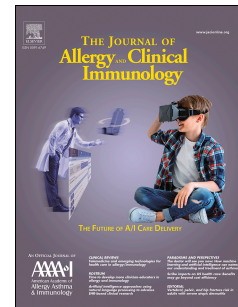


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Normal B cell ranges in infants: A systematic review and meta-analysis

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La Roche Ltd at the time of the study. T. Derfuss has no conflicts of interest to declare. L. Law is an employee of Oxford PharmaGenesis, which has received funding from F. Hoffmann-La Roche Ltd to perform the systematic literature review and medical writing of this article, in accordance with Good Publications Practice 3 (GPP3) guidelines (<http://www.ismpp.org/gpp3>). K. Rand is an employee of Maths in Health, which has received funding from F. Hoffmann-La Roche Ltd to perform the statistical analyses of this study.

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Abstract (current word count: 250/250)

Background: During the first year of life, B cell level is a valuable indicator of whether external factors, such as exposure to B cell depleting therapies, have an adverse impact on immune system development. However, there are no standard reference ranges of B cell levels in healthy infants by age.

Objective: To estimate the normal range of B cell levels in infants, by age, during the first year of life, by pooling data from published studies.

Methods: Studies reporting B cell levels measured using flow cytometry and CD19 markers in healthy infants were identified via a systematic literature review. Quality and feasibility assessments determined suitability for inclusion in meta-analyses by age group and/or continuous age. Means and normal ranges (2.5th–97.5th percentile) were estimated for absolute and percentage B cell levels. Sensitivity analyses assessed the impact of various assumptions.

Results: Of 37 relevant studies identified, 28 were included in at least 1 meta-analysis. Means and normal ranges of B cell levels were found to be 707 (123–2324) cells/ μ L in cord blood, 508 (132–1369) cells/ μ L at age 0–1 month, 1493 (416–3877) cells/ μ L at age 1–6 months and 1474 (416–3805) cells/ μ L at age >6 months. The continuous age model showed that B cell levels peaked at week 26. Trends were similar for the percentage B cell estimates and in sensitivity analyses.

Conclusion: These meta-analyses provide the first normal reference ranges for B cell levels in infants, by week of age, during the first year of life.

Key messages

- We used meta-analyses to pool data from up to 28 published studies to estimate the normal range of B cell levels in healthy infants, by each week of life, up to 1 year of age.
- Our findings provide robust reference values for mean and upper and lower limits of normal B cell levels; these can be used to assess whether B cell development in infants is being adversely affected by external factors, such as exposure to B cell depleting therapies.

Capsule summary

Findings from our meta-analyses provide the first normal reference ranges for B cell levels week-by-week in healthy infants, in the first year of life.

Key words: *B cell; CD19; flow cytometry; normal range; reference range; lower limit of normal; newborns; infants; cord blood.*

Abbreviations used

PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
SLR	Systematic literature review
SE	Standard error

INTRODUCTION

B cells, or B lymphocytes, have multiple roles in the immune response, including secreting cytokines and acting as antigen-presenting cells to stimulate T-cell activation, as well as producing different isotypes of antibodies.¹ Their role is particularly evident in the context of primary and secondary immunodeficiencies in which lack of antibodies and/or B cells is associated with a high risk of infection.²

The development of B cells begins before birth, with precursor B cells detectable in fetal liver from 7 weeks gestation and mature B cells detectable after 9 weeks gestation.^{3,4} Beginning in the second trimester and continuing after birth, B cells develop in the bone marrow via sequential maturation steps involving the rearrangement of immunoglobulin or B cell receptors.⁵ Immature B cells are then released from the bone marrow into the circulation, and subsequent maturation occurs in secondary lymphoid organs (for example, spleen and lymph nodes), and the cells eventually progress into mature B cells, ready to fight infection with the secretion of various types of immunoglobulin.¹

A number of conditions can cause quantitative alterations to B cell levels.⁶ For example, some primary immunodeficiencies result from genetic defects that interfere with the expression of pre-B cell receptors, and reduce the number of circulating mature B cells.⁶ Alterations in B cell levels can also result from therapeutic interventions; B cell-depleting therapies are commonly used to treat hematological malignancies or autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus, owing to the dysregulation of B cells that occurs with these illnesses.^{7,8} Importantly, when B cell-depleting therapies are used during pregnancy or breastfeeding, the drug may pass from mother to child.⁹ This may lead to B cell depletion in the child, as has been observed with some monoclonal antibodies,¹⁰⁻¹² although it is unclear whether this affects the child's ability to fight infection.

