (26% within moderate group). Patients with a poor health status were alive with sequelae without Ig therapy (64% within poor group) or with Ig therapy (36% within poor group) (data not published, SCETIDE database, Lankester et al.). In the Netherlands, approximately 25% of SCID patients experience grade 2–4 graft versus host disease (GvHD) after stem cell transplantation. This percentage is in line with the findings of Heimall and Cowan [15]. All patients with a poor health status suffered from GvHD,

whereas approximately 46% of the moderate health status group suffered from clinical problems due to GvHD (data not published, SCETIDE database, Lankester et al). It was assumed that a relatively larger part of the early detected SCID patients had a better outcome of the treatment (80% good, 15% moderate, and 5% poor) in comparison to later patients detected (50% good, 30% moderate, and 20% poor). The children diagnosed with non-SCID were not included in the effectiveness outcomes because of the uncertainty about the benefits. However, costs for their diagnosis and treatment were included in the calculations, subdivided into three variants of non-SCID (transient, idiopathic, and other).

Screening parameters

The percentage of children needing a retest on the same heel prick blood sample obviously depends on the cutoff value for the TREC test. In the literature, all children with SCID had less than 25 TREC/μl, so this cutoff value seems safe. It may even be possible to choose a lower cutoff value. At a cutoff value of < 20, 0.20% of all children needed a retest [1]. Therefore, our model value of 0.39% needing a retest is a conservative choice.

In some countries, NBSSCID is already implemented. The percentage of children needing a second heel prick blood sample because of prematurity or a low amount of β-actin in the first sample ranges from 0.08 to 0.41% [9, 19, 31, 33].

Van der Spek et al. [30] reported the percentages of screened children being referred for diagnostics from 16 studies using the TREC test. This varies between 0.01 and 0.14%. The cutoff values used in these studies varied, but there is no clear correlation between the cutoff value for the TREC test and the percentage of referrals. A baseline value of 0.08% was assumed.

Kwan et al. and Van der Spek et al. [20, 30] reported a sensitivity of 100% for finding SCID at a cutoff value of < 25 TREC/μl: no SCID patients were initially missed but later discovered.

Cost parameters

The cost of the TREC test was estimated at €4 per test plus €0.36 analytical support plus €0.35 for maintenance and depreciation costs, totaling €4.71 (expert opinion). As these costs are quite uncertain, in the sensitivity analysis a wide range of €3.50 to €5.50 is used. The cost of a retest in duplicate on the same blood sample is twice these costs. The cost of blood collection and logistics were not included for the first test and retests on the same sample, as heel prick blood samples are already processed for other screening purposes. In case a second heel prick sample is needed for SCID, costs are € 29.01, consisting of test costs and €24.30 for blood collection and sample processing.

Diagnostics for children who are referred after screening were expected to consist of a visit to the pediatrician (€102) and the cost of flow cytometry including a clinic visit (€396 + €102). In addition 2/3 of the children were assumed to need a second flow cytometry, and finally, 1/3 of the children also need genetic screening (€2000, expert opinion). This estimation is based on the follow-up protocol of the NBS SCID pilot. The protocol states that newborns with abnormal or low T cells and without HSCT indication will undergo additional immunological diagnostics such as a second flow cytometry test. In the situation without screening, the cost of diagnostics, consisting of a visit to the pediatrician, two flow cytometry tests, and a genetic test, were included for children with SCID. Children with non-SCID were expected to have the same costs of diagnostics as children with SCID both in a situation with and without screening. In addition, in a situation without screening, SCID will occasionally be suspected in children who do not appear to have SCID after further diagnostics. We have assumed that for each child with SCID, a tenfold number of children without SCID will be tested using flow cytometry.

The costs of transplantation have been investigated in France [10]. Transplantation after the age of 3 months resulted in much higher costs (€205,000) than earlier transplantation (€90,000), as late transplant patients often had active infections that contributed to high costs. A wide range of uncertainty in the sensitivity analysis was assumed.

