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Clinical and economic aspects of newborn screening for severe combined immunodeficiency: DEPISTREC study results

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ABSTRACT

Purpose: Severe combined immunodeficiency (SCID) refers to a group of genetic disorders characterized by greatly compromised cellular and humoral immunity. Children with SCID are asymptomatic at birth, but they die from infections within the first months of life if not treated. Quantification of T-cell receptor excision circles is an extremely sensitive screening method for detecting newborns who may have SCID.The goal of the DEPISTREC study was to evaluate the feasibility of nationwide newborn screening for severe T-cell lymphopenia in France as well as its economic and clinical utility.

Methods: The test universally used for neonatal screening for SCID was the quantification of TRECs on Guthrie cards. We compared a group of 190,517 babies from 48 maternities across the country who underwent newborn SCID screening with a control group of 1.4 million babies out of whom 28 were diagnosed with SCID without such screening during the course of the study.

Results: Within the screening group, 62 babies were found to be lymphopenic, including three with SCID. The cost of screening ranged from 4.7€ to €8.15 per newborn. The average 18-month cost was €257,574 vs €204,697 in the control group.

Conclusions: In this large-scale study, we demonstrate that routine SCID screening is feasible and effective. This screening offers the additional benefit of aiding in the diagnosis of non-SCID lymphopenia. Economic evaluation allowed us to calculate the cost per test. Newborn screening may also prevent death by SCID before any curative treatment can be administered. The difference in cost between screened and control children could not be ascertained because of the very low numbers and death of one of the children tested.

Abbreviations: ADA, Adenosine Deaminase; DBS, dried blood spot; SCID, severe combined immunodeficiency; TREC, T-cell receptor excision circle; HSCT, Hematopoietic Stem Cell Transplantation; NBS, New Born screening

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1. Introduction

Severe combined immunodeficiency (SCID) encompasses a group of genetic disorders characterized by greatly disabled cellular and humoral immunity. Although children with SCID are asymptomatic when born, they die from infections within the first months of life without treatment and are very vulnerable to secondary infections associated with the injection of live vaccines. Curative treatment options consists of allogenic hematopoietic stem cell transplantation (HSCT) or gene therapy. Enzyme replacement therapy is a mainstay therapy for patients with ADA deficiency. The latest studies suggest an estimated SCID incidence of one out of 58,000 live births. SCID meets criteria for newborn screening (NBS): affected children are asymptomatic at birth; treatments are available; children die before the age of one year if not treated, and the chance of survival is higher if treatment is received before three and a half months of age (96% survival rate, versus 66% if treatment administered when the child is older), and before any infection [1,2].

Diagnosis of SCID before symptoms develop allows for rapid provision of medical care (i.e. anti-infectious prophylaxis) in preparation for curative treatment. Early care and treatment result in greater HSCT success, a higher chance of survival, and fewer complications—hence less secondary medication—and better quality of life.

Screening for SCID through quantification of T-cell receptor excision circles (TRECs) was described in 2005. This method relies on Guthrie card dried blood spot (DBS) samples. TRECs are DNA rings formed in the process of T-cell receptor (TCR) rearrangement during T-cell maturation. Thus TREC quantification is an indicator of thymic output of mature T-cells [3,4]. As the absence of TRECs reflects severe T-cell lymphopenia, TREC quantification is an extremely sensitive screening method for identifying children who may have SCID. Diagnosis is later confirmed by studying lymphocyte subsets and performing a genetic analysis.

Given the low incidence of the disease, the unit cost of a test is the key component for cost analysis of a screening strategy. The expected benefits included reduced mortality and morbidity as well as potential cost savings resulting from earlier diagnosis and treatment. Decision-analytic models support the case for universal screening [5–7], which has been implemented in several States/ regions in the USA, Canada, Israel, Sweden, Germany, Spain [8,9].

Here we report the results of a study financed by the French Ministry of Health evaluating the feasibility of routine newborn SCID screening in France and its economic and clinical utility. The study compared a group of infants undergoing SCID screening to a control group of children diagnosed with SCID without such screening.