B cell levels can be captured by the measurement of CD19 antigens on the surface of B lymphocytes; this transmembrane protein is expressed throughout B cell development.¹³ Other markers expressed in B cells, such as CD20, have a more limited expression, especially in early-stage cells and plasma cells.¹⁴ As such, the CD19 marker is the most reliable, and most widely used, biomarker to enable B cell monitoring.¹³ Such monitoring would allow

assessment of the impact of conditions or interventions on B cell levels in children, showing, for example, if B cell depletion has occurred. To aid this assessment, it is important to know what normal B cell levels to expect at particular ages, especially normal upper and lower limits. A key period for monitoring is the first 12 months of life, when B cell levels are most dynamic and play a fundamental role in the response to vaccines administered during early development. Currently, there are no standard reference values for the upper and lower limits of normal for the first year of infancy. Many studies have measured B cell levels in populations of healthy infants, but given the variation in laboratories and analytical approaches across studies, the use of reference ranges from a single study may not be appropriate.

We performed a systematic review of the literature to identify studies reporting B cell levels in healthy infants estimated using flow cytometry and CD19 markers. Using this evidence, values were pooled across studies through meta-analyses to estimate the normal range of B cell levels, across different age strata, during the first year of life.

METHODS

Systematic review of the literature

A systematic literature review (SLR) was performed that followed the latest statement of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020).¹⁵ Searches were conducted on 20 January 2021 in the following electronic databases: (1) MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® and (2) Embase (electronic search strings are presented in Table E1 in the Online Repository). Additional supplementary searches were performed by cross-checking reference lists of articles identified by the searches. Titles and abstracts of identified publications were screened manually, by 1 reviewer, followed by review of full texts of selected articles against predefined eligibility criteria (Table I). Eligible studies were included for data extraction, which included country, sample size, age group and summary statistics of age (e.g. median and mean) for the study sample, timing of umbilical cord blood sampling (if cord blood was assessed), the flow cytometry protocol used for B cell measurement (gating strategy, single/dual platform, instrument and quantification method used), summary statistics (mean/median, measure of dispersion [e.g. range, percentiles and confidence intervals]) for absolute B cell levels and the percentage of B cells relative to the number of total lymphocytes.

Quality assessment and feasibility for meta-analysis

To assess the feasibility of conducting a meta-analysis to estimate B cell levels, each study included in the SLR was reviewed using a bespoke quality assessment (Table E2 in the Online Repository).^{5,16-51} The key inclusion criteria for this assessment were reporting of a measure of dispersion (e.g. standard deviation, percentile) for B cell estimates and reporting of age groups with a range shorter than 6 months. Given the expected dynamics of B cell levels throughout different stages of the first year of life,^{5,20} study publications reporting only wide age ranges (e.g. 0–12 months or more) were not included in the meta-analysis. Age ranges used in each study were also examined to determine if there were enough data across studies to support meta-analyses within specific age groups.

Meta-analysis

Outcomes of interest. The most commonly used definition of the reference range is the interval of values containing the central 95% of a healthy population. Thus, the reference limits are the values at the 2.5th percentile (lower limit of normal) and 97.5th percentile (upper limit of normal), respectively.⁵² The 5th and 95th percentiles were also calculated. Measures of central tendency included mean and median.

Statistical analysis. Two types of meta-analysis were selected to estimate B cell levels across studies: (1) individual meta-analyses of age group data, which pooled B cell levels across study populations of similar age; and (2) an overall meta-analysis that included data from all eligible studies and estimated B cell levels as a function of continuous age (i.e. B cell level was estimated at every age, using data from all studies). For each type of meta-analysis – by age group and by continuous age – both absolute levels of B cells and the percentage of B cells relative to the number of total lymphocytes were estimated. Four meta-analyses by age group were performed, to estimate B cell levels in cord blood, and in infants aged 0–1 month, 1–6 months and more than 6 months (see Results for details and the rationale for selection of age groups). Study data from age groups that did not fit into one of the 4 groups of interest were excluded. For the meta-analysis by continuous age, B cell levels across all ages from birth to 12 months were included, with the exception of levels measured in cord blood samples. Detailed methods are provided in Online repository text E1.

Sensitivity analyses. Sensitivity analyses were used to investigate the impact on the primary results under different scenarios, including: different model assumptions, removal of outlier data; exclusion of specific age groups; exclusion of studies with unclear or different gating strategies in the measurement of B cells. These analyses are described in detail in Online repository text E2.

RESULTS

Overview of studies

After screening the titles and abstracts of 292 articles identified from the electronic database searches, 127 articles were included for full text review. A total of 37 articles met the SLR eligibility criteria and were included for data extraction (Fig 1). Of the 37 studies included in this SLR, 36 had an observational design,^{5,16-47,49-51} and 1 was a non-randomized study⁴⁸ with different feeding interventions (human milk vs fortified human milk vs formula).

