# Newborn Screening for Severe Combined Immunodeficiency. The Time Is Now

João Farela Neves[1,2], Isabel Esteves[3]

Port J Pediatr 2019;50:257-9
DOI: https://doi.org/10.25754/pjp.2019.18525

It is well established that the use of population-based newborn screening (NBS) for common or rare genetic diseases enables early detection. Therefore, it is a very useful tool for preventing morbidity and mortality associated with those diseases. Over 50 years ago, Robert Guthrie proposed for the first time the use of NBS for the early detection of phenylketonuria, and in 1968, the 10 principles that are still used to guide the selection of suitable candidates for NBS were published.[1] The successful history of NBS in Portugal goes back to 1979, when phenylketonuria was the first disease to be successfully screened. Two years later, congenital hypothyroidism was added to the NBS and, thanks to the generalization of mass spectrometry, over 23 other metabolic diseases and also cystic fibrosis have been added to the routine NBS in our country.[2]

Severe combined immunodeficiency (SCID) is a heterogeneous group of very rare diseases with an estimated incidence of 1:40,000-58,000 newborns, depending on the degree of consanguinity of the population.[3,4] They are the most severe forms of primary immunodeficiencies, and encompass a group of genetic disorders that lead to the absence or dysfunction of T, B, and sometimes NK cells.[4] Children born with SCID are usually well at birth, and subsequently develop a failure to thrive, chronic diarrhea, and recurrent infections caused by parasites, fungi, viruses, or bacteria.[5] An additional risk is the administration of live vaccines in the asymptomatic period, such as bacillus Calmette-Guerin (BCG) or rotavirus, which can cause vaccine-associated life-threatening conditions.[4,5] Eventually, until the age of 2 years, every patient with this disease succumbs to death unless timely curative treatment is given: an allogeneic hematopoietic stem cell transplantation or, in some selected cases, gene therapy.[6] The outcome of hematopoietic stem cell transplantation is clearly dependent on the age of the child at the time of the transplant, as this is directly related to the probability of having an active infection. In fact, a child affected with SCID who receives hematopoietic stem cell transplantation before the age of 3.5 months has a 94% probability of being alive five years after the procedure. If the transplant occurs after that age, the probability decreases to 50% if they have an active infection and 82% if they have an infection that has resolved before the hematopoietic stem cell transplantation.[7] This highlights the importance of establishing an early diagnosis.

A 15-year (2000-2014) retrospective analysis of all the diagnosed SCID patients in Portugal was presented in 2016 (Isabel Esteves et al., unpublished data). The analysis included 29 children diagnosed with SCID in that period, corresponding to an estimated incidence of 1:43,500 newborns, meaning that the majority of the SCID cases were probably not missed in our country in that period. On the other hand, most children were diagnosed very late in life, with a mean age at diagnosis of 6.9 months (median 5 months). This means that most patients (70%) were already struggling with an active infection, in most cases a viral infection but some already with bacterial sepsis or disseminated BCG-osis. Moreover, the time from diagnosis to transplant (mean 3.2 months, median 2.1 months) also needs to be improved, but with the recent increase of the capacity of the bone marrow transplant units, this will not be an issue in the years to come. Having said that, it is not surprising that the overall survival rate of 40% in the Portuguese cohort is, in our view, unacceptably low. At a time when NBS for SCID is being implemented all around the globe (in 48 states of the United States of America, Israel, Taiwan, Switzerland, Norway, and pilot projects in Spain, Italy, the Netherlands, Sweden, Finland, and France),[8] the inclusion of SCID in the national NBS program in Portugal has to be addressed.