Costs for non-SCID patients depend on the non-SCID variant. For temporary or transient non-SCID, costs of four flow cytometry tests, two CBCs (blood tests), five outpatient visits to an immunologist, and treatment with antibiotic prophylaxis were counted (in total € 2200), while for idiopathic and other forms of non-SCID, costs of 12 flow cytometry tests, two CBCs, 13 outpatient visits, and treatment with antibiotic prophylaxis have been taken (a total of € 6200) [12]. In the baseline analysis, we assumed that all these children would also have been found in a situation without screening and also had these costs. In contrast, the sensitivity analysis assumed that non-SCID children were not detected in a situation without screening.

Ding et al. [12] assumed that costs of treatment of a child with SCID who dies before transplantation are three times as high as the costs of transplantation after early detection. After consulting experts, this estimation seems too high. We assumed that these costs are only one and a half times the costs of transplantation after early discovery (€135,000).

The model also included the annual cost of treatment of SCID patients throughout the rest of their lives. Patients with a good health outcome after transplantation were assumed to visit the immunologist (€102) and have laboratory research (€26) once every 5 years. Patients with a moderate health outcome after transplantation had these costs once every 3 years. Moreover, 68% of them received immunoglobulin therapy of €26,600 per year. For patients with a poor health outcome, the costs of annual visits to the immunology and

laboratory research was included, and it was assumed that 36% of them received immunoglobulin therapy.

SCID patients with a moderate and poor health outcome after transplantation were also assumed to have extra care costs in the 5 years before their death due to for instance pulmonary disease or malignancies. These costs during the last 5 years amount to € 6000 a year (www.kostenvanziekten.nl; www.volksgezondheidenzorg.info).

In the sensitivity analysis, also productivity losses due to the absence of paid work from the SCID patients have been included using the friction cost method according to the Dutch guideline [18, 32]. The model assumes that SCID patients with a good health outcome after transplantation do not have additional absenteeism. Of SCID patients with a moderate health outcome after transplantation, 25% is assumed to have paid work, with productivity losses for 4 weeks a year, and on average have a working week of 30 h (expert opinion) and an hourly wage of €35 after indexation [17]. SCID patients with poor post-transplantation outcome were assumed to never participate in the workforce during their life, and according to the friction cost method no productivity costs were included for them.

Results

Base case analysis

The model assumptions resulted in an expected number of newborns with SCID of 1.72 per 100,000 newborns. In a situation with NBSSCID, all the SCID patients were assumed to be detected. In a situation without screening 0.34 infants with SCID would be detected due to a positive family history, the remaining 1.38 infants would be clinically diagnosed at a later stage. Additionally, 7.14 infants with non-SCID would be detected.

Due to earlier detection the number of deaths due to SCID per 100,000 newborns was assessed to decrease from 0.57 to 0.23 newborns and a number of 11.7 QALYs gained (discounted) was expected.

In the base case analysis total costs of screening and diagnostics were €578,200 per 100,000 newborns higher than in a situation without screening (see Table 2).

Treatment costs of SCID patients were € 187,400 lower in a situation with NBSSCID compared to a situation without screening. This was the result of lower number of infants with SCID who die before definitive treatment (€29,800), a shift from late to early transplantation resulting in lower transplantation costs (€ 103,900) and in an improvement in health status during remaining lifetime associated with lower costs (€53,700). In the base case analysis no difference in costs of treatment of non-SCID patients was assumed between a situation with NBSSCID and without screening.

Total healthcare costs, including costs of screening, diagnostics, and treatment, were, respectively, €390,800 higher in a situation with NSBSCID compared to a situation without screening. Dividing the difference in these costs by the 11.7 QALYs gained, resulted in a cost-utility ratio of €33,400 per QALY gained.

