

1 **Online Repository Text**

2 **Methods**

3 **Systematic review**

4 A systematic review was conducted on NBS for SCID and (case) definitions used in pilot studies and
5 population based screening. The findings were reported according to the principles outlined in Preferred
6 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement ([www. prisma-
7 statement.org](http://www.prisma-statement.org)).

8 **Literature search**

9 An electronic search was performed on MEDLINE (PubMed), EMBASE (excluding MEDLINE),
10 Cochrane library and Scopus databases on 16 February 2020. The keywords included synonyms for
11 'newborn screening' and 'primary immunodeficiencies/severe combined immunodeficiency/inborn
12 errors of immunity'. Checking the reference lists of included studies identified additional publications.
13 The search strategy is shown below in the [Search Strategy](#).

14 **Eligibility criteria**

15 The initial search strategy was aimed at identification of all studies using definitions in NBS for SCID
16 not discriminating between larger cohort studies and case studies. Systematic reviews, meta-analyses,
17 randomized control trials, case reports, case-control studies, cohorts studies, letters to the editor without
18 language restrictions were included in the initial search strategy. Exclusion criteria included publication
19 of editorials, commentaries, unpublished manuscripts, dissertations, books and book chapters, lectures
20 and speeches.

21 **Study selection/Screening for inclusion**

22 The study selection flow diagram is shown in [Figure 1](#). Titles and abstracts of all the records retrieved
23 from the electronic database searches were screened in a standardized manner. Records that were not
24 clearly related to NBS for SCID and records that did not meet the eligibility criteria were excluded.
25 Eligible articles were assessed based on full text. Reviews were only included if classifications or definitions
26 differed from previous original published articles. Case series describing retrospective TREC analysis
27 of specific groups of PID patients were excluded.

28 **Data extraction**

29 Items that were extracted from included articles were: author, year, study design, study location,
30 population based screening/pilot study, used TREC-assay (in house or CE-IVD marked assays), using
31 second tier test option after TREC analysis, TREC cut-off value, number of newborns screened, number
32 of retest on initial NBS cards, number of repeat DBS requested and number of referrals for follow-up
33 diagnostics. If studies used an anonymized study population, presumptive positives rates were
34 assumed referral rates. In addition, definitions on screening results, definitions or classifications used
35 in screening algorithms and classifications of outcomes/diagnoses after follow-up were collected.
36 Finally, definitions of premature birth and adjustments for premature infants in screening algorithms
37 were extracted. The final selection of publications was discussed with the panel.

38 **Quality assessment**

39 The reviewer examined reports for completeness of reporting on screening outcomes, screening
40 algorithms and classifications after follow-up. In some cases, multiple records described the same
41 screening population. If the used definitions were consistent between these records, the most recent
42 record was included. If information was missing in one of both studies, both articles would be included.
43 Given the descriptive nature of this review, results were not combined for meta-analysis and a formal
44 statistical analysis was not performed.

45 **Search strategy (conducted on February 16, 2021)**

46 **PubMed**

47 **#1 (28444 hits)**

48 "Newborn screening"[tiab] OR "Neonatal screening"[tiab] OR ("Newborn"[tiab] AND "Screening"[tiab])
49 OR ("Neonatal"[tiab] AND "Screening"[tiab]) OR "Guthrie card"[tiab] OR "Guthrie test"[tiab] OR "Dried
50 blood spot"[tiab] OR "Dried blood spots"[tiab] OR "T cell receptor excision circle"[tiab] OR "T cell
51 receptor excision circles"[tiab] OR "T-cell receptor excision circle"[tiab] OR "T-cell receptor excision
52 circles"[tiab] OR "TREC"[tiab] OR "TRECs"[tiab] OR "Kappa deleting recombination excision
53 circle"[tiab] OR "Kappa deleting recombination excision circles"[tiab] OR "Kappa-deleting
54 recombination excision circle"[tiab] OR "Kappa-deleting recombination excision circles"[tiab] OR
55 "KREC"[tiab] OR "KRECs"[tiab] OR "Neonatal screening"[MeSH] OR "Dried Blood Spot
56 Testing"[MeSH]

