EXPERTISE AND SERVICE PROVISION
QUALITY OF LABORATORIES

CLINICAL BIOLOGY COMMISSION
COMMITTEE OF EXPERTS

EXTERNAL QUALITY ASSESSMENT
IN CLINICAL BIOLOGY

DEFINITIVE GLOBAL REPORT

FLOW CYTOMETRY: LYMPHOCYTE SUBSET ANALYSIS

SURVEY 2021/1

Sciensano/Flow cytometry/77-E

Expertise and service provision
Quality of laboratories
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A preliminary version of this report was submitted to the experts EQA Flow Cytometry on: 17/03/2021
This report was discussed at the meeting of the committee of experts EQA Flow Cytometry on: 23/03/2021

Authorization to release the report: By Lobna Bouacida, scheme coordinator, on 20/04/2021.

Lobna Bouacida
Digitally signed by Lobna Bouacida
Date: 2021.04.20 15:04:31 +02'00'

All the reports are also available on our webpage:
https://www.wiv-isp.be/QML/activities/external_quality/rapports/_nl/rapports_annee.htm
https://www.wiv-isp.be/QML/activities/external_quality/rapports/_fr/rapports_annee.htm

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INTERPRETATION OF THE INDIVIDUAL REPORT

Besides this global report, an individual report is at your disposal via toolkit.

Below you can find information to help you interpreting this report.

The position of your quantitative results is presented on the one hand in comparison with the results from all the participants and on the other hand in comparison with the results of the laboratories using your method.

Following information is provided:

- Your result (R)
- Your method
- Global median (M_G):
  central value of the results obtained by all laboratories (all methods together).
- Global standard deviation (SD_G):
  measure of the spread of the results obtained by all the laboratories (all methods together).
- Global median of your method (M_M):
  central value of the results obtained by the laboratories using your method.
- Standard deviation of your method (SD_M):
  measure of the spread of the results obtained by the laboratories using your method.
- The coefficient of variation CV (expressed in %) for all laboratories and for the laboratories using your method:
  $CV_M = (SD_M / M_M) * 100$ (%) and $CV_g = (SD_G / M_G) * 100$ (%).
- Z score:
  difference between your result and the median of your method (expressed as a number of SD): **$Z_M = (R – M_M) / SD_M$ and $Z_G = (R – M_G) / SD_G$**.
  The result is flagged when **$|Z_M| > 3$**.
- U score:
  relative deviation of your result from the median of your method (expressed in %):
  $U_m = ((R – M_M) / M_M) * 100$ (%) and $U_G = ((R – M_G) / M_G) * 100$ (%).
  The result is flagged when **$|U_M| > d$**, where "d" is a parameter-dependent fixed limit, namely the percentage maximal deviation from the method median.
- A graphical interpretation of the position of your result (R), towards the results of all the participants as well as the results of the participants using your method, based on the method of Tukey, for each parameter and for each analyzed sample.

  R : your result

  $M_{M/G}$: median

  $H_{M/G}$: percentiles 25 en 75

  $I_{M/G}$: internal limits (M ± 2.7 SD)

  $O_{M/G}$: external limits (M ± 4.7 SD)

The global graph and the one of your method are presented on the same scale, which allows you to compare them. These graphs give you a rough estimation of the position of your result (R) with respect to the medians ($M_{M/G}$).

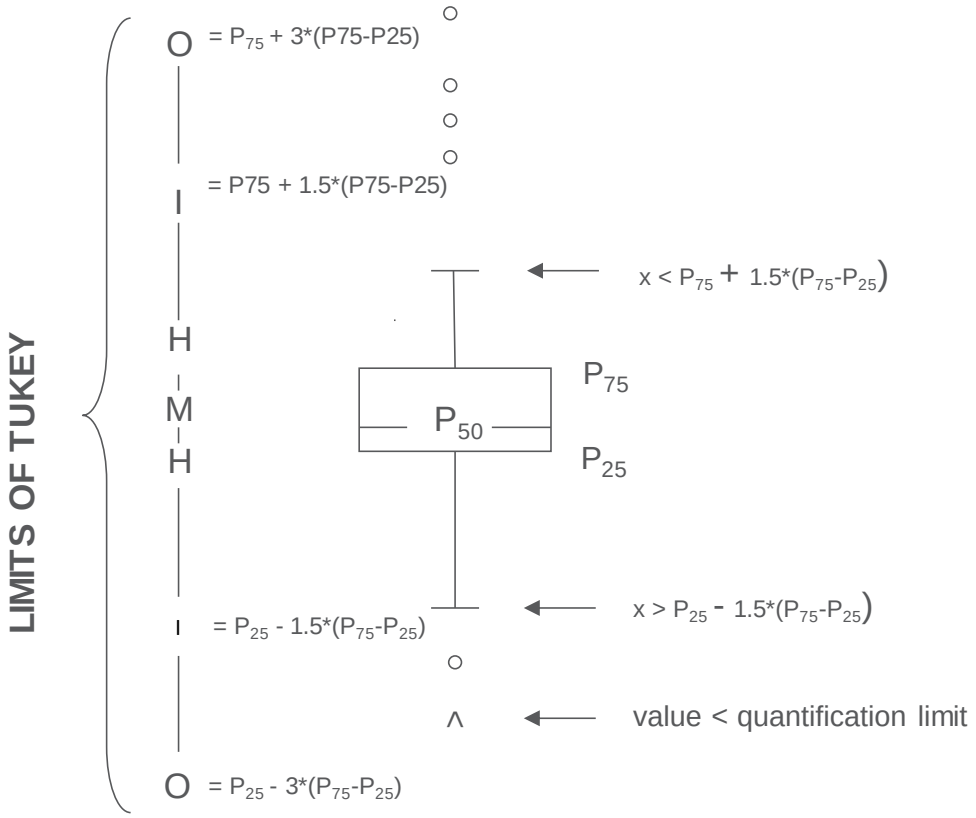
More information can be found in 3 brochures available on our website (only in Dutch and French):
https://www.wiv-isp.be/QML/index_nl.htm
https://www.wiv-isp.be/QML/index_fr.htm
(Choose “brochures” in the menu)
or directly on the following webpage (only in Dutch and French):
https://www.wiv-isp.be/QML/activities/external_quality/brochures/_nl/brochures.htm
https://www.wiv-isp.be/QML/activities/external_quality/brochures/_fr/brochures.htm

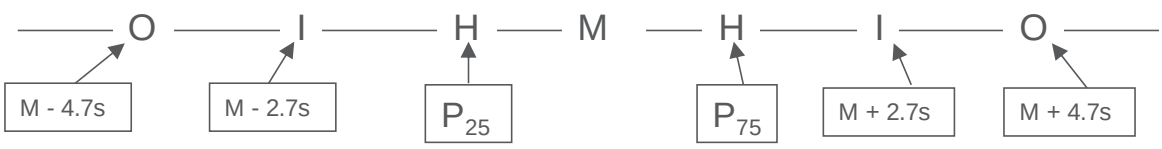
1. Informatiebrochure over de externe kwaliteitsevaluatieprogramma's voor klinische laboratoria (Algemene informatiebrochure over de externe evaluatie)/
   https://www.wiv-isp.be/QML/Informatiebrochure_EKE.pdf
   Brochure d’information sur les programmes d’évaluation externe de la qualité pour les laboratoires cliniques (Brochure d’information générale sur l’évaluation externe).
   https://www.wiv-isp.be/QML/Brochure_information_EEQ.pdf
2. Statistische brochure (Algemene statistische berekeningsprocedure opgesteld door Professor Albert)/ Brochure statistique (Procédure générale de calcul statistique mis au point par le professeur Albert).
3. Verwerking van gecensureerde waarden (Statistische berekeningsprocedure toegepast op de gecensureerde waarden opgesteld door Professor Albert)/
   Traitement des valeurs censurées (Procédure de calcul statistique appliquée aux valeurs censurées rédigée par le Professeur Albert).

Graphical representation

Besides the tables with the results a "Box and whisker" plot is added. It contains the following elements for the methods with at least 6 participants:

- a rectangle ranging from percentile 25 (**P_{25}**) to percentile 75 (**P_{75}**)
- a central line representing the median of the results (**P_{50}**)
- a lower limit showing the smallest value **$x > P_{25} - 1.5 * (P_{75} - P_{25})$**
- an upper limit representing the largest value **$x < P_{75} + 1.5 * (P_{75} - P_{25})$**
- all points outside this interval are represented by a dot.





Corresponding limits in case of normal distribution

SAMPLE MATERIAL

Two blood samples (FC/17921 and FC/17922) collected on K2EDTA were sent to the laboratories.

These two samples were collected from two healthy and voluntary blood donors and distributed into aliquots at Sciensano.

The samples were sent by Taxipost 24h and the laboratories were informed by e-mail of the send-out of the control material (day 0).

The samples tested negative for HIV 1 and 2, hepatitis B surface antigen and hepatitis C. Homogeneity was confirmed based on white blood cells determination.

Control analysis on the day of collection and distribution yielded the following results (UZ Brussel):

FC17921

	%	10^9/L
Leukocytes		8.1
Lymphocytes	39.0	
$CD3^+$ cells	82.5	2.61
$CD4^+CD3^+$ cells	63.3	2.00
$CD8^+CD3^+$ cells	18.2	0.57
$CD19^+$ cells	8.2	0.26
NK cells	7.5	0.24
κ % B lymphocytes	66.6	
λ % B lymphocytes	33.4	
κ/λ ratio	1.99	

FC17922

	%	10^9/L
Leukocytes		7.4
Lymphocytes	32.3	
$CD3^+$ cells	61.3	1.47
$CD4^+CD3^+$ cells	34.9	0.83
$CD8^+CD3^+$ cells	25.6	0.61
$CD19^+$ cells	11.5	0.27
NK cells	25.5	0.61
κ % B lymphocytes	67.0	
λ % B lymphocytes	33.0	
κ/λ ratio	2.03	

PARTICIPATION

Fifty-two laboratories (1 Canadian and 51 Belgian clinical laboratories) participated in the survey 2021/1 (send-out of blood samples on February 22, 2021 (day 0)).

RESULTS

100% of the Belgian laboratories received the samples on day 1 or 2. 47 laboratories (92%) received the samples on day 1 and four (8%) received them on day 2.

82% (n=42) of the Belgian laboratories performed the analyses on day 1, 16% (n=12) on day 2 and 2% (n=1) on day 3.

Since the samples are fresh and not stabilised, it is extremely important to perform sample testing as soon as possible upon receipt.

Statistics for the evaluation are solely based on the results of the Belgian clinical laboratories (n=51). Statistics for the evaluation of the WBC count, the percentage of lymphocytes by haematology analyser as well as the absolute counts for the different lymphocyte subsets are solely based on the results of the Belgian clinical laboratories that performed the analyses on day 1 or 2 (n=50).