2. Methods

2.1. Screening group

This group included 190,517 newborns from 48 maternities across France. Forty eight French maternity hospitals, with > 2000 deliveries per year participated to this study. They were spread throughout the country.The protocol was integrated into the existing newborn screening routine. As in other European countries and the USA, the newborn blood spot test involves taking a small sample of baby's blood to screen it for rare but serious health conditions. Two additional drops of blood from each child were deposited on Guthrie cards after at least one parent gave informed consent. Samples were sent by the regional testing associations to one of the two laboratories participating in the study for further analysis. The choice of laboratory depended on where a sample was acquired. If the result was positive for a preterm baby, or inconclusive for a baby born at term, an additional sample was requested (Fig. 1). In either case, ie positive for a newborn at term, or positive again for a preterm newborn, prompted scheduling of an appointment with the local primary care paediatrician for clinical evaluation and additional analyses was organized. T-cell lymphopenia were classified according to their origin (Table 1).

Data for this group of 190,517 infants made it possible to determine the screening cost, percentage of patients recalled due to positive or inconclusive results, follow-up rate, turnaround for receiving results, incidence of the disease, and the number of non-SCID lymphopenia cases detected. They also revealed the frequency of false positives and the specificity of the screening method.

2.2. Control group

The control group consisted of all children born in France during the study period (December 2014 to February 2017), excluding those born in the 48 screening group maternities. Within the control group, 28 children were diagnosed with SCID without recourse to TREC screening. They were identified by primary care paediatricians participating in the DEPISTREC study or through the French registry of primary immunodeficiencies (CEREDIH). Only after their diagnosis with SCID was DBS TREC analysis requested. In addition, the DBS collected from each at birth, for other screening tests, was recovered and analysed whenever possible.

2.3. Biological analysis

The TREC analysis was based on a commercial kit from PerkinElmer (Enlite™ Neonatal TREC kit, Turku, Finland).

TREC results are expressed qualitatively and depend on the assigned cut-off value. Fig. 1 summarizes the test interpretation guidelines applied.

2.4. Economic evaluation

The prospective economic evaluation was conducted from the healthcare perspective to determine the cost of systematic screening compared to usual care over an 18-month period. Both hospital and non-hospital resources (for screening) were considered. Screening costs were obtained with a bottom-up microcosting approach that identified all relevant cost components of the screening and diagnosis process and valued each component using duration of the test, staff, supplies, number of recall and consultations as variables. Cost per test was calculated by dividing the total per test run by the number of tests (3×78) per run.

Patient-level diagnosis related groups (DRG) for all hospitalization (including episodes of severe infections) from the date of delivery up to 18 months were retrieved for both screened and control babies, using record linkage to ensure data exhaustively for both cases and controls.The analysis represented healthcare system costs as limited to the provision of hospital treatments. We used the DRG-specific daily costs and the actual length of stay to estimate patient-specific costs for neonatal and pediatric intensive care units and pediatric hematology wards for each admission. Expensive medications prescribed or delivered by hospitals were included. All costs are in 2018 Euros (€) (1US $ = 0.83 €) € and not discounted.

Costs were estimated for the entire population in each group and by type of allograft. We also analysed costs by vital status, and age at transplant.

The minimum sample size was calculated to identify at least 1 SCID in the screening group and was based on prevalence data from the literature (1/70,000 newborns) assuming a Poisson distribution. The sample size was calculated using the nQuery 7.0 (Statistical Solutions, Ltd., Cork, Ireland) software.

Statistical analyses were performed according to a pre-specified statistical analysis plan (SAP reference). Variables are described using means with standard deviations or raw numbers and percentages. SAS