57 **#2 (34356 hits)**

58 "PID"[tiab] OR "primary immune deficiency"[tiab] OR "primary immune deficiencies"[tiab] OR "primary
59 immunodeficiency"[tiab] OR "primary immunodeficiencies"[tiab] OR "SCID"[tiab] OR "Severe
60 combined immunodeficiency"[tiab] OR "T cell lymphopenia"[tiab] OR "T cell lymphopenias"[tiab] OR
61 "T-cell lymphopenia"[tiab] OR "T-cell lymphopenias"[tiab] OR "T cell deficiencies"[tiab] OR "T-cell
62 deficiency"[tiab] OR "T-cell deficiencies"[tiab] OR "T cell deficiency"[tiab] OR "inborn errors of
63 immunity"[tiab] OR "Severe Combined Immunodeficiency"[MeSH] OR "Primary Immunodeficiency
64 Diseases"[Mesh:NoExp]

65 **#3 (515 hits)**

66 #1 AND #2

67

68 **EMBASE**

69 **#1 (10400 hits) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)**

70 'Newborn screening':ti,ab OR 'Neonatal screening':ti,ab OR 'Guthrie card':ti,ab OR 'Guthrie test':ti,ab
71 OR 'Dried blood spot':ti,ab OR 'Dried blood spots':ti,ab OR 'T cell receptor excision circle assay':ti,ab
72 OR 'T cell receptor excision circles':ti,ab OR 'T-cell receptor excision circle assay':ti,ab OR 'T-cell
73 receptor excision circles':ti,ab OR TREC:ti,ab OR TRECs:ti,ab OR 'Kappa deleting recombination
74 excision circle':ti,ab OR 'Kappa deleting recombination excision circles':ti,ab OR 'Kappa-deleting
75 recombination excision circle':ti,ab OR 'Kappa-deleting recombination excision circles':ti,ab OR #13
76 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)KREC:ti,ab OR KRECs:ti,ab OR 'Newborn
77 screening'/exp OR 'Dried Blood Spot Testing'/exp

78 **#2 (27614) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)**

79 pid:ab,ti OR 'primary immune deficiency':ab,ti OR 'primary immune deficiencies':ab,ti OR 'primary
80 immunodeficiency':ab,ti OR 'primary immunodeficiencies':ab,ti OR scid:ab,ti OR 'severe combined
81 immunodeficiency':ab,ti OR 't cell lymphopenia':ab,ti OR 't cell lymphopenias':ab,ti OR 't-cell
82 lymphopenia':ab,ti OR 't-cell lymphopenias':ab,ti OR 't cell deficiencies':ab,ti OR 't-cell deficiency':ab,ti
83 OR 't-cell deficiencies':ab,ti OR 't cell deficiency':ab,ti OR 'inborn errors of immunity':ab,ti OR 'severe
84 combined immunodeficiency'/exp OR 'primary immunodeficiency diseases'/mj

85 **#3 (533 hits)**

86 #1 AND #2

87 **#4 (110 hits)**

88 #3 AND ('article'/it OR 'article in press'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR
89 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)

90

91 **Cochrane**

92 **#1 (1112 hits)**

93 "Newborn screening" or "Neonatal screening" or "Guthrie card" or "Guthrie test" or "Dried blood spot"
94 or "Dried blood spots" or "T cell receptor excision circle" or "T cell receptor excision circles" or "T-cell
95 receptor excision circle" or "T-cell receptor excision circles" or "TREC" or "TRECs" or "Kappa deleting
96 recombination excision circle" or "Kappa deleting recombination excision circles" or "Kappa-deleting

97 recombination excision circle" or "Kappa-deleting recombination excision circles" or "KREC" or
98 "KRECs":ti,ab,kw

99 **#2 (1688 hits)**

100 "PID" or "primary immune deficiency" or "primary immune deficiencies" or "primary immunodeficiency"
101 or "primary immunodeficiencies" or "SCID" or "Severe combined immunodeficiency" or "T cell
102 lymphopenia" or "T cell lymphopenias" or "T-cell lymphopenia" or "T-cell lymphopenias" or "T-cell
103 deficiency" or "T cell deficiency" or "T-cell deficiencies" or "T cell deficiencies":ti,ab,kw

104 **#3 (8 hits)**

105 #1 AND #2