The following table shows the medians and coefficients of variation obtained by the Belgian clinical laboratories for the samples FC/17921 and FC/17922:

FC/17921	Median	SD	CV,%	N
WBC 10E9/L	7.84	0.22	2.8	49
Lympho% haematology analyser	37.7	0.7	2.0	46
Lympho% flow cytometer	37.4	1.8	4.7	46
CD3 %	76.8	1.2	1.5	51
CD3 10E9/L	2.290	0.126	5.5	49
CD4 %	57.2	1.5	2.6	51
CD4 10E9/L	1.726	0.120	6.9	49
CD8 %	18.0	0.9	5.2	51
CD8 10E9/L	0.521	0.041	8.0	49
CD19 %	12.6	0.7	5.9	51
CD19 10E9/L	0.370	0.033	8.8	49
NKcells %	10.0	1.1	11.2	51
NKcells 10E9/L	0.298	0.044	14.9	49
Kappa % B lymphocytes	66.3	1.5	2.2	45
Lambda % B lymphocytes	33.0	1.4	4.3	45
Kappa/lambda	2.00	0.14	7.2	45
Sum K+L % B lymphocytes	99.7	0.7	0.7	45
Lymphosum %	99.4	0.7	0.7	51

FC/17922	Median	SD	CV,%	N
WBC 10E9/L	7.34	0.19	2.6	49
Lympho% haematology analyser	32.7	1.0	2.9	46
Lympho% flow cytometer	32.4	2.0	6.2	46
CD3 %	63.5	1.1	1.7	51
CD3 10E9/L	1.531	0.087	5.7	49
CD4 %	35.3	1.1	3.1	51
CD4 10E9/L	0.850	0.050	5.9	49
CD8 %	26.4	0.9	3.4	51
CD8 10E9/L	0.640	0.044	6.9	49
CD19 %	11.0	1.2	10.8	51
CD19 10E9/L	0.260	0.036	13.7	49
NKcells %	24.7	1.8	7.4	51
NKcells 10E9/L	0.600	0.070	11.6	49
Kappa % B lymphocytes	62.2	2.6	4.2	44
Lambda % B lymphocytes	36.1	3.5	9.6	44
Kappa/lambda	1.75	0.24	13.5	44
Sum K+L % B lymphocytes	99.8	0.7	0.7	44
Lymphosum %	99.1	1.1	1.1	51

For sample FC/17922, six laboratories reported the presence of a subset of NK cells expressing weakly the B cell antigen CD19. This population was estimated at +/- 40% of the NK cells.

The apparent NK cell expression of CD19 by flow cytometry is an infrequent finding. The primary potential clinical consequence is misinterpretation of these CD19 positive NK cell subpopulations as an abnormal B lymphoblast population in minimal residual disease analysis for B lymphoblastic leukemia[1].

Since CD19+NK cells may represent a significant percentage of the lymphocyte population, the potential clinical consequence can be exapanded to even possibly masking low values of B lymphocytes or inducing an over-quantification of the B cell subset by taking the CD19+ NK cells as true B cells. Another potential confounding factor would result from the analysis of the routine memory B lymphocytes compartment through the quantification of CD19+CD27+ cells, when evaluating B cell profile. Since this antigen was negative in all CD191NK cells, those cells would qualify as nonmemory B cells by standard analysis and these patients would appear to have lower memory B cells[2].

It is thus recommended that when evaluating lymphocyte populations there should be at least one tube in which CD19 and CD56 are combined together as a way to easily detect if there is a population CD56+ and CD19+dim which should be further characterized to verify its NK lineage assignment[2]. Additional markers should also be used.

However, the clinical significance of this population is unknown. If there are no clinical symptoms, additional examinations are not recommended.

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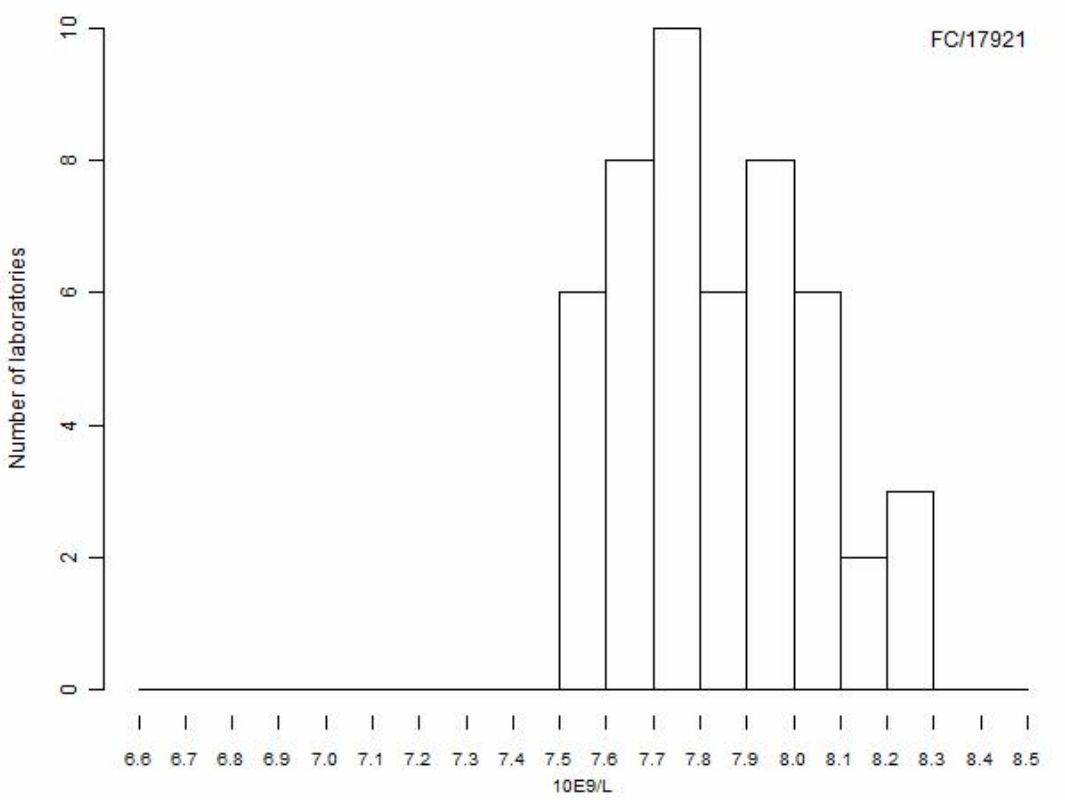
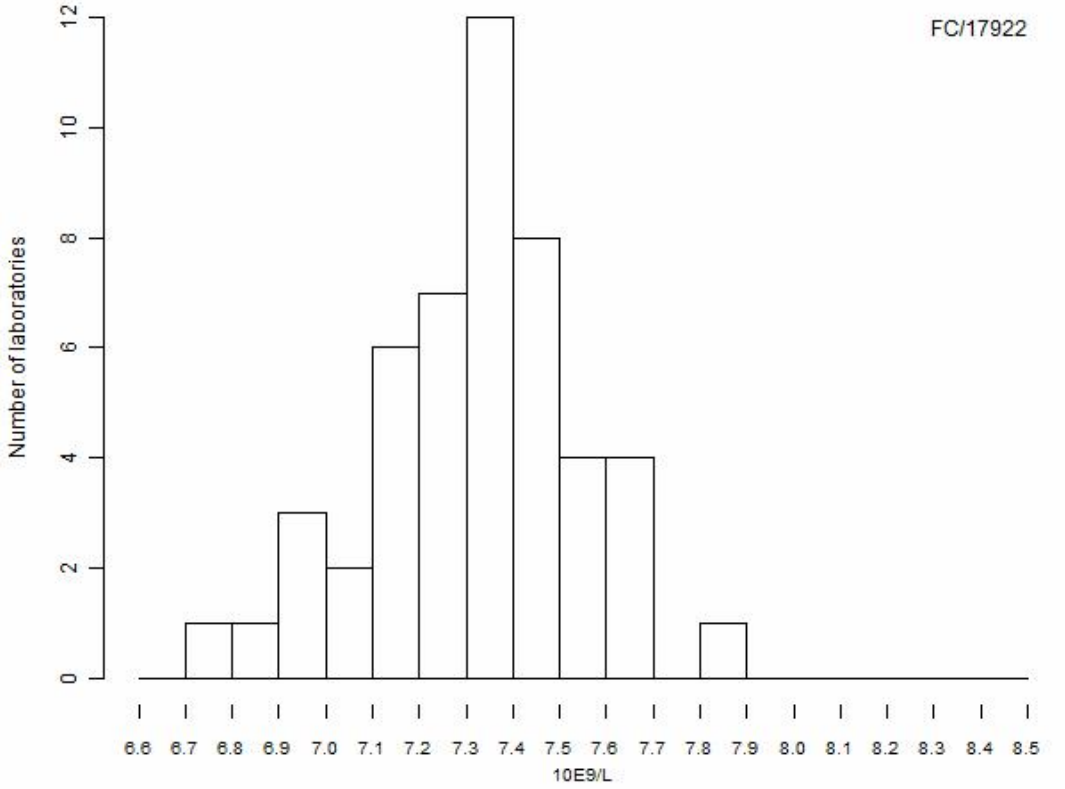
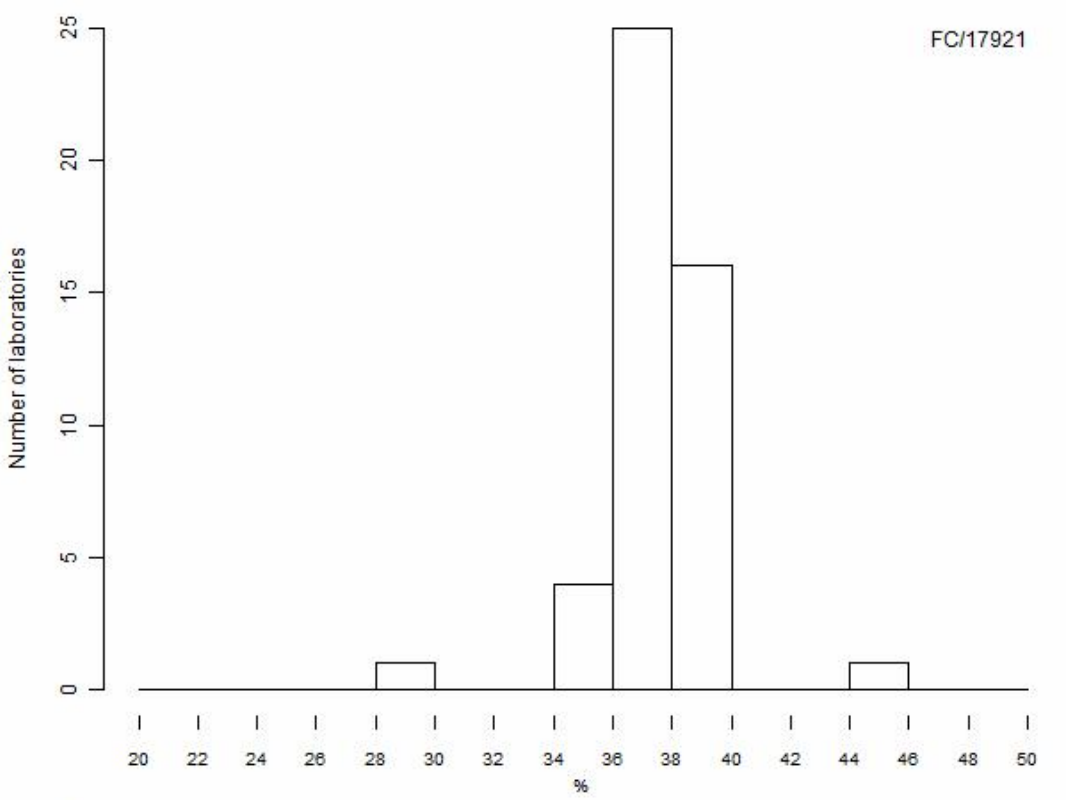
1. Soma L, Wu D, Chen X, et al. Apparent CD19 expression by natural killer cells: a potential confounder for minimal residual disease detection by flow cytometry in B lymphoblastic leukemia. *Cytometry B Clin Cytom. 2015*;88:145.
2. Korol C, Rossi J, Sanz M, Bernasconi A. NK cells expressing the B cell antigen CD19: Expanding the phenotypical characterization and the potential consequences from misinterpretation of this subset population. *Cytometry B Clin Cytom. 2015*;88(6):358–360.