Sensitivity analysis

In the univariate sensitivity analysis, we changed base case parameters with the minimum and maximum values presented in Table 1. Incidence of SCID, the percentage of infants with flow cytometry in a situation of screening, costs of the screening test, costs of late treatment, and survival after late treatment have the largest impact on the cost-effectiveness estimates (see Fig. 1).

Including all parameters together in a multivariate sensitivity analysis leads to a worst case scenario of €230,000 per QALY for a situation with NBSSCID compared to a situation without screening, while in the best case scenario, newborn screening will lead to both cost savings of €211,300 and a gain in quality of life of 28.7 QALY per 100,000 infants.

Two additional sensitivity analyses on the discount rate and perspective of the cost-effectiveness analysis were performed. Using the discount rates from the Dutch guideline for economic evaluation [33] of 4.0% for costs and 1.5% for effects results in a cost-effectiveness ratio of €23,000 per QALY gained.

Broadening the healthcare perspective towards a societal perspective by including productivity costs of SCID patients using the friction cost method did not lead to changes in the cost-effectiveness ratio.

Discussion

A cost-effectiveness ratio of €33,400 per QALY gained was found for adding newborn screening for SCID. This estimate was based on literature data and expert opinions. This might be acceptable for several European countries, given their (explicit or implicit) threshold for the willingness to pay per QALY [6, 26]. As shown in the sensitivity analysis there is still a lot of uncertainty around the cost-effectiveness of newborn SCID screening. To reduce this uncertainty further research is needed, especially on the incidence of SCID, the percentage of infants with flow cytometry in a situation of screening, costs of the screening test, costs of late treatment, and survival after late treatment.

Our results are comparable with the results of Chan et al. [7] and Ding et al. [12] of, respectively, €31,930 per QALY gained and €34,672 per life-year gained (in 2016 €), despite several differences between the models. We extended the model of Ding et al. by not only including the life-years

Table 2 Healthcare costs per 100,000 infants in a situation with and without newborn screening for SCID (2016 €)

	Situation with NBSSCID	Situation without NBSSCID
Cost of screening and diagnostics	609,800	31,600
Test and retest (if necessary)	474,700	n.a.
Second heel prick	7200	n.a.
Flow cytometry and genetic testing	127,900	31,600
Cost of SCID treatment	269,000	456,400
Costs of infants who die before Tx	14,000	43,800
Transplantation costs	145,900	249,700
Long-term treatment costs	109,100	162,900
Cost of non-SCID treatment	42,300	42,300
Total healthcare costs	921,100	530,300

gained of infants that will not die prematurely due to SCID but also by assuming a better quality of life as a result of earlier transplantation. Furthermore, parameters were adapted to values that are assumed applicable to the Dutch situation, including lower treatment costs. McGhee et al. [21] found a cost-effectiveness ratio of $53,560 (i.e., €67,290) per QALY. It is not entirely clear where this difference stems from as the description of their modeling results is quite limited. However, the assumed high costs of IVIG treatment for 65% of the patients may be a contributing factor. For the Dutch situation, the percentage of SCID patients with Ig treatment was assumed to be lower, approximately 25% (data not published, SCETID-database, Lankester et al.).

In addition to the previous studies the perspective was broadened from a healthcare perspective into a societal perspective in the sensitivity analysis, by adding productivity costs using the friction cost method. If the human capital method would have been used instead also the productivity loss of patients with a poor prognosis, which were assumed to never participate in the workforce during their life, would have been included. As the number of patients with a poor prognosis would be lower as a result of newborn screening, this would have led to more favorable cost-effectiveness results. The perspective could be broadened further by also including informal care in the analysis. This would also lead to more favorable cost-effectiveness results due to less informal care needed as result of better health states after early detection.

For the Dutch situation, in which differential discounting of 4.0% for costs and 1.5% for effects should be used according to the guideline for conducting economic evaluations in health care [15], a cost-effectiveness ratio of €23,000 per QALY was obtained, which is close to the €20,000 per QALY that is deemed to be acceptable for prevention [28]. A pilot study on the implementation of SCID to reduce the current uncertainty around the costs and effects of SCID screening is therefore warranted.