When we look into the Wilson and Jungner principles for screening programs,[1] it is clear that SCID fulfills every single criteria,[9] as detailed below:

1. The condition sought should be an important health problem.

1. Primary Immunodeficiencies Unit, Hospital Dona Estefânia, Centro Hospitalar e Universitário Lisboa Central, Lisbon, Portugal,
2. CEDOC, Chronic Diseases Research Center, NOVA Medical School, Lisbon, Portugal
3. Pediatric Infectious Diseases Unit, Pediatrics Department, Hospital de Santa Maria, Centro Hospitalar e Universitário Lisboa Norte, Lisbon, Portugal
**Corresponding Author**
João Farela Neves
joao.farelaneves@gmail.com
Pediatrics Department, Hospital Dona Estefânia, Centro Hospitalar e Universitário Lisboa Central, Rua Jacinta Marto, 1169-045 Lisbon, Portugal,
Received: 23/08/2019 | Accepted: 02/09/2019 | Published: 01/10/2019
© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use.

2. There should be a recognizable latent or early symptomatic stage.
3. The natural history of the condition, including development from latent to declared disease should be adequately understood;
4. Case finding should be a continuing process and not a "once for all" project.

Severe combined immunodeficiency natural history is perfectly understood (as described above). Indeed, it is impossible to diagnose SCID based on the physical examination and the disease has an asymptomatic phase, allowing for proper management if diagnosed during that period.

Adding to this, the discussion of the meaning of an important health problem arises. Are rare, genetic, and lethal but treatable diseases important? Severe combined immunodeficiency is, according to its severity and lethality, clearly an important health problem, especially in a country where its mortality differs from most developed countries. Recently, revisions and additions to the NBS criteria have been proposed and one of the major proposals is that it must have been shown that early intervention in the disease improves the outcome, which is also the case for SCID.[10] Luckily, we can now address these questions based on the knowledge of the outcome of the NBS for SCID all around the globe. In the United States of America, where it was first implemented, it has been shown to be highly effective,[8] even in states where the outcome of SCID, in terms of overall survival, prior to the implementation of NBS was already very satisfactory.[11]

5. There should be an accepted treatment for patients with a recognized disease.
6. Facilities for treatment should be available.
7. There should be an agreed policy on who to treat as patients.

There is a curative treatment for SCID, the hematopoietic stem cell transplantation. Every single patient with SCID should receive appropriate curative treatment. In Portugal, we have both the facilities and know-how to address this.

8. Facilities for diagnosis should be available.
9. There should be a suitable test or examination.
10. The test should be acceptable to the population.
11. The cost of case finding (including the diagnosis and treatment of patients diagnosed) should be economically balanced in relation to the possible expenditure on medical care as a whole.

The T-cell receptor allows for the recognition of diverse antigens by T-cells, thus being crucial for the adequate defense against pathogens. It is a protein heterodimer composed of two chains (αβ or γδ) that pair during the maturation process. During the T-cell receptor rearrangement, pieces of intervening deoxyribonucleic acid (DNA) are generated and are called T-cell receptor excision circles (TREC), which can be quantified by real-time polymerase chain reaction (qRT-PCR). In SCID patients, TRECs are absent or very low and this is the basis of the TREC assay.[12] This technique has a very high sensitivity, and there have been no documented SCID cases missed by NBS using this assay.[12] The test is well developed and generalized in the genetics and immunology laboratories in Portugal.

The test is performed in dried blood spots obtained with the same heel punch already used, meaning that it is absolutely acceptable to the population.

Finally, multiple studies have shown that NBS for SCID is cost-effective.[13-16] Early diagnosis allows for early hematopoietic stem cell transplantation, reduced health care costs, reduced probability of needing to be transferred to an international hematopoietic stem cell transplantation unit, fewer hospitalizations, and fewer visits to the outpatient clinic. And these studies have not addressed the additional benefit of the diagnosis of non-SCID significant T-cell lymphopenia, which would increase the benefit.[13]

In Portugal, it would be even more cost-effective, as most patients are still diagnosed and transplanted later in the course of their disease, differently from countries like France, the Netherlands, and Norway.

Including severe combined immunodeficiency in newborn screening in Portugal is a moral imperative that must be seriously looked into in the coming months.

The time is now.