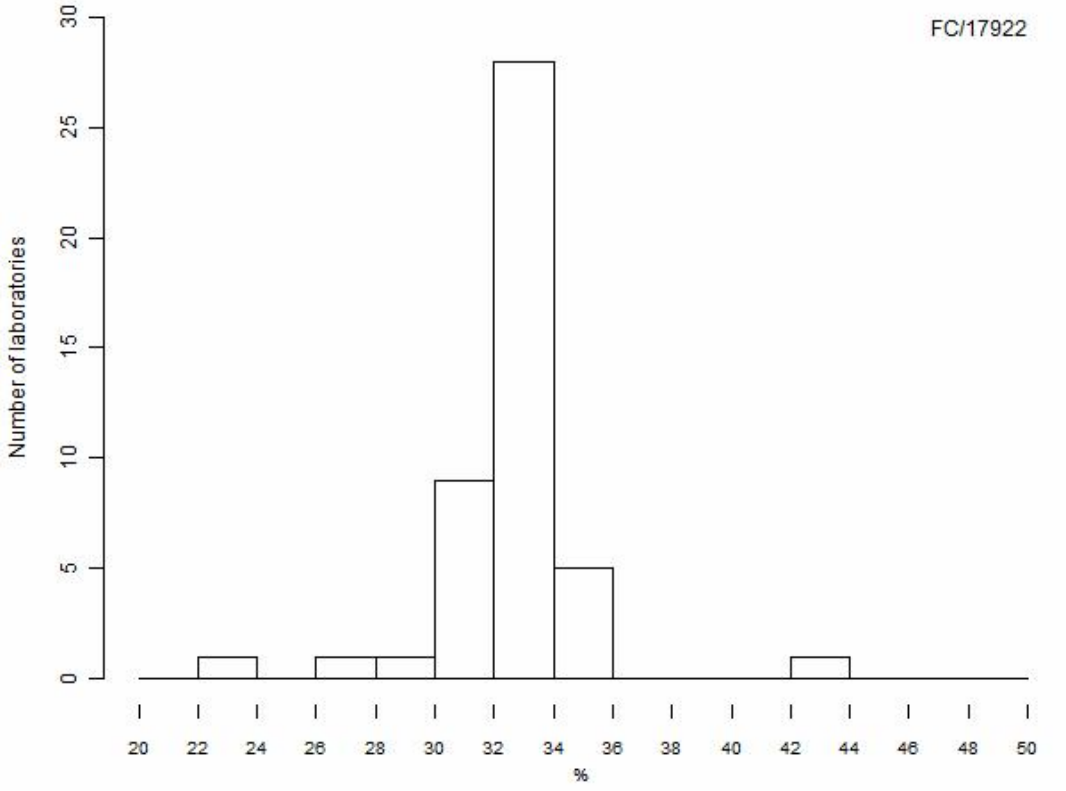
WBC 10E9/L


FC/17921
Number of laboratories
0
2
4
6
8
10
6.6 6.7 6.8 6.9 7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7 7.8 7.9 8.0 8.1 8.2 8.3 8.4 8.5
10E9/L

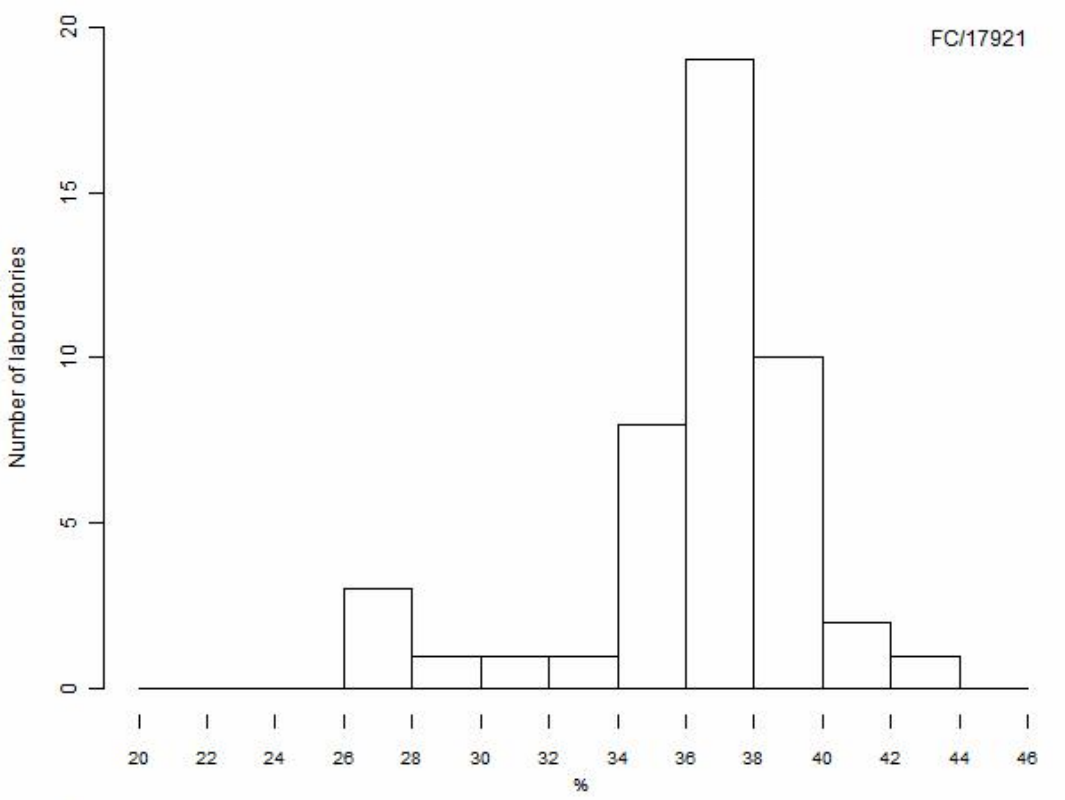

FC/17922
Number of laboratories
0
2
4
6
8
10
12
6.6 6.7 6.8 6.9 7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7 7.8 7.9 8.0 8.1 8.2 8.3 8.4 8.5
10E9/L