In this pilot, also potential detrimental effects that are not included in the current analysis should be studied. A detrimental effect of screening programs is that part of the infants with a positive screening test will be found to have a false-positive screening result after further diagnostic testing or even after

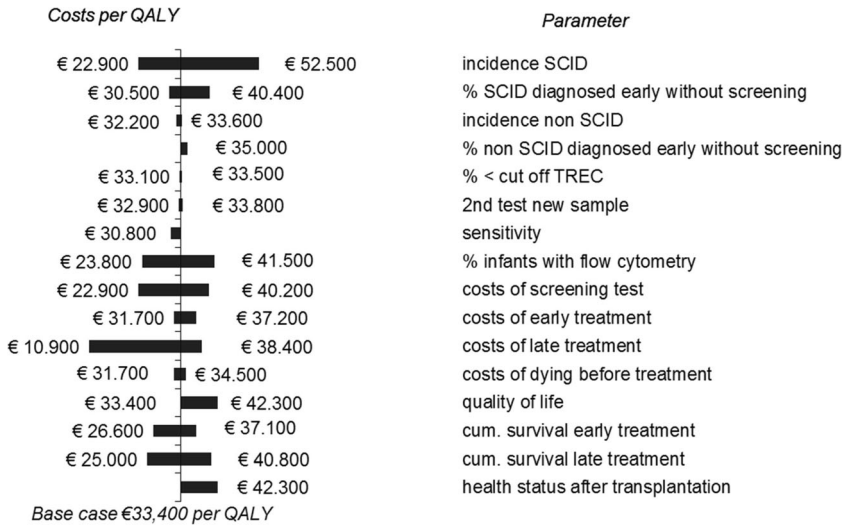

Fig. 1 Univariate sensitivity analysis: cost-effectiveness ratio (cost per QALY) for minimum and maximum values of the input parameters

longer follow-up. The parents of these infants have been made unjustly worried, and this may even remain after reassurance by their physicians. This has been found in other screening programs, even in case of non-life-threatening diseases as for example newborn hearing screening [29].

In our analysis model parameters were partly based on literature estimates on SCID. As SCID can be viewed as a heterogeneous group of primary immunodeficiency disorders that have varying manifestations and prognoses, this means that we implicitly assumed that the composition of the SCID populations from the literature is also representative for our setting. If more specific data will become available for the different types of SCID, this can be used to further improve the model. Similarly, transplant methods and donor types may affect clinical outcomes and costs [15, 16]. By using data from literature for our estimates, we implicitly assumed that these are also representative for our setting.

Developments in gene therapy in children with SCID [2] may change the cost-effectiveness of NBSSCID. Cost of this one-time therapy is high but it is likely to provide important clinical benefits. The use of autologous cells abolishes the risk of rejection and graft-versus-host disease, and as high-dose conditioning is no longer indicated, treatment-related organ toxicity is diminished [14]. If gene therapy is becoming clinical practice, and its costs and effectiveness are more clear, this should be added in the cost-effectiveness analyses of NBSSCID.

In conclusion, based on literature data and expert opinion newborn screening for SCID we found that SCID screening might be cost-effective. However, there is still a lot of uncertainty around this estimate. Pilot screening projects are warranted to obtain more accurate estimates for the European situation.

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Authors' contributions Kitty Van der Ploeg contributed to the study design, conducted the literature search and interpretation into model parameters, contributed to the model development and analyses and interpretation of the results, and prepared and reviewed the manuscript.

Maartje Blom contributed to the literature search, data collection and interpretation, and critically reviewed the manuscript.

Robbert Bredius contributed to the study design, data collection and interpretation, and critically reviewed the manuscript.

Mirjam van der Burg and Peter Schielen contributed to data collection and data interpretation, and reviewed the manuscript.

Paul Verkerk contributed to the study design, interpretation of the study results, and critically reviewed the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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