Geographical distribution covered Europe (20 studies),^{5,17,18,20,22,26,27,29,31,32,34,36,38,40,42,43,47-49,51} North America (6 studies),^{16,19,35,37,44,46} Asia (5 studies),^{23,30,33,45,50} Africa (4 studies),^{24,25,31,41} South America (2 studies)^{21,39} and Australasia (1 study) (Table E3).²⁸ Study populations included healthy infants in all cases, often defined as infants with no history of immunologic or hematologic diseases (Table E3).

All studies identified B cell levels using flow cytometry and the CD19 marker (Table E3). Of 27 studies that reported type of anticoagulant used for the blood sample, 26 used ethylenediaminetetraacetic acid and 1 used citratephosphate-dextrose (Table E3). Almost half of the studies reported the time period between blood sample collection and analysis, and in all cases this period was less than 24 hours; for the remaining studies, these details were not reported (Table E3). The most common gating strategy was forward and side scatter (16 studies),^{5,16,18-22,25,28,33,35-37,46,47,49} where visible light scatter is measured in the forward and perpendicular direction, to capture both the relative size and complexity of the cell.⁵³ Among the remaining studies, 7 used CD45 versus side scatter,^{17,23,24,26,34,38,44} and for 14 studies, details of the gating strategy were unclear or not reported (Table E4 and Table E5).^{27,29-32,39-43,45,48,50,51} Most articles (> 70%) did not provide specific details about number of lymphocyte events collected or required for analysis; of 10 articles that did provide this information, the number of events stated ranged from 6500 to 10,000 (Table E3).

Overall, total sample sizes ranged from 6 to 301 and the age range of the study populations was preterm newborn to 2 years (Table E4). Thirty-one publications reported absolute B cell levels^{5,16-20,22-24,26-29,33-35,37-51} and 6 reported only percentage levels;^{21,25,30-32,36} 26 articles reported both absolute and percentage B cell levels (Table E4).

Meta-analysis

Selection of studies and age ranges. As part of the feasibility assessment for meta-analysis, the age ranges represented across studies were examined (Fig 2). In addition to cord blood (17 studies), 3 commonly reported age groups were identified: 0–1 month (12 studies), 1–6 months (10 studies) and older than 6 months (10 studies). In 3 studies, B cell levels were measured in infants aged 1 week to 2 months. Data from this age group were not included in the primary analysis because it overlapped with competing age groups of interest (0–1 month and 1–6 months), but are included in the supplementary results. Nine studies were completely excluded from the meta-analyses and 6 studies were partially excluded (i.e. some age groups were used while others were not considered relevant according to the quality and feasibility assessment criteria) (Table E2 in the Online Repository). Overall, data from 28 studies were used across all meta-analyses performed.

B cell level estimates by age group. Findings from the 4 meta-analyses by age group showed that pooled mean (standard error [SE]) absolute B cell levels decreased from 707 (25) cells/ μ L in cord blood to 508 (23) cells/ μ L in the first month of life (Table II). An increase occurred between the ages of 0–1 month and 1–6 months, then levels remained similar after 6 months, having reached 1474 (70) cells/ μ L. The lower limit of normal, represented by the 2.5th percentile, was lowest in cord blood (123 cells/ μ L), then increased with age (416 cells/ μ L in both the 1–6 months and older than 6 months age groups) (Table II). The upper limit of normal, represented by the 97.5th percentile, followed a slightly different trend to the lower limit; the pooled estimate was lowest at age 0–1 month (1369 cells/ μ L), rather than in cord blood, then increased to a peak at age 1–6 months (3877 cells/ μ L) (Table II). Meta-analyses of data for the percentage of B cells relative to the number of total lymphocytes produced a similar trend to absolute levels, with the pooled mean (SE) level initially decreasing from 14.0% (0.3%) in cord blood to 12.0% (0.5%) in infants aged 0–1 month, then increasing to 23.5% (0.9%) in infants older than 6 months (Table II). Estimates for the overlapping age group, 1 week to 2 months, supported the overall trend in the primary analysis (Table E6 in the Online Repository).