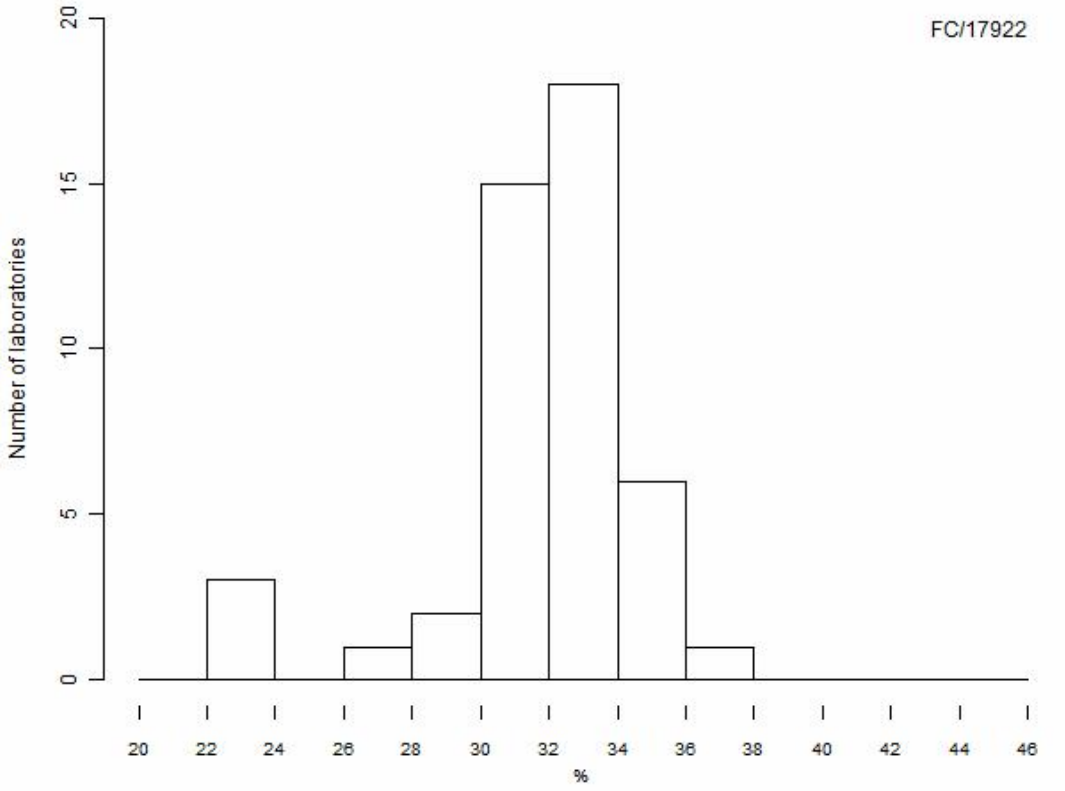
Lympho% haematology analyser



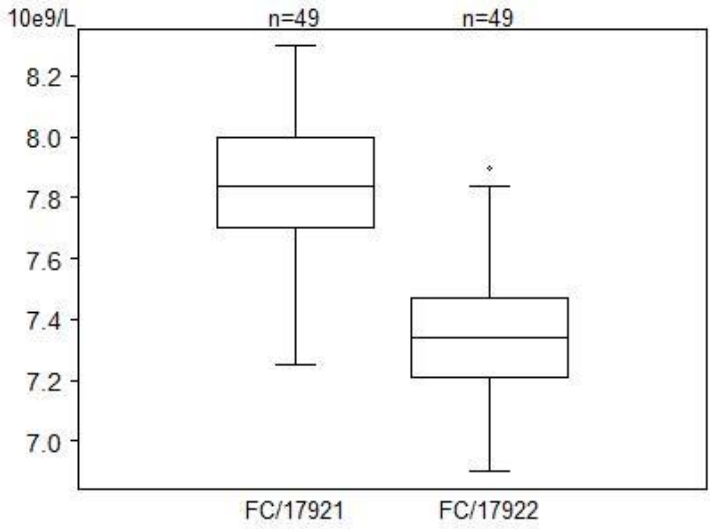


Lympho% flow cytometer





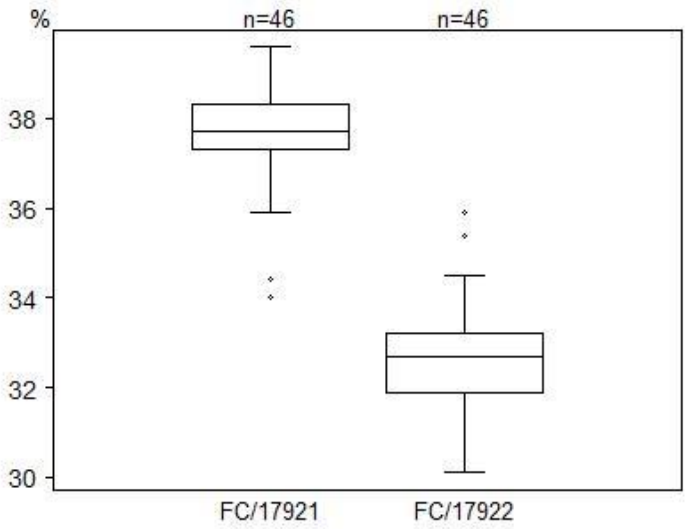
WBC 10E9/L



Results not represented on the graph

FC/17921 = 7700 10e9/
FC/17922 = 6.72 10e9/l
FC/17922 = 7210 10e9/

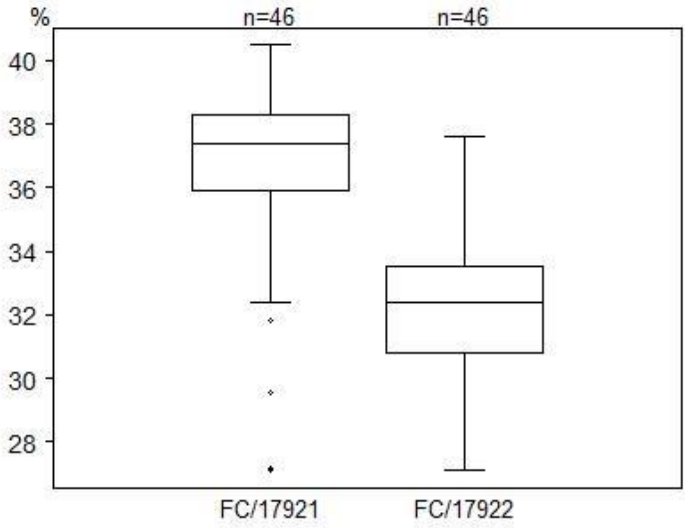
Lympho% haematology analyser



Results not represented on the graph

FC/17921 = 29.6 %
FC/17921 = 46 %
FC/17922 = 2.4 %
FC/17922 = 22.4 %
FC/17922 = 27.8 %
FC/17922 = 28.5 %
FC/17922 = 43 %

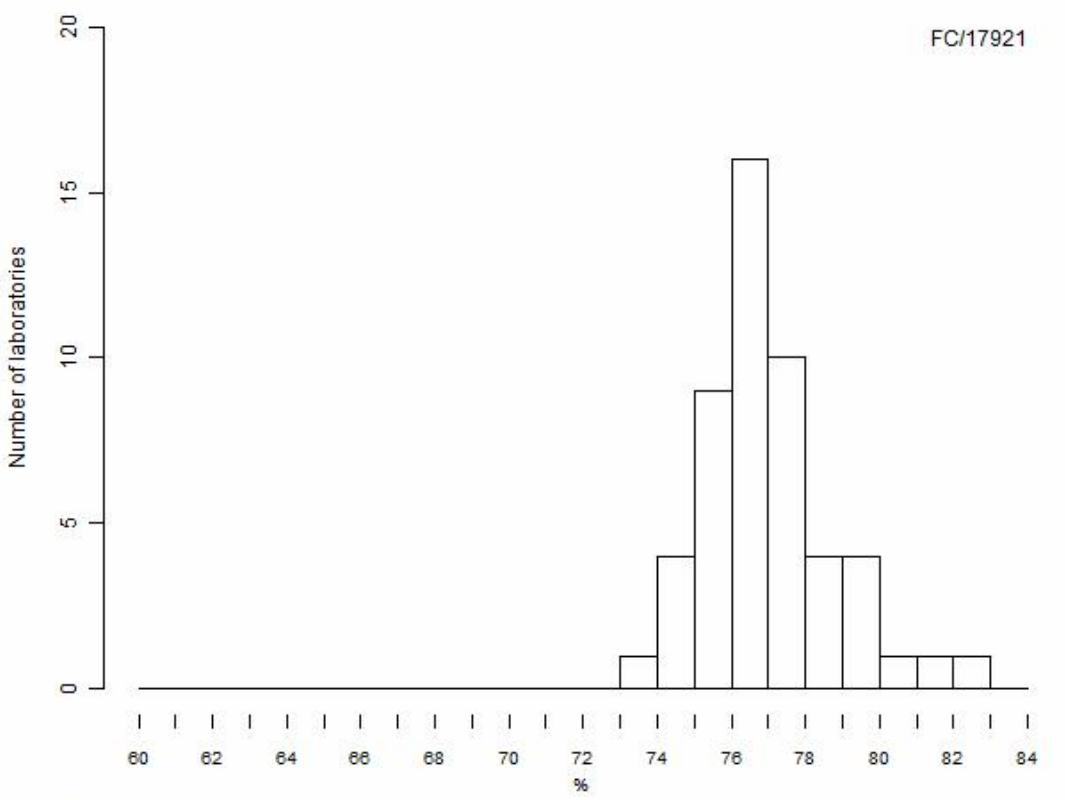
Lympho% flow cytometer

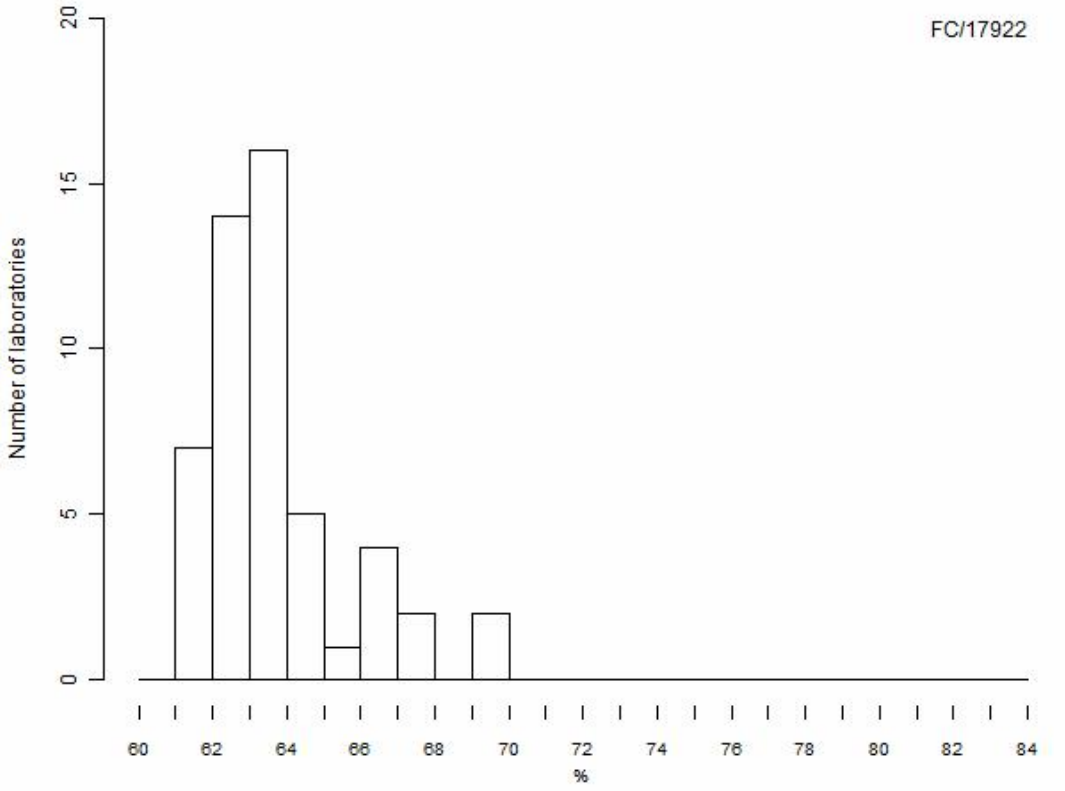