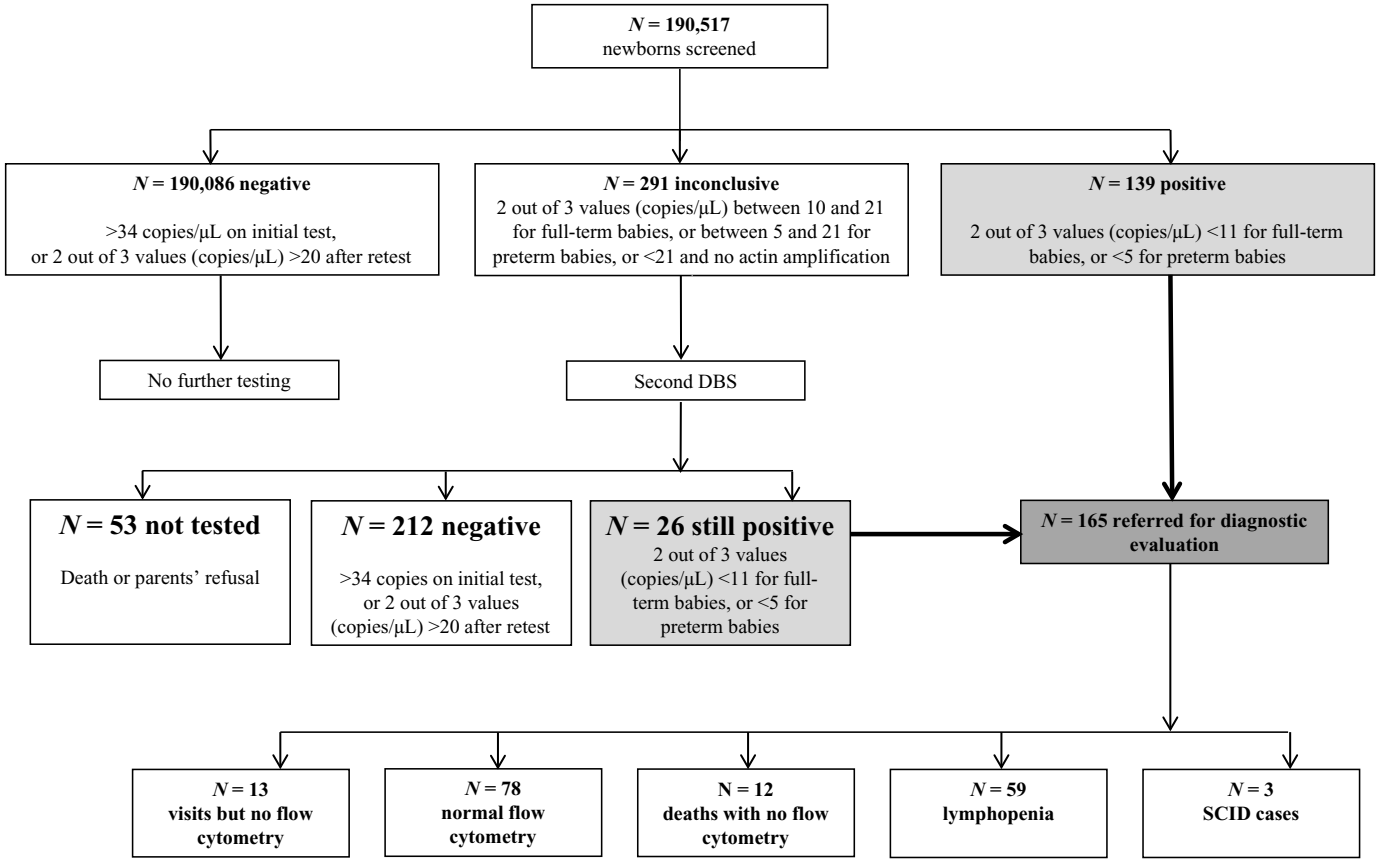

Fig. 1. Decision-making algorithm and flow diagram for screened samples.

Table 1
Lymphopenia classification.

Category	Definition
SCID	Persistent lymphopenia; < 300 autologous CD3+ T-cells/μL.
Leaky SCID and Omenn syndrome	300–1499 autologous CD3+ T-cells/μL; associated with a genetic defect in a known SCID gene. Omenn syndrome includes erythroderma, hepatosplenomegaly, eosinophilia, and oligoclonal T-cells.
Variant SCID (T-cell lymphopenia)	300–1499 autologous CD3+ T-cells/μL; functional T-cell impairment; no defect in known SCID genes.
T-cell impairment syndrome	Genetic syndrome that includes impairment within its spectrum of clinical findings, e.g. DiGeorge syndrome or Down's syndrome.
Secondary T-cell impairment	Presence of congenital malformation or disease process that causes greater loss of T-cells, e.g., congenital cardiac defects, gastroschisis, intestinal lymphangiectasia, or hydrops.
Preterm alone	Preterm infants with no preexisting conditions who have low T-cell levels.