B cell estimates by continuous week of age. In the meta-analyses by continuous age, the shape of the association between age and B cell level reflected the results observed for individual age groups for both absolute and percentage B cell levels (Fig 3 and Fig 4). Levels gradually increased from a mean of 452 cells/ μ L (or 11.3%) in the first week of life, to a peak of 1726 cells/ μ L (or 26.1%) at 26 weeks of life, then gradually decreased and levelled off to 1347 cells/ μ L (or 22.5%) at 52 weeks (Table III; see Tables E7 and E8 in the Online Repository for SEs and 95% CIs). Mean estimates of the lower limit of normal (2.5th percentile) were 127 cells/ μ L and 4.6% in the first week of life, 486 cells/ μ L and 10.7% at week 26, and 379 cells/ μ L and 9.3% at week 52 (Table III; see Tables E7 and E8 in the Online Repository for SEs and 95% CIs). Mean estimates of the upper limit of normal (97.5th percentile) were 1165 cells/ μ L and 23.1% in the first week of life, 4453 cells/ μ L and 53.5% at week 26, and 3475 cells/ μ L and 46.3% at week 52 (Table III, Table E7, Table E8). Estimates in cord blood were not included in these models.

282 **Sensitivity analyses.** Overall, the primary findings were supported by trends observed
283 in the sensitivity analyses, including different model assumptions (Fig E1 in the Online
284 Repository), removal of outlier data (Fig E2 and E3); exclusion of specific age groups (Table
285 E9); exclusion of studies with unclear or different gating strategies in the measurement of B
286 cells (Fig E4).

DISCUSSION

In this study a systematic review of the literature was conducted and meta-analytic methods were used to pool data from up to 28 studies to estimate reference ranges for B cell levels (absolute counts and percentage levels) in the first year of life for healthy infants. Our findings provide B cell reference ranges for each week of age, as well as specific age groups, including the first day of life (B cells measured from umbilical cord blood taken minutes after delivery), age 0–1 month, 1–6 months and older than 6 months. To the best of our knowledge, this is the first study to provide a continuous model of age-matched reference ranges in the first 12 months of life.

Our results illustrate dynamic changes in B cell levels throughout the first year of life which can be summarized as follows: (1) initial decrease in B cell levels from cord blood to the first week of life, followed by (2) rapid expansion in the next 2 months, and (3) further expansion until maximum levels are reached at approximately 6 months of age, after which (4) levels decrease progressively, and (5) possibly plateauing around 12 months of age. Trends observed in the pooled values recapitulate those observed for individual studies that estimated national reference values,^{5,18,22,23,34,38} and likely reflect the development of the immune system as infants are exposed to environmental antigens.

The initial decrease in B cell levels from cord blood to the first week of life is thought to be related to the significant B cell phenotypic changes occurring in the first few days of life,⁵⁴ where a transient drop in immature/transitional and naïve B cells is observed, which is not accompanied by expansion of other B cell subsets.^{19,20,38} For this reason, cord blood measurements are generally considered poor predictors of postnatal immunity.⁵⁴ The subsequent period of rapid expansion is marked by a significant increase of B cell production in the bone marrow and release of high numbers of immature/transitional and naïve B cells into the peripheral blood, accompanied by an initial expansion of memory B cell (MBC) and plasma cell (PC) subsets.^{19,20} At approximately 6 months of age, B cell levels reach a lifetime peak and this coincides with the maximum levels of immature/transitional and naïve B cell subsets; thereafter these subset counts gradually decrease whereas the counts of MBC and PC continue to expand.^{19,20,38} Our results suggest that B cell levels appear to plateau by the age of 12 months, and this is confirmed by multiple studies included in the SLR. Evidence from the literature suggests that this plateau further extends to the second year of life after which a

gradual decrease is observed until adulthood (18 years), and levels remain relatively stable afterwards, at around 200–300 cells/ μ L.^{19,38,43,45} During adulthood, the number of immature/transitional and naive B cells remains stable, whereas MBC and PC counts gradually decrease in individuals older than 60 years.⁵⁵ These observations make it clear that B cell levels in adults cannot be used to inform expected levels during childhood, and the knowledge on normal ranges of B cells during infancy is therefore highly relevant. Normal ranges in infancy enable more adequate monitoring of the potential impact of autoimmune diseases on infant B cells, or the impact of B cell depleting therapies passed on by the mother during pregnancy or breastfeeding.

B cell trafficking between bone marrow, lymphoid tissues and peripheral blood is a continuous process,⁵⁶ and may explain the dynamic changes and the phenotypic complexity observed in the first 12 months of life. It is uncertain whether the changes are due to a real expansion of B cells, a redistribution from tissues to blood, or a combination of both mechanisms. This uncertainty is an important point in terms of monitoring the impact of B cell-depleting therapies because there will be a strong impact of these therapies on circulating B cells. The nature of this impact is unclear in terms of the effect of B cell depletion in different compartments; thus, while B cell monitoring is valuable, it may be limited to some extent.