Results not represented on the graph

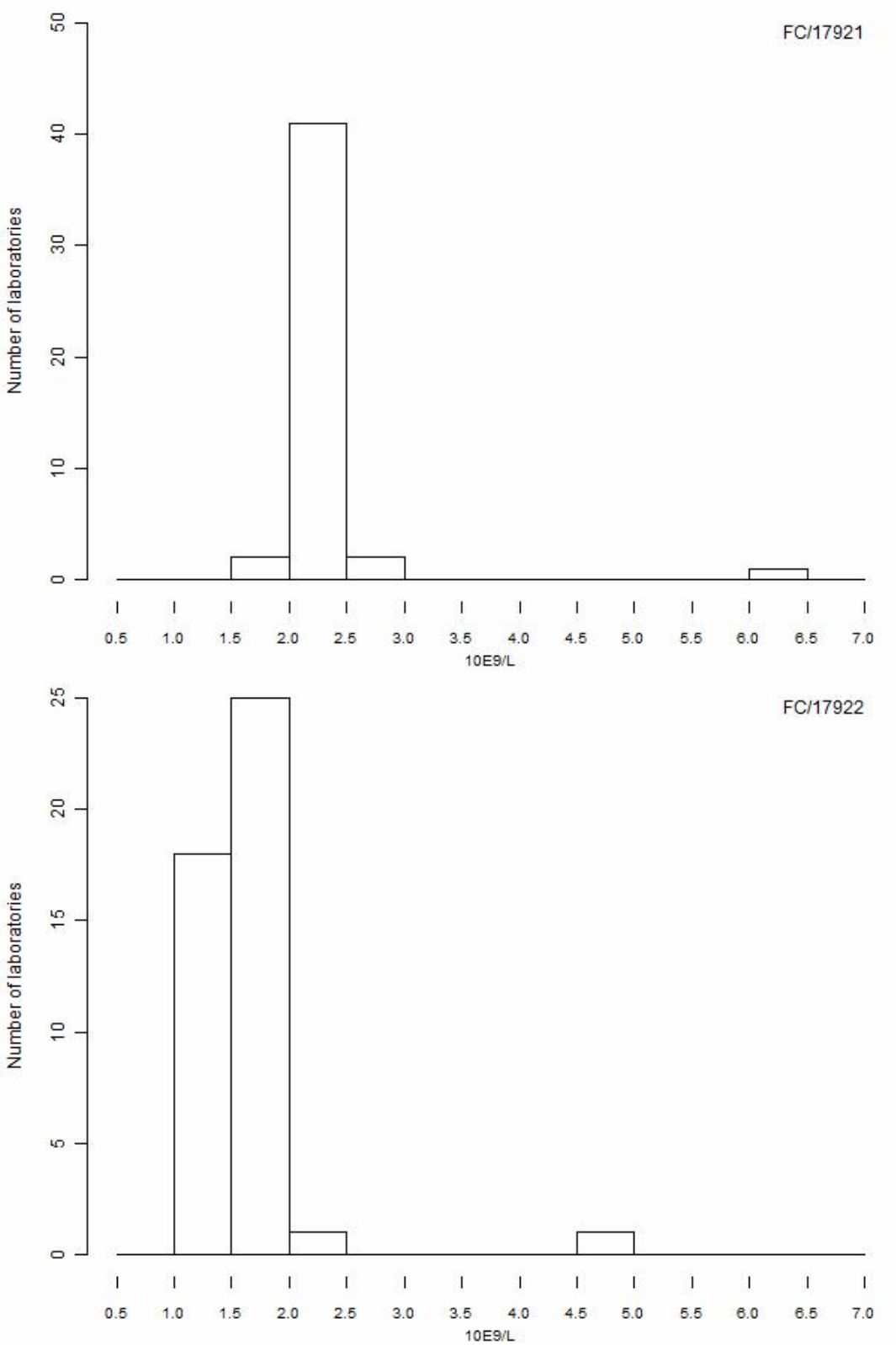
FC/17921 = 26.4 %
FC/17921 = 42 %
FC/17921 = 42.1 %
FC/17922 = 22.8 %
FC/17922 = 22.9 %
FC/17922 = 22.9 %

CD3 %

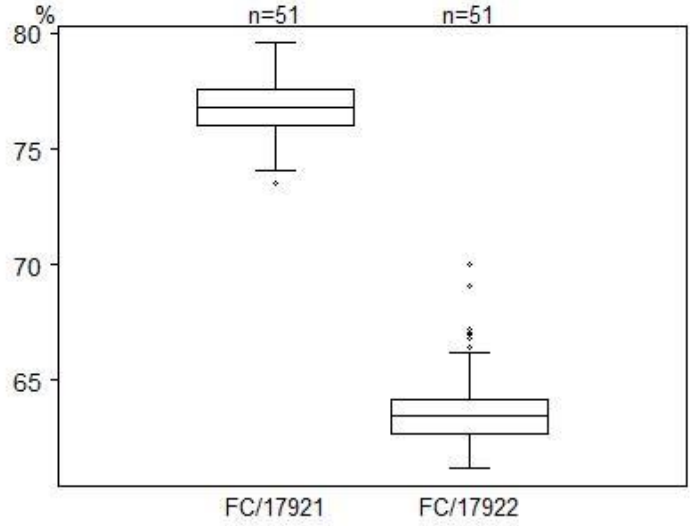

FC/17921
Number of laboratories
0
5
10
15
20
60
62
64
66
68
70
72
74
76
78
80
82
84
%


FC/17922
Number of laboratories
0
5
10
15
20
60
62
64
66
68
70
72
74
76
78
80
82
84
%

CD3 10E9/L


FC/17921
Number of laboratories
0
10
20
30
40
50
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
10E9/L
FC/17922
Number of laboratories
0
5
10
15
20
25
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
10E9/L