(Version 9.3, SAS Institute, Cary, NC) was used for statistical analysis. Cost data are reported as means, standard deviations in the control group and ranges.

3. Results

3.1. Efficacy of method of biological analysis

The efficacy of the method of biological analysis is described elsewhere [10]. In summary, for our study, test sensitivity for SCID detection was 100% and specificity was 99·92%. Mean turnaround for results—that is, average time elapsed between date of birth and availability of test results—was 14·5 days (median: 14 days).

The median length of time between an initial positive result and patient recall was 18 days. The median length of time between date of birth and an initial appointment for a child presumed to be positive was 26 days (24 days for an appointment following analysis of the first DBS; 41 days for one following analysis of an additional DBS). The follow-up rate—that is, the percentage of children for whom the entire screening procedure was completed—was 99·99%. We observed a higher frequency of false positives for preterm babies, i.e.:1·36% of all children born before 37 weeks of gestation—but only 0·23% of the entire screened group—were recalled for an additional DBS or appointment.

3.2. Screening group clinical analysis

Between 3 December 2014 and 4 February 2017, 190,517 children were included in this group, results for which are shown in Fig. 2. A total of 291 children were recalled for an additional DBS; 165 were considered positive and examined during appointments.

Of the 62 identified lymphopenia cases, three were confirmed as SCID through genetic analysis (*IL2RGγ, RAG2, gene unknown*). The child with gene *unknown* mutation died at 6 months of age, after two failed HSCTs. She had systemic neonatal infection from her date of birth, likely reflecting the fact that her SCID phenotype included permanent and G-CSF- resistant agranulocytosis (0 PMN/μL of blood from birth