This study has multiple strengths. The analyses were informed by data identified via a rigorous, PRISMA-compliant SLR. We did not use a formal risk of bias or quality assessment tool, but employed a bespoke checklist to inform feasibility for meta-analysis, which allowed inclusion of the most suitable data for pooling estimates of interest. Each meta-analysis used data from at least 8 studies and as many as 17 studies, depending on age group and reporting of absolute number versus percentage of B cells. The studies in the meta-analyses were conducted in a large number of countries and regions, supporting the generalizability of the results. In addition, various sensitivity analyses were performed and demonstrated that the results were robustly consistent with those of the primary analysis.

Some limitations of this work should be noted. The models did not use individual patient data as these were not available in the published literature; instead, we relied on distributions of B cells based on summary estimates reported for each study. The estimated distributions may

have introduced some level of uncertainty in the results. In addition, our models are applicable only up to the age of 12 months, based on the available data, and thus do not provide information on B cell levels in older infants. The levelling off of B cell levels observed around 12 months could possibly persist into the second year of life, but further research is needed to explore normal ranges in older infants. We were unable to explore the impact of patient characteristics that may influence B cell levels, such as gender and ethnicity, as sufficient data were not available for these subgroups. Instead, our reference values are intended to be applicable internationally, for male and female infants. However, specific reference ranges by subgroup would be valuable in future, given observed differences in B lymphocyte counts by gender (higher in females vs males)⁵⁷ and ethnicity (higher in African Americans than European Americans).⁵⁸ Other limitations are related to the gating strategy used to identify B cells. Estimates of relative B cell levels can vary depending on the gating strategy used, and can vary between laboratories. This variation could introduce heterogeneity into the meta-analyses. For this reason, a sensitivity analysis was performed to restrict inclusion to studies with the same or a similar gating strategy. We found that removal of studies with differing or unclear strategies had very little impact on the pooled estimates and their trend over time, supporting the robustness of our primary analyses. Other potential variations in methodology are type of anticoagulant used, which informs the stability of the sample, and the number of lymphocyte events that contributed to the flow cytometry analysis. In the current study, most studies used the same anticoagulant and blood samples were typically processed on the same day as collection; thus, it is not expected that anticoagulant type influenced the results. The impact of lymphocyte event threshold used (e.g., 10,000 vs 100,000) is less certain, as many studies did not report this level of detail; thus, this should be noted when interpreting findings. Lastly, the scope of the current reference ranges was focused on total B cell levels only. Similar research into normal levels of B cell subsets, such as transitional, naive and memory B cells, would be valuable in enabling a more detailed monitoring of infants' immune system development.

The pooled estimates of B cell levels in infants found in this study will be clinically valuable as normal reference ranges for infants aged up to 12 months. In particular, the lower limits of normal may be used to assess whether immunity in newborns and infants may have been impaired, for example by autoimmune diseases or by an external factor such as exposure to B cell-depleting therapies.

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FIGURES

FIG 1. PRISMA flow diagram.

Electronic searches were conducted on 20 January 2021.

NR, Not reported; *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

FIG 2. Age ranges used in studies identified by the systematic literature review that estimated B cell levels in peripheral blood.

Note, these age ranges represent the timing of peripheral blood assessment only. Assessment of cord blood is not included; thus, studies that examined cord blood only do not appear in this figure.

FIG 3. Estimation of absolute B cell count according to age (week of life), including the normal range.

This model was informed by data from 17 studies. Estimates in cord blood are not included.

FIG 4. Estimation of percentage of B cells according to age (week of life), including the normal range.

This model was informed by data from 14 studies. Estimates in cord blood are not included.

Table I. Eligibility criteria for identification of relevant studies

Category	Inclusion criteria	Exclusion criteria
Population	Healthy neonates, babies, infants and children Preterm neonates, babies, infants and children Samples of umbilical cord blood	Infants with comorbidities (e.g. autoimmune diseases) Older children and adults
Interventions	Any	No exclusion criteria
Comparator	Any	No exclusion criteria
Outcomes	CD19 B cell* or B lymphocyte counts/levels/ranges determined via	Counts for other immune cells

Category	Inclusion criteria	Exclusion criteria
	flow cytometry in cord blood (at birth) and/or peripheral blood up to 15 months after birth	Counts for time points beyond 15 months Counts determined using other methodology
Study design	Any	No exclusion criteria
Language	English	Non-English
Date restriction	Articles published in 1995 and later	Articles published before 1995

*Other markers, such as CD20, were not included.