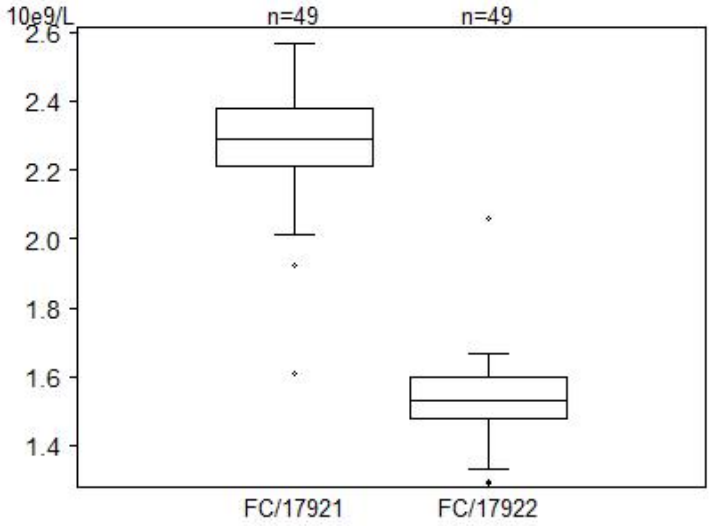
CD3 %



Results not represented on the graph

FC/17921 = 81 %
FC/17921 = 81.7 %
FC/17921 = 82.1 %

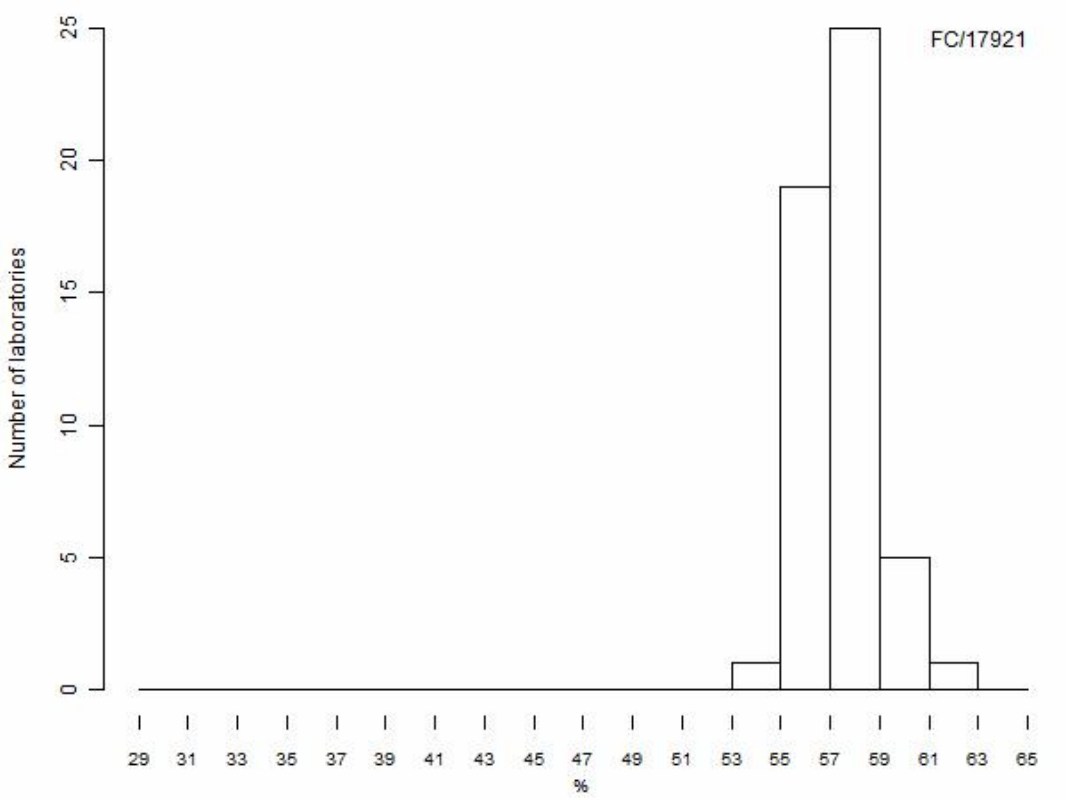
CD3 10E9/L

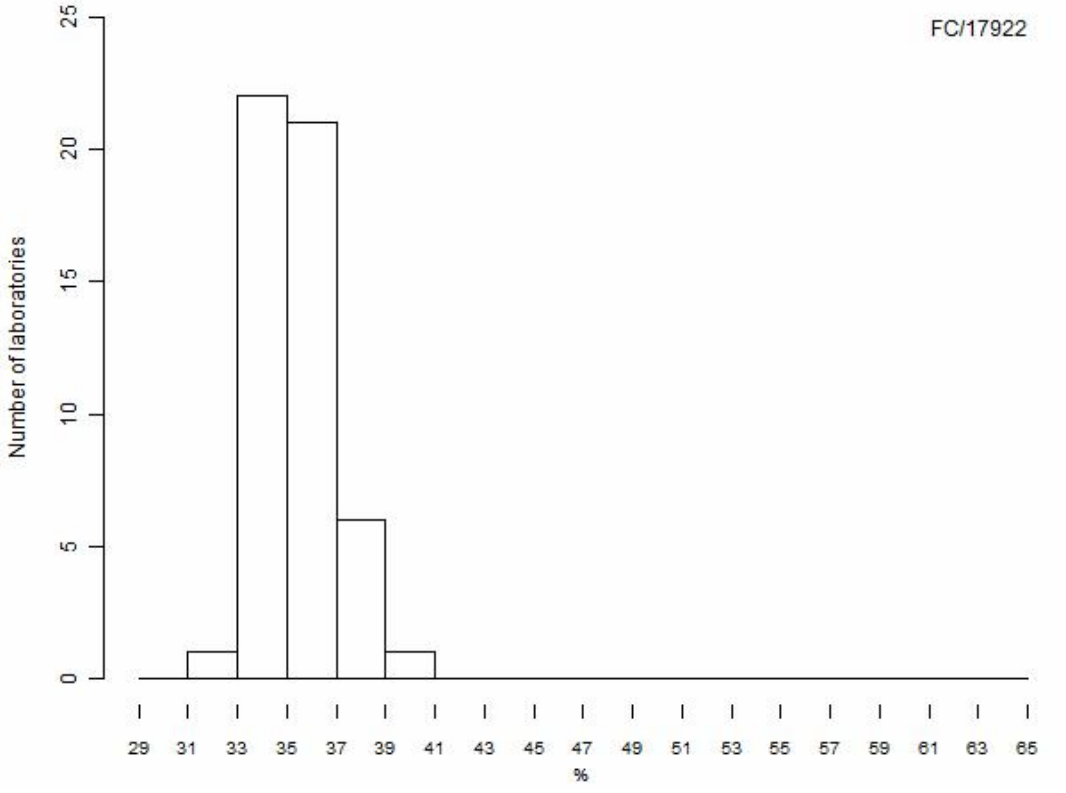


Results not represented on the graph

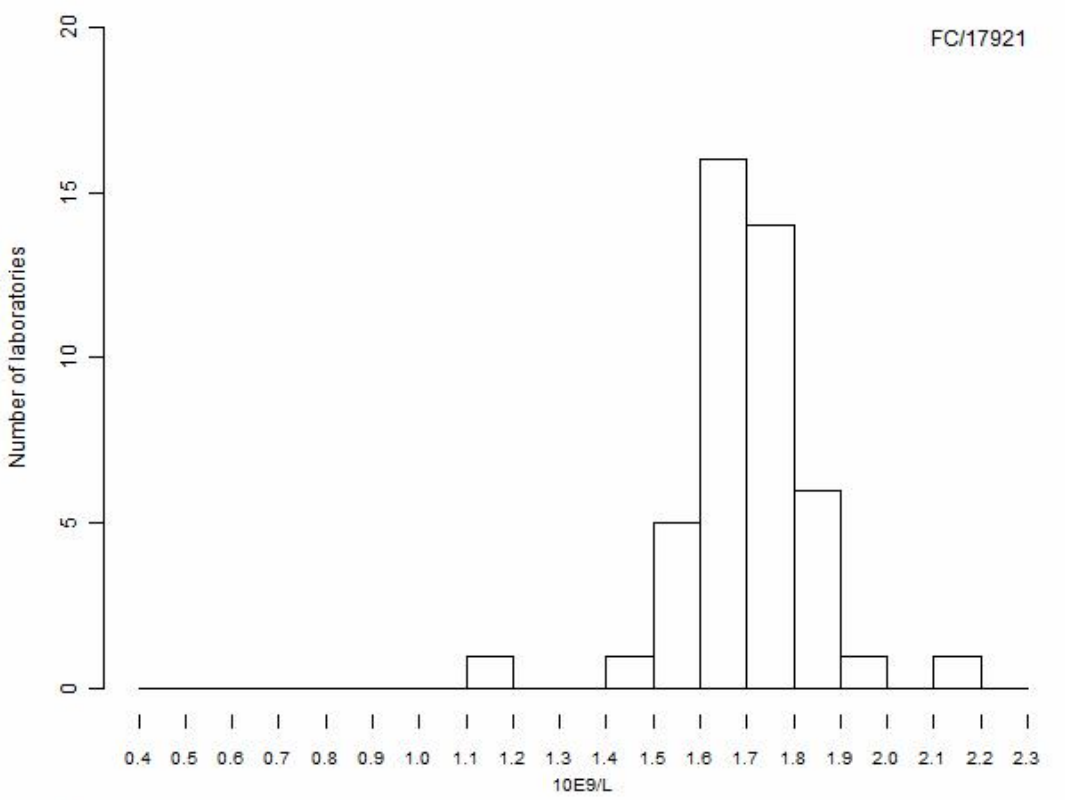
FC/17921 = 2.917 10e9
FC/17921 = 6.12 10e9/l
FC/17921 = 1621 10e9/
FC/17921 = 2225 10e9/
FC/17921 = 2247 10e9/
FC/17921 = 2260 10e9/
FC/17922 = 1.1 10e9/L
FC/17922 = 4.63 10e9/l
FC/17922 = 1097 10e9/
FC/17922 = 1508 10e9/
FC/17922 = 1587 10e9/
FC/17922 = 1599 10e9/
FC/17922 = 1650 10e9/

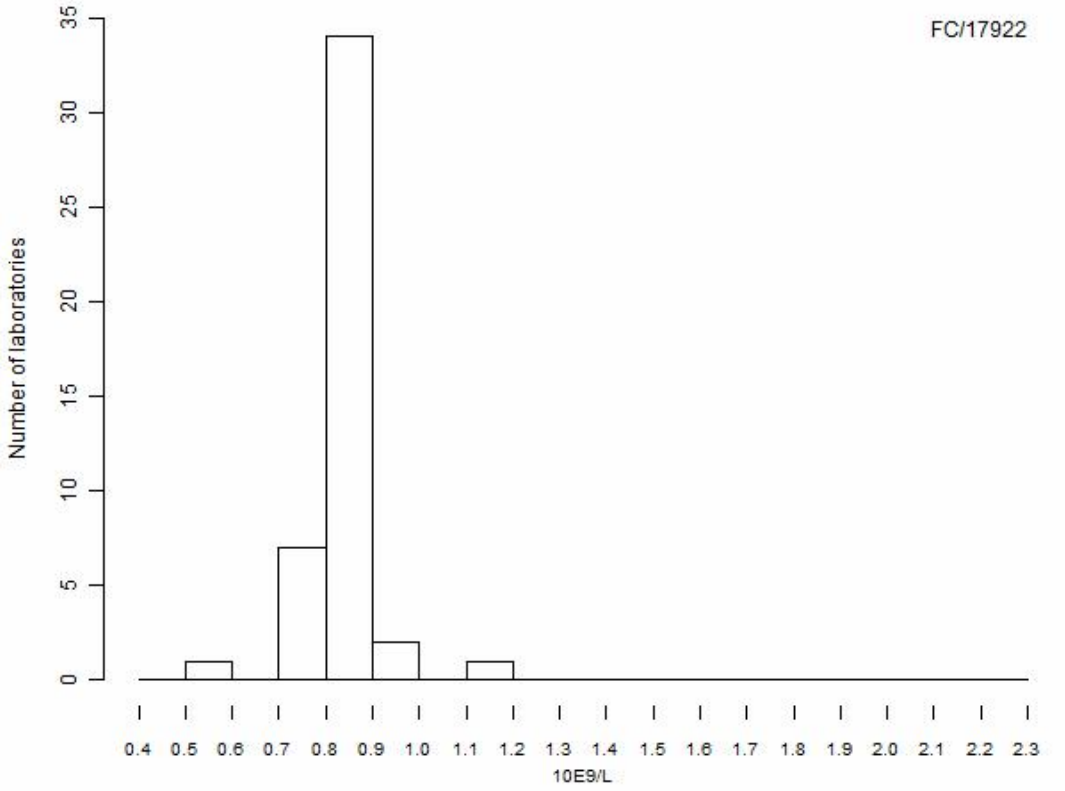
CD4 %


FC/17921
Number of laboratories
0
5
10
15
20
25
29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65
%

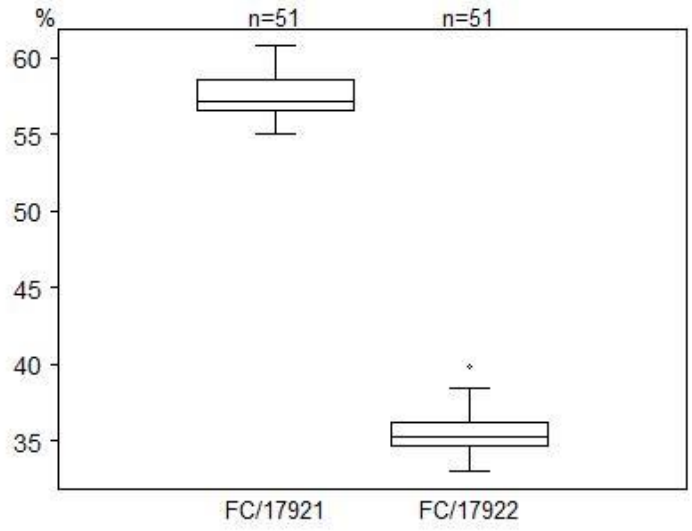

FC/17922
Number of laboratories
0
5
10
15
20
25
29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65
%

CD4 10E9/L


FC/17921
Number of laboratories
0
5
10
15
20
0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3
10E9/L


FC/17922
Number of laboratories
0
5
10
15
20
25
30
35
0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3
10E9/L