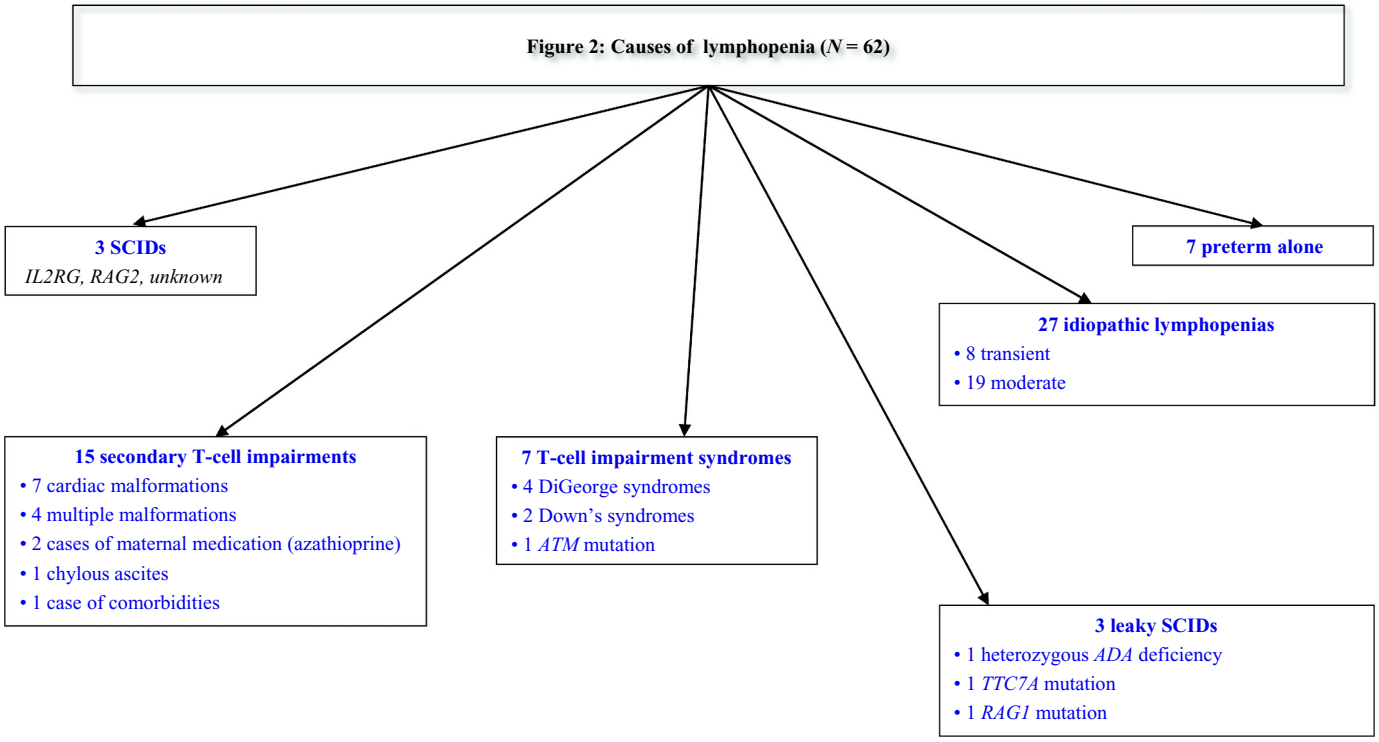

Fig. 2. Causes of lymphopenia.

onwards). Despite multiple lines of anti-infectious therapy and two HSCT attempts, infection could not be controlled and eventually led to death.

The *IL2RG* mutated patient has a familial medical history of SCID. The mother was aware of the diagnosis since an antenatal diagnosis has been performed. An intra-familial donor was identified with the foetus's HLA typing. A toxoplasmic seroconversion occurred during the pregnancy, and an in utero transplant was achieved at 26 weeks of gestation. The DEPISTREC test was performed at birth, at term. The TREC analysis was abnormally low. The analysis of blood lymphocyte population highlighted a progressive reconstitution after the birth. At 18 months of age, results of clinical examination and immune testing were normal and postvaccine serology was positive, no other therapy being administered.

Fig. 2 summarizes causes of the lymphopenias. Three children were diagnosed with leaky SCIDs associated with genetic anomalies: respectively, a heterozygous *ADA* pathogenic variant; compound heterozygous *RAG1* mutations; and a compound heterozygous *TTC7A* mutation. Seven children were diagnosed with T-cell impairment syndromes, including DiGeorge syndrome (four cases), Down's syndrome (two cases), and ataxia telangiectasia (one case). In the secondary T-cell impairment group, there were two neonatal cases associated with maternal azathioprine medication, including one severe, prolonged case (three months). We showed that the latter baby was homozygous for the *TPMT*3A* mutant allele [11]. This group also included cardiac malformations (seven) and malformations with lymphangiectasia (four). Of the 27 babies diagnosed with lymphopenia of unknown origin, later testing revealed that eight had reached normal lymphocyte counts in the meanwhile (six babies by one month, one by two months, and one by three months) while 19 remained moderately lymphopenic (i.e. 1500–2500 $CD3^+$ lymphocytes/μL).

3.3. Clinical analysis of the control group

As stated above, 28 control group children (16 boys, 12 girls) were diagnosed with SCID during the study without TREC screening. They were included by paediatricians involved in the DEPISTREC study as investigators or through CEREDIH. The age at time of SCID diagnosis ranged from 0 to 21 months (mean: 5·6 months; median: 4·5 months). Three children (nos. 5, 13, and 34) were diagnosed during the neonatal period on the basis of family history. Genetic causes were identified in 27 cases. We analysed DBS samples (collected at birth) for 21 of the 28 SCID control children. TREC test results for all these samples were positive. Thus a very early diagnosis would have been possible for these infants.