584 **Table II.** Results of individual meta-analyses: pooled absolute B cell levels (cells/ μ L) and percentage B cells (%) by age group

Estimate	Cord blood	Age 0–1 month	Age 1–6 months	Age >6 months
<i>Absolute B cell levels (cells/μL)</i>				
Number of studies used in analysis	12	11	10	10
Mean (SE)	707 (25)	508 (23)	1493 (48)	1474 (70)
SD (SE)	616 (42)	332 (25)	925 (61)	905 (83)
Median (SE)	533 (17)	425 (18)	1269 (38)	1256 (55)
2.5th percentile (SE) [95% CI]	123 (7) [109, 137]	132 (8) [117, 149]	416 (22) [375, 461]	416 (30) [358, 475]
97.5th percentile (SE) [95% CI]	2324 (132) [2080, 2599]	1369 (86) [1210, 1546]	3877 (205) [3493, 4297]	3805 (283) [3286, 4396]
<i>Percentage B cells (%)</i>				
Number of studies used in analysis	16	8	9	9
Mean (SE)	14.0 (0.3)	12.0 (0.5)	23.9 (0.7)	23.5 (0.9)
SD (SE)	7.8 (0.4)	6.5 (0.6)	9.2 (0.5)	9.3 (0.8)
Median (SE)	12.3 (0.2)	10.6 (0.5)	22.3 (0.6)	21.9 (0.8)
2.5th percentile (SE) [95% CI]	4.5 (0.2) [4.1, 4.8]	3.9 (0.3) [3.4, 4.5]	10.7 (0.4) [9.9, 11.6]	10.4 (0.6) [9.2, 11.5]
97.5th percentile (SE) [95% CI]	33.8 (1.3) [31.5, 36.4]	28.6 (2.0) [24.9, 32.8]	46.3 (1.9) [42.7, 50.1]	46.2 (2.7) [41.2, 51.9]

585 *CI*, Confidence interval; *SD*, Standard deviation; *SE*, Standard error

586 **Table III.** B cell reference ranges by week of life: absolute and percentage counts

Week	Absolute B cell count (cells/ μ L)			Percentage B cell count (%)		
	Mean	LLN*	ULN [†]	Mean	LLN*	ULN [†]
1	452	127	1165	11.3	4.6	23.1
2	513	144	1322	12.1	5.0	24.9
3	577	163	1489	13.1	5.4	26.8
4	645	182	1664	14.0	5.8	28.7
5	716	202	1846	14.9	6.1	30.5
6	788	222	2033	15.8	6.5	32.4
7	863	243	2225	16.7	6.9	34.3
8	937	264	2418	17.6	7.2	36.1
9	1012	285	2612	18.4	7.6	37.8
10	1087	306	2803	19.3	7.9	39.5
11	1159	327	2991	20.0	8.3	41.1
12	1230	346	3172	20.8	8.6	42.7
13	1297	365	3346	21.5	8.9	44.1
14	1361	383	3511	22.2	9.1	45.5
15	1420	400	3665	22.8	9.4	46.8
16	1475	416	3807	23.4	9.6	47.9
17	1525	430	3935	23.9	9.8	49.0
18	1570	442	4050	24.3	10.0	49.9
19	1609	453	4151	24.7	10.2	50.7
20	1642	463	4237	25.1	10.3	51.5
21	1670	470	4308	25.4	10.5	52.1
22	1692	477	4364	25.6	10.6	52.5
23	1708	481	4406	25.8	10.6	52.9
24	1719	484	4435	25.9	10.7	53.2
25	1725	486	4450	26.0	10.7	53.4
26	1726	486	4453	26.1	10.7	53.5
27	1723	485	4445	26.1	10.8	53.5
28	1716	483	4426	26.1	10.7	53.5
29	1705	480	4398	26.0	10.7	53.3
30	1691	476	4362	25.9	10.7	53.2
31	1675	472	4319	25.8	10.6	52.9
32	1656	466	4270	25.6	10.6	52.6
33	1635	460	4216	25.5	10.5	52.3
34	1613	454	4159	25.3	10.4	51.9

Week	Absolute B cell count (cells/ μ L)			Percentage B cell count (%)		
	Mean	LLN*	ULN [†]	Mean	LLN*	ULN [†]
35	1589	448	4099	25.1	10.3	51.5
36	1566	441	4037	24.9	10.3	51.0
37	1541	434	3975	24.7	10.2	50.6
38	1517	427	3912	24.4	10.1	50.1
39	1494	421	3851	24.2	10.0	49.7
40	1471	414	3792	24.0	9.9	49.2
41	1449	408	3735	23.8	9.8	48.8
42	1428	402	3682	23.6	9.7	48.4
43	1409	397	3632	23.4	9.6	48.0
44	1391	392	3588	23.2	9.6	47.6
45	1376	388	3548	23.0	9.5	47.3
46	1363	384	3515	22.9	9.4	47.0
47	1352	381	3488	22.8	9.4	46.7
48	1345	379	3468	22.7	9.3	46.5
49	1340	377	3456	22.6	9.3	46.3
50	1339	377	3452	22.5	9.3	46.2
51	1341	378	3458	22.5	9.3	46.2
52	1347	379	3475	22.5	9.3	46.3

LLN, Lower limit of normal; ULN, Upper limit of normal.