**Keywords:** Infant, Newborn, Diseases; Neonatal Screening; Portugal; Severe Combined Immunodeficiency/diagnosis

## Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

## Funding Sources

There were no external funding sources for the realization of this paper.

## Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

## Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

## Provenance and peer review

Not commissioned; externally peer reviewed

## References


1. Wilson JM, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization; 1968.
2. Instituto Nacional de Saúde Doutor Ricardo Jorge. Programa nacional de diagnóstico precoce [accessed 22 August 2019]. Available at: http://www.insa.min-saude.pt/category/areas-de-atuacao/genetica-humana/programa-nacional-de-diagnostico-precoce
3. Cirillo E, Giardino G, Gallo V, D'Assante R, Grasso F, Romano R, et al. Severe combined immunodeficiency - an update. Ann N Y Acad Sci 2015;1356:90-106. doi: 10.1111/nyas.12849.
4. Chinn IK, Shearer WT. Severe combined immunodeficiency disorders. Immunol Allergy Clin North Am 2015;35:671-94. doi: 10.1016/j.iac.2015.07.002.
5. Fischer A. Severe combined immunodeficiencies (SCID). Clin Exp Immunol 2000;122:143-9.
6. Rivers L, Gaspar HB. Severe combined immunodeficiency: Recent developments and guidance on clinical management. Arch Dis Child 2015;100:667-72. doi: 10.1136/archdischild-2014-306425.
7. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. N Engl J Med 2014;371:434-46. doi: 10.1056/NEJMoa1401177.
8. Dorsey MJ, Puck JM. Newborn screening for severe combined immunodeficiency in the united states: Lessons learned. Immunol Allergy Clin North Am 2019;39:1-11. doi: 10.1016/j.iac.2018.08.002.
9. Accetta Pedersen D, Verbsky J, Routes JM. Screening newborns for primary T-cell immunodeficiencies: Consensus and controversy. Expert Rev Clin Immunol 2011;7:761-8. doi: 10.1586/eci.11.25.
10. Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: A review of screening criteria over the past 40 years. Bull World Health Organ 2008;86:317-9. doi: 10.2471/blt.07.050112.
11. Dvorak CC, Puck JM, Wahlstrom JT, Dorsey M, Melton A, Cowan MJ. Neurologic event-free survival demonstrates a benefit for SCID patients diagnosed by newborn screening. Blood Adv 2017;1:1694-8. doi: 10.1182/bloodadvances.2017010835.
12. Thakar MS, Hintermeyer MK, Gries MG, Routes JM, Verbsky JW. A practical approach to newborn screening for severe combined immunodeficiency using the T cell receptor excision circle assay. Front Immunol 2017;8:1470. doi: 10.3389/fimmu.2017.01470.
13. Thomas C, Durand-Zaleski I, Frenkiel J, Mirallié S, Léger A, Cheillan D, et al. Clinical and economic aspects of newborn screening for severe combined immunodeficiency: DEPISTREC study results. Clin Immunol 2019;202:33-39. doi: 10.1016/j.clim.2019.03.012.
14. Clément MC, Mahlaoui N, Mignot C, Le Bihan C, Rabetrano H, Hoang L, et al. Systematic neonatal screening for severe combined immunodeficiency and severe T-cell lymphopenia: Analysis of cost-effectiveness based on French real field data. J Allergy Clin Immunol 2015;135:1589-93. doi: 10.1016/j.jaci.2015.02.004.
15. Gardulf A, Winiarski J, Thorin M, Heibert Arnlind M, von Döbeln U, Hammarström L. Costs associated with treatment of severe combined immunodeficiency-rationale for newborn screening in Sweden. J Allergy Clin Immunol 2017;139:1713-6.e6. doi: 10.1016/j.jaci.2016.10.043.
16. Hays LH. Societal value of newborn screening for severe combined immune deficiency in Arkansas: An economic analysis. Public Health Nurs 2019;36:541-4. doi: 10.1111/phn.12614.