In all, 20 children (out of 28) underwent HSCT, and they are all alive and well. The age at the time of transplantation ranged from 1 to 20 months (mean: 7·1 months; median: 6·4 months). Three children initiated ADA enzyme replacement therapy. Five children (nos. 28, 29, 30, 31, and 33) died before they could undergo HSCT, all from severe infections (RSV, CMV, adenovirus, norovirus, nocardia, or *Pseudomonas aeruginosa*). For these five children, the age at time of SCID diagnosis ranged from 2·4 to 11·9 months (mean: 5·7 months). The mean age at death was 7 months. Table 2 summarizes the data for the 28 SCID control children.

3.4. Economic evaluation

3.4.1. Calculation of mean cost of testing and diagnosis as a function of total number of tests to perform

The cost of diagnosis per newborn varied with the volume of laboratory work and the price of consumables (reagents), ranging from €4.70 (for the lowest discounted price of reagent) to €8.15 (catalogue price). The total cost of testing 190,517 babies could be therefore estimated between €900,000 _to €1.5 million. Fig. 3 shows the variation in screening test cost as a function of total test volume, assuming equipment is used almost exclusively for screening purposes. Equipment and personnel costs to perform testing are described in Table 4.

Complete data on the 18-month follow up was available for the 2 children with confirmed SCID in the screening group and 26 in the control group. The third child screened was excluded from the economic study because of an in utero transplant.

Table 2
Control group characteristics and outcomes.

ID no.	Age at time of diagnosis (days)	Treatment	Age at time of HSCT (days)	HSCT	Genetics	Outcome
1	16	HSCT	57	genoidentical	*RAG1*	AW
2	40	HSCT	129	phenoidentical	*RAG1*	AW
3	430	HSCT	594	phenoidentical	*LIG1*	AW
4	107	HSCT	144	genoidentical	*ADA*	AW
5	3	HSCT	28	genoidentical	*JAK3*	AW
7	387	HSCT	496	genoidentical	*RAG1*	AW
8	115	HSCT	178	haploidentical	*JAK3*	AW
9	631	pegademase	NA	NA	*ADA*	AW
10	11	pegademase	NA	NA	*ADA*	AW
12	208	HSCT	266	phenoidentical	*JAK3*	AW
13	6	HSCT	57	phenoidentical	*RAG2*	AW
15	160	HSCT	199	haploidentical	*IL2RG*	AW
16	28	HSCT	100	haploidentical	*CD3E*	AW
17	90	HSCT	114	genoidentical	*IL2RG*	AW
18	172	HSCT	192	genoidentical	*JAK3*	AW
19	221	HSCT	287	UCB	*JAK3*	AW
22	206	HSCT	249	UCB	*JAK3*	AW
23	135	HSCT	193	UCB	*JAK3*	AW
24	129	HSCT	194	phenoidentical	*IL2RG*	AW
25	213	pegademase	NA	NA	*ADA*	AW
26	138	HSCT	198	UCB	*DCLRE1C*	AW
28	130	NA	NA	NA	*IL2RG*	died
29	161	NA	NA	NA	*DCLRE1C*	died
30	136	NA	NA	NA	*ADA*	died
31	357	NA	NA	NA	*PNP*	died
32	441	HSCT	558	phenoidentical	*RAG1*	AW
33	72	NA	NA	NA	ND	died
34	7	HSCT	56	phenoidentical	*DNAPK*	AW

AW: alive and well; HSCT: hematopoietic stem cell transplantation; NA: not applicable; ND: not determined; UCB: unrelated cord blood.

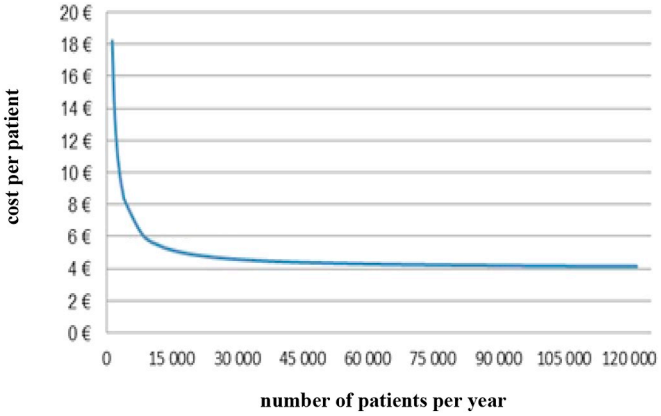

Fig. 3. Mean test cost as function of total number of tests.