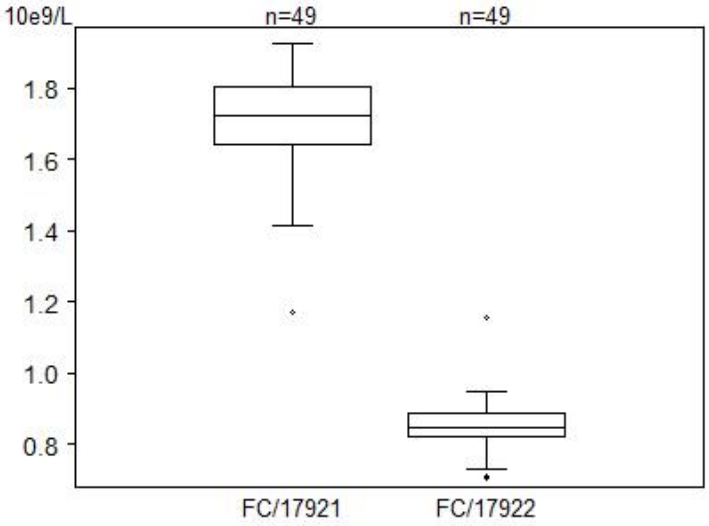
CD4 %



Results not represented on the graph

FC/17921 = 62.1 %

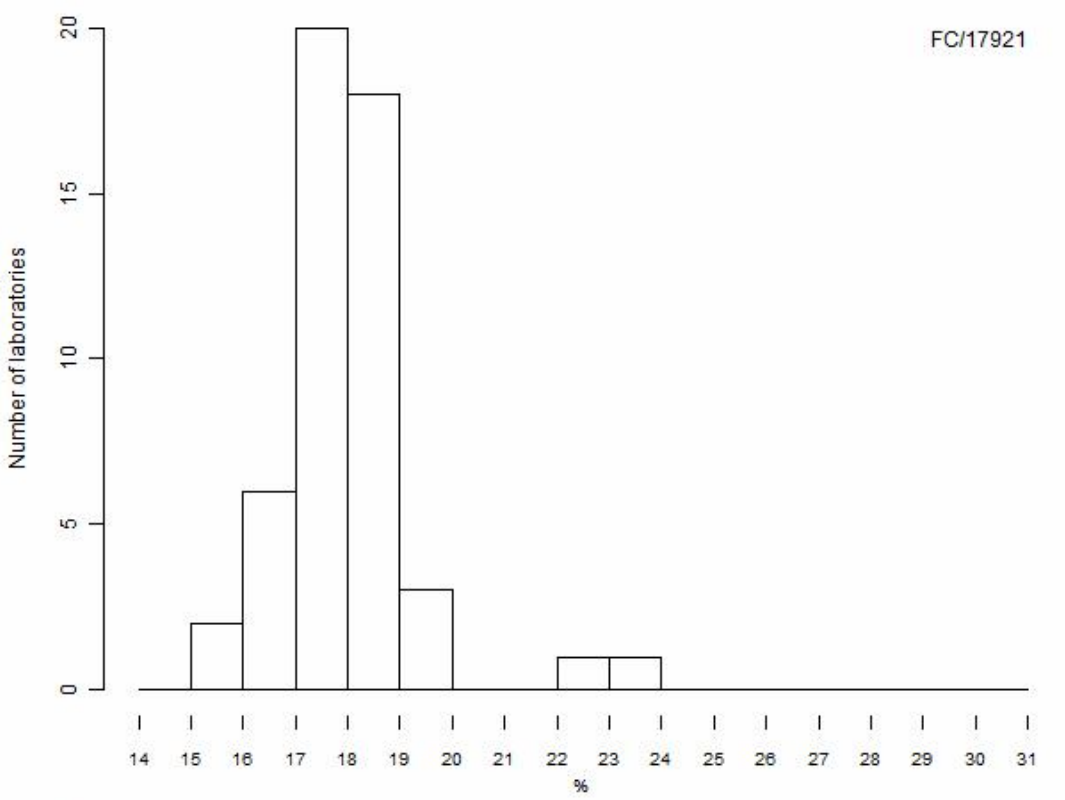
CD4 10E9/L

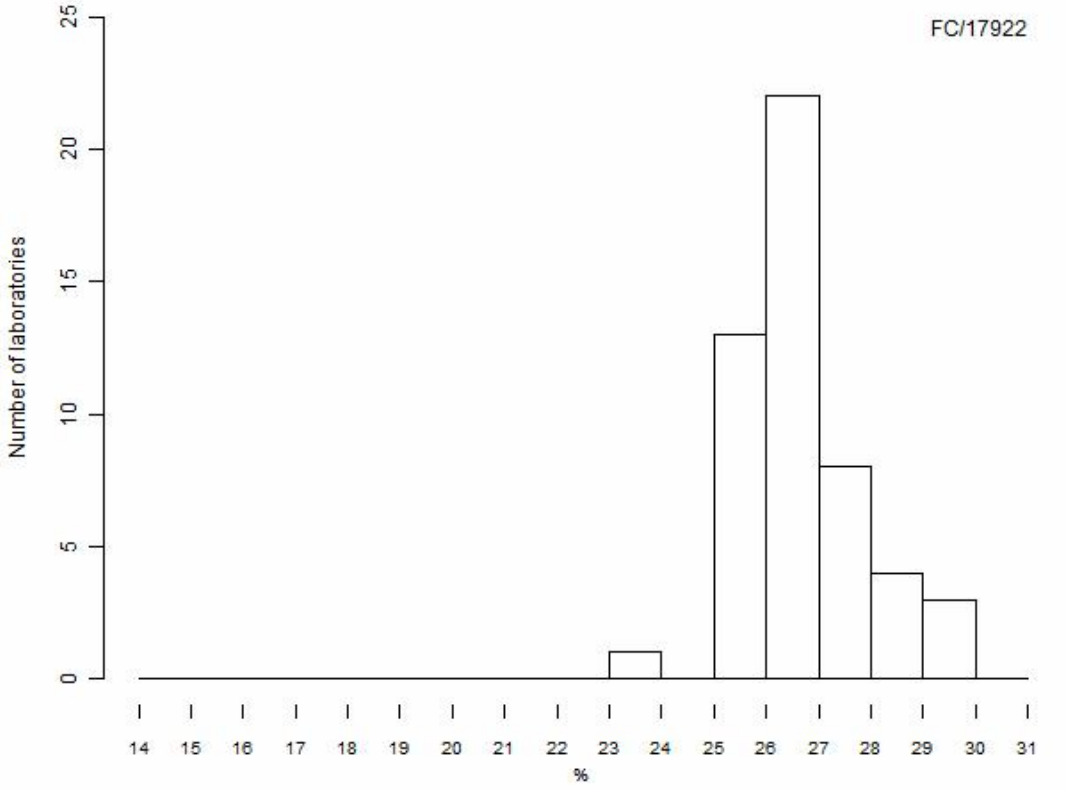


Results not represented on the graph

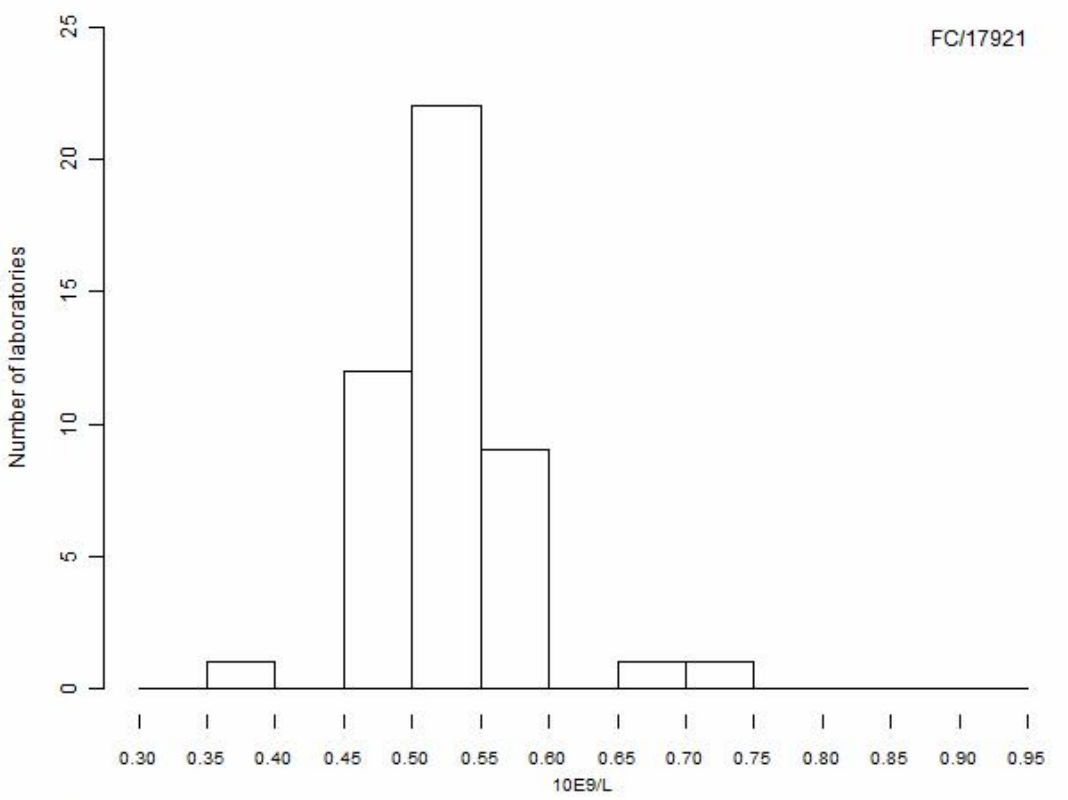
FC/17921 = 2.148 10e9
FC/17921 = 4.68 10e9/l
FC/17921 = 1180 10e9/
FC/17921 = 1635 10e9/
FC/17921 = 1675 10e9/
FC/17921 = 1726 10e9/
FC/17922 = 0.57 10e9/l
FC/17922 = 2.79 10e9/l
FC/17922 = 570 10e9/L
FC/17922 = 864 10e9/L
FC/17922 = 897 10e9/L
FC/17922 = 914 10e9/L

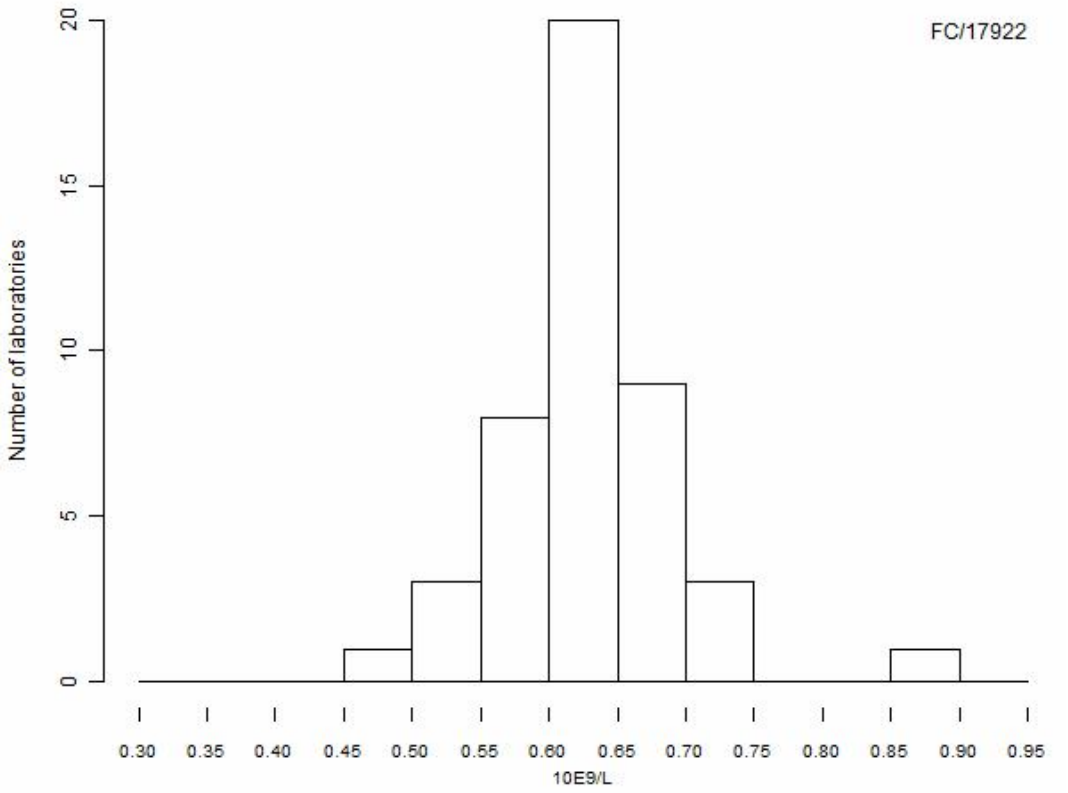
CD8 %


FC/17921
Number of laboratories
0
5
10
15
20
14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
%

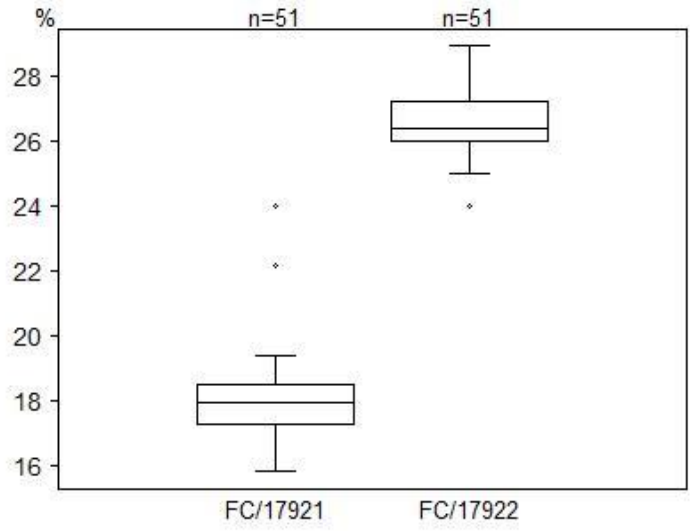

FC/17922
Number of laboratories
0
5
10
15
20
25
14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
%