*Defined as the 2.5th percentile of B cell count.

[†]Defined as the 97.5th percentile of B cell count.

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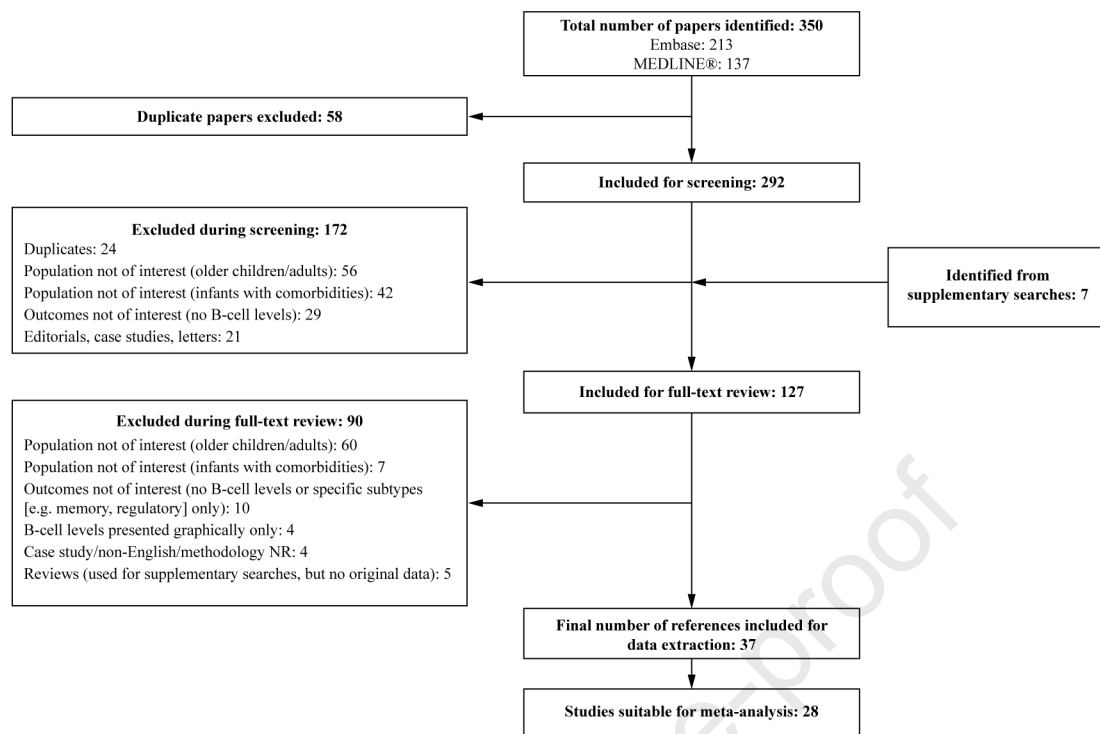