The total number of transplants in the screening group was three because of the two procedures performed in the baby with the *unknown* mutation. In the control group, 21 survivors were treated with allograft (18 children) or PEGADA (3 children) and five babies died before allograft. The average 18-month cost was €257,574 in the screening vs €204,697 in the control group. The average 18-month cost for the three patients treated with PEGADA was €157,760. Results are summarized in Table 3 and Table S1.

In summary, the main cost driver was the unit cost of the test, followed by the rate of false positives leading to retest and possibly consultations. The pre-per post-transplant split of the costs is presented in Table S1. We found no reduction in pretransplant costs in the screening group (Table S1). In the control group, the median age at transplant was 6.4 months. The age at the time of transplant was not found to predict total costs, early transplant (up to 3 months) costs were on average

Table 4
Equipment and personnel costs to perform testing.

Item	cosyt
Equipment total	44,273 €
Supplies per year	5480 €
Consummables per test	3 €
Personnel per test	1€
Depreciation (over 5 years)	4%
Maintenance per year	10%

Table 3
18-month resource utilization and costs (€) for screening and control groups.

Variable		Screening group (N = 2)	Control group (N = 26)
Number of admissions per patient		21	13.5
Total number of HSCT procedures		3	18
Mean total days per patient (std) [range]		190 (NA) [176;203]	137 (75) [36;283]
Mean total 18-month cost per patient (std) [range]		257,574 (NA) [246,503; 268,644]	172,664 (101,110) [26,366; 361,534]
Mean total 18-month cost per patient in control group, excluding 3 pegademase patients (std) [range]		NA	204,697 (N = 18)
HSCT	Haploidentical	246,503	242,603 (N = 4)
	Phenoidentical	NA	170,839 (N = 10)
	Cord blood	268,644	251,436 (N = 4)
Deceased		246,503 (N = 1)	52,894 (N = 5)

HSCT: hematopoietic stem cell transplantation; NA: not available.

€200,483 compared to €212,789 after 3 months. We studied the contribution of infection to total costs. Both screened babies had pre transplant infections; in the control group, 5/18 babies had pre transplant infections. The 18 month cost of patients with pre transplant infection (N = 7) compared to patients without infection (N = 13) was €237,083 vs €211,096.

4. Discussion

This is the first large-scale prospective French study of newborn SCID screening with a Neonatal TREC kit.

When validating the test method, our analysis showed kit performance was comparable to that claimed by the supplier and to that reported by researchers in other countries (Netherlands and United Kingdom) [12,13]. We also showed that preterm infants had lower TREC levels than those born at term. Nevertheless, we do not believe that the recall rate for preterm children (1·36%), though higher than for the general infant population (0·23%), requires a change in test cut-off values.

The findings of our clinical analysis largely overlap those in the literature: SCID incidence was one out of 58,000 in the 2014 US study and one out of 63,000 in this study. We determined that cases of non-SCID lymphopenia in our study had their origin in secondary causes (e.g. heart defects and chylous effusions) and congenital genetic disorders (i.e. DiGeorge syndrome; Down's syndrome; and mutations in *TTC7A*, *RAG1*, and *ATM*, three genes involved in primary immunodeficiencies) [14,15]. In addition, our study revealed the role of medication taken by the mother during pregnancy: one infant whose mother had taken azathioprine for an intestinal inflammatory disease suffered from severe lymphopenia for three months [10]. We have shown elsewhere that the median TREC level was lower in HIV-exposed uninfected newborns than in children of the general population, especially among newborns whose mothers were on zidovudine during pregnancy [16].

If newborn screening for severe T-cell lymphopenia were routine in France, 25 of the 28 control group patients diagnosed with SCID without screening would have directly benefited (3 had family history of SCID). All transplanted patients from the control groups are alive. It is remarkable to observe that 5 patients died because they were diagnosed late and did not reach in time a dedicated HSCT unit. This is exactly the point made showing that newborn screening would have detected them, leading to implementing early likely a life saving HSCT procedure that would have also spare a significant amount of medical costs.

The patient who presented with neonatal onset had a phenotype combining agranulocytosis designated in the literature as reticular dysgenesis (RD). Most of the patients with RD carry biallelic mutations in the adenylate kinase 2 gene which was not the case in this patient. It happened that this child was multi infected (bacterial and fungal sepsis from birth), infections that could never been controlled despite very aggressive therapy, leading to her ultimate death. Because of day 1 infection and immunological phenotype, the diagnosis would not have been missed – unlike what happened for the 5 patients of the control group -. This is why it is an unusual case, that overall accounts for < 1% of SCID cases.

This study also provided an economic evaluation, calculating the mean cost of testing and diagnosis as a function of the total number of tests performed. The total cost of screening was not offset by the reduction in transplant costs in the screened group. This result must be considered in the light of the low number of patients in the screened group. The phenotype of T-cell lymphopenia associated with agranulocytosis, as observed in the *RAC2* deficiency case, is extremely unusual among SCID patients (< 1% of all cases) [17]. Newborn screening is not useful in such cases because patients are symptomatic from birth.

The 18-month cut-off was necessary for the purposes of the clinical study but a longer follow-up would have more accurately represented the higher costs for two control group patients whose grafts were delayed.

We did not undertake the cost effectiveness analysis initially planned. Trial-based analysis proved to be of little value as there were few patients in the screened group. Mortality in the group may actually have been higher, as suggested by the death of the *unknown gene* mutated baby.

The presence of this extremely rare disease in our screened group was not anticipated. Estimate of a more accurate mortality rate in the screened group would have required a longer period of inclusion and more funding, which conflicted with the requirements from the authorities in charge of screening approval. This is an instance where model-based studies prove a very useful complement to trial based studies.

Model-based studies suggest that SCID screening is cost-effective. In a 2005 article, McGhee et al. argue routine newborn SCID screening is beneficial to public health. They calculate its cost to be $53,860 per quality-adjusted life year (QALY), or about €40,000 per year of life gained [7].

In 2011, Chan et al. applied a Markov model to extrapolate the cost-effectiveness of a nationwide American SCID programme from data for a test population in five US states [5]. Estimating a screening cost of $4.22 per child, they conclude that newborn SCID screening would probably be a cost-effective means of enhancing and extending the lives of sick children.

More recently, Yao Ding's model for evaluating cost-effectiveness and net benefit argues strongly in favour of implementing a programme of routine newborn SCID screening through DBS TREC analysis in the State of Washington [18].

5. Conclusions

Our study confirms the feasibility of routine newborn screening for severe T-cell lymphopenia in France. The screening test could be performed neonatally using DBS samples, alongside other screening tests. Offering high sensitivity and high specificity, TREC assay seems appropriate for such a programme, as long as test validation rules and guidelines for interpretation are clearly established.

We identified three SCID cases through screening, confirming an incidence of approximately one out of 60,000. Moreover, we detected 59 cases of non-SCID lymphopenias, demonstrating the test's usefulness for diagnosing most of these illnesses.

Five children in the control group died from SCID before they could receive HSCTs. Neonatal screening would undoubtedly have saved their lives by allowing earlier treatment.

The economic evaluation revealed that the main cost determinants are incidence and price per test. Our study allowed us to calculate incidence and provides information for evaluating budgetary impact. If the costs of screening were added, a 5€ test would add one million€ to the screening strategy or 500,000€ to the cost of each baby screened in our study. This disappointing economic result is due to the one very severely ill baby in the screening group, and should be weighted by results from modeling studies which use distributions instead of point estimates for the costs of treatments.

The inclusion of SCID testing in recommended routine screening programmes for France and other European countries should be considered.

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Authorship contributions

Conception and design of the study: MA, SM, CT, CD, VS, IDZ, AF, NM.

Acquisition of data: MA, CT, DC, CP, AL.

Analysis, interpretation of data: MA, CT, AL, AF, MR, NM.

Economic evaluation: IDZ, JF, HR, VPR.

Declaration of interests

The authors declare no competing interests.

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