Figure 1

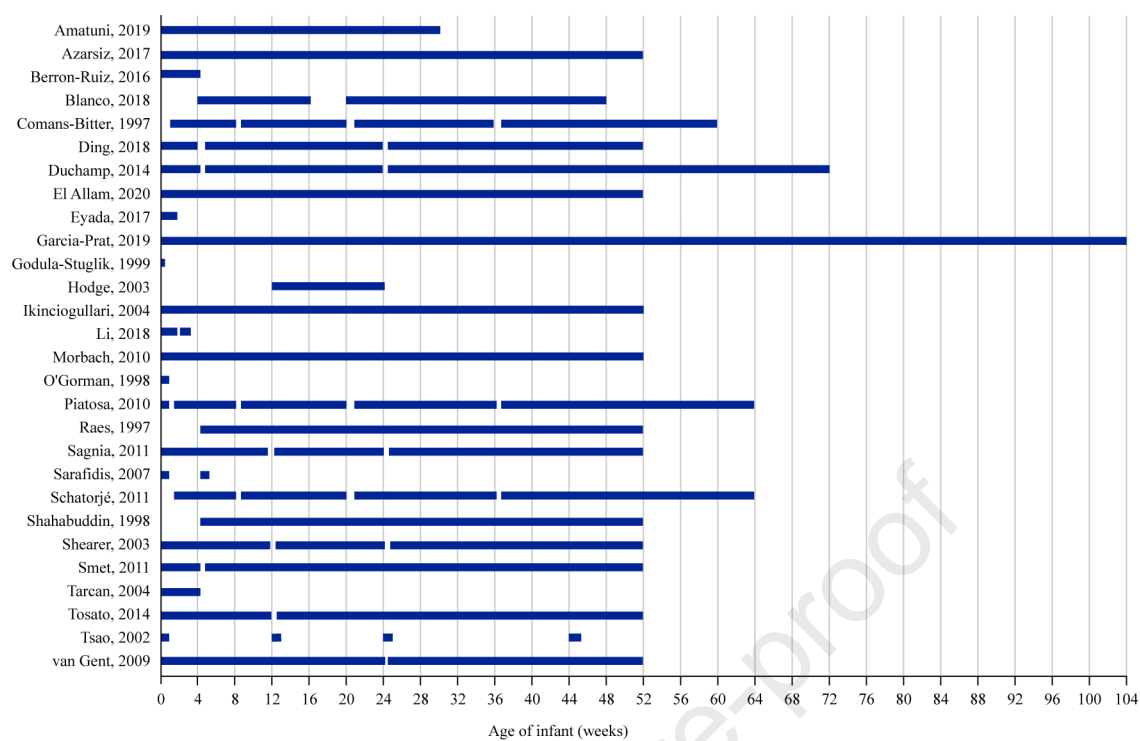


Figure 2

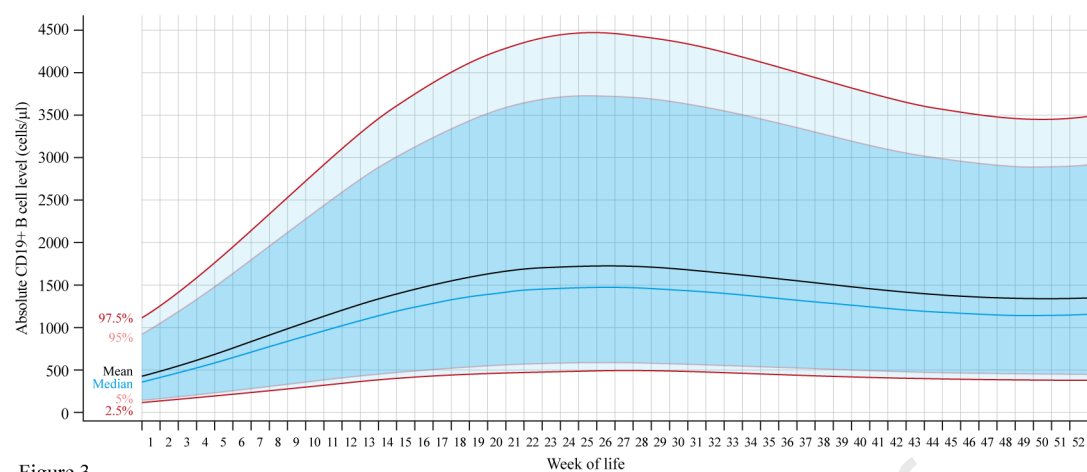


Figure 3

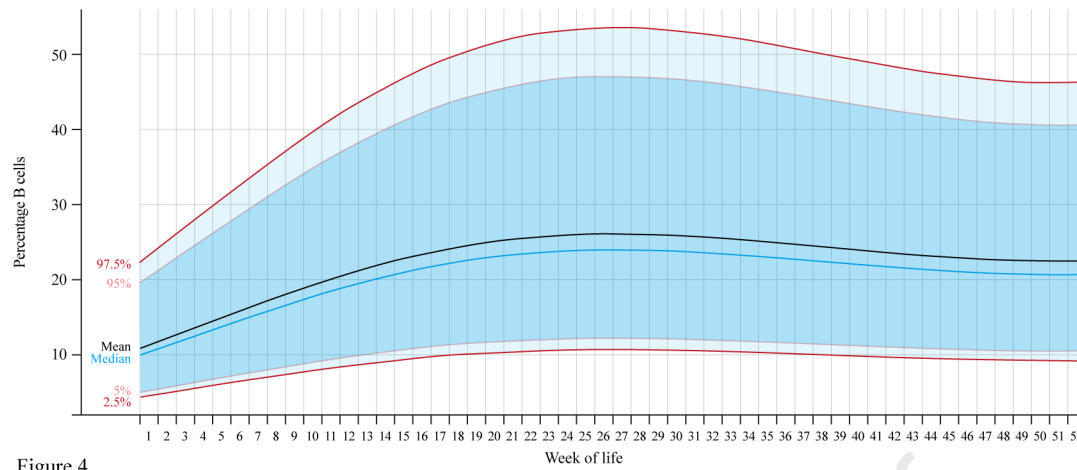


Figure 4