CD8 10E9/L


FC/17921
Number of laboratories
0
5
10
15
20
25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
10E9/L


FC/17922
Number of laboratories
0
5
10
15
20
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
10E9/L

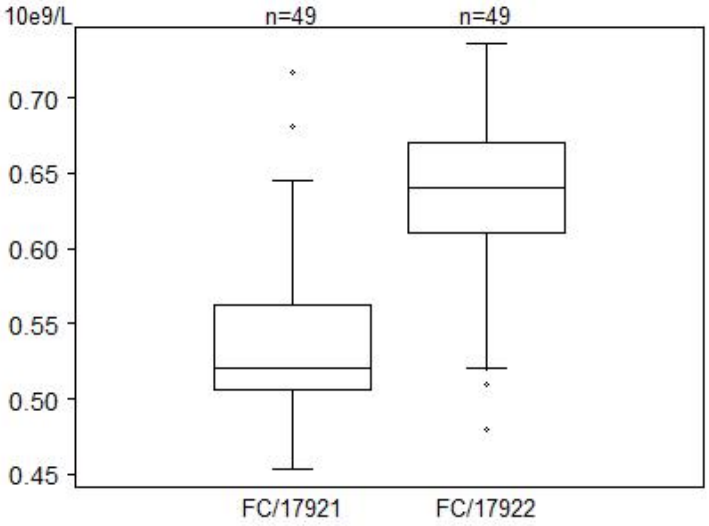
CD8 %



Results not represented on the graph

FC/17922 = 29.6 %
FC/17922 = 29.7 %
FC/17922 = 29.7 %

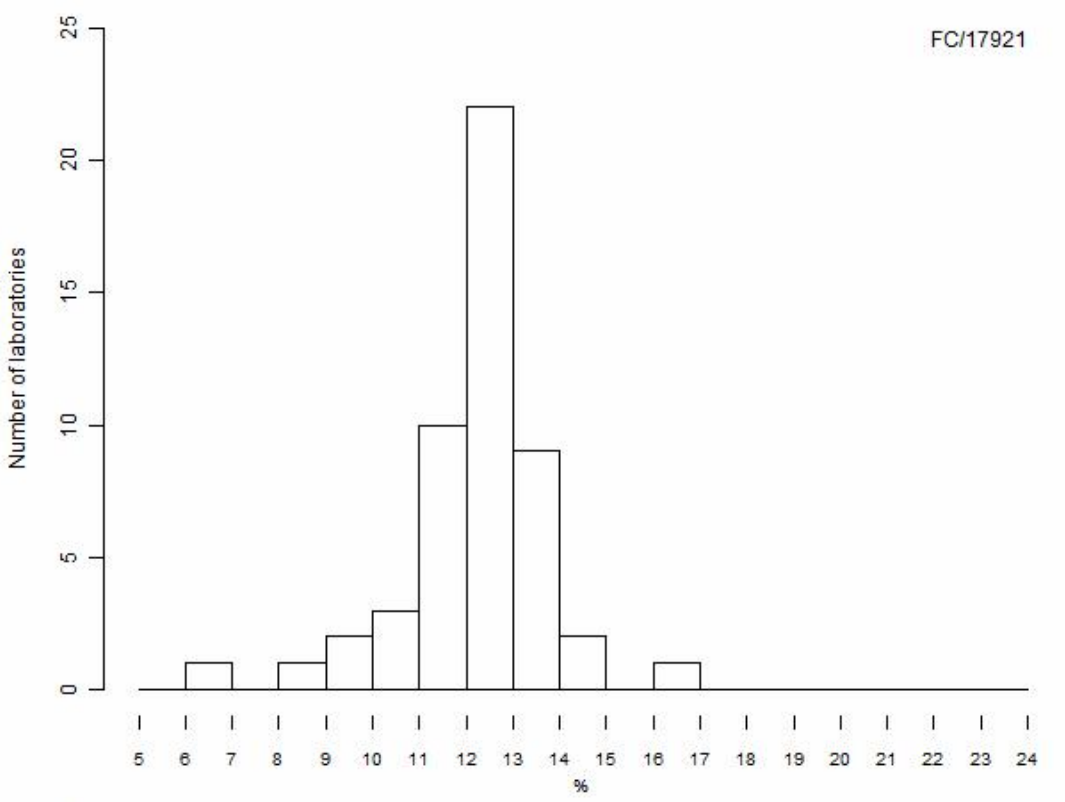
CD8 10E9/L

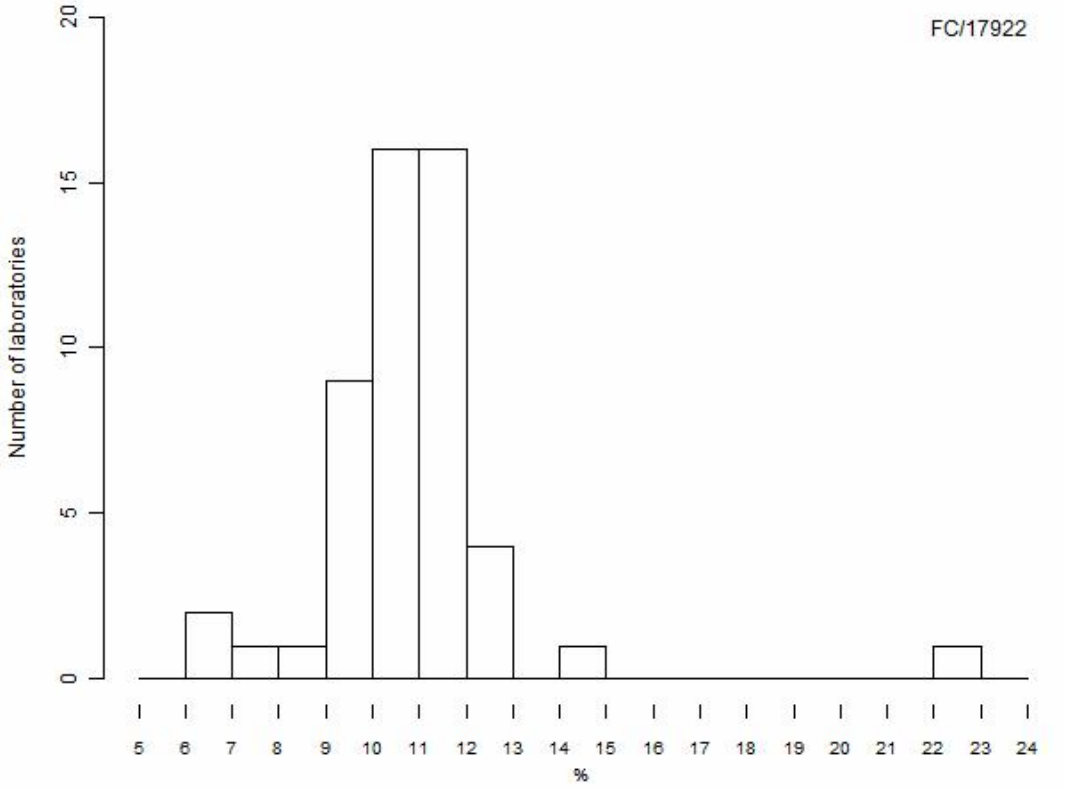


Results not represented on the graph

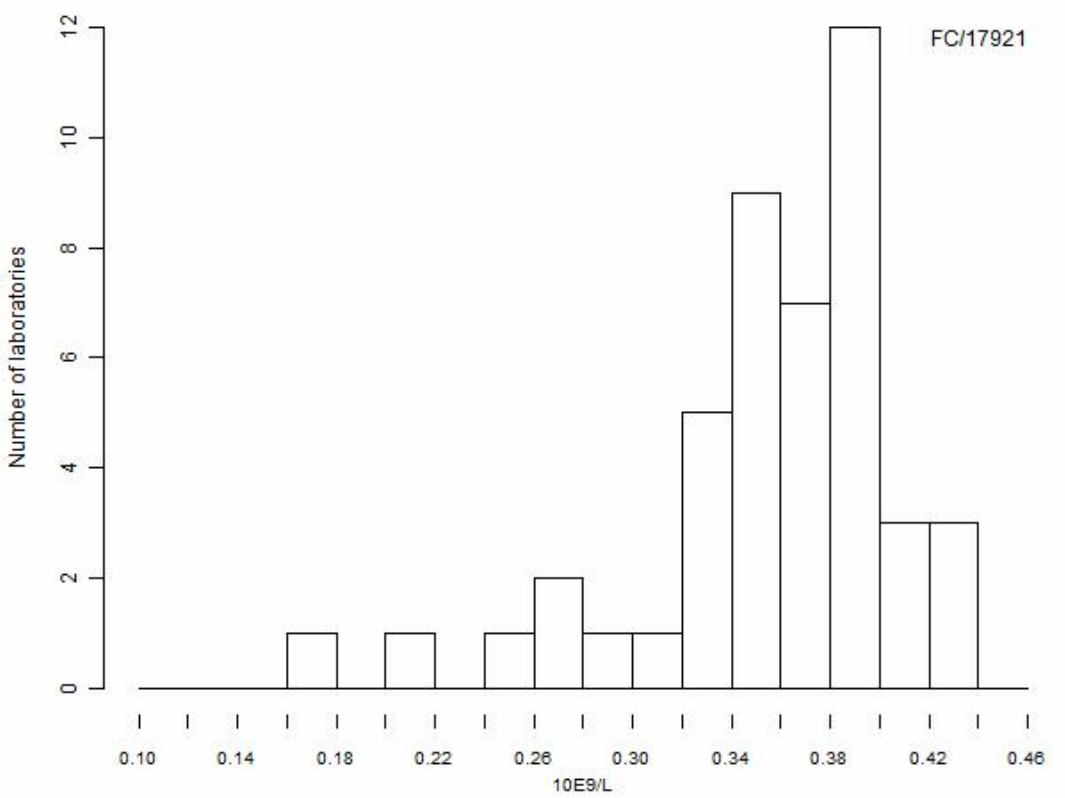
FC/17921 = 0.4 10e9/L
FC/17921 = 1.77 10e9/l
FC/17921 = 402 10e9/L
FC/17921 = 482 10e9/L
FC/17921 = 527 10e9/L
FC/17922 = 0.875 10e9
FC/17922 = 2.12 10e9/l
FC/17922 = 486 10e9/L
FC/17922 = 654 10e9/L
FC/17922 = 660 10e9/L
FC/17922 = 666 10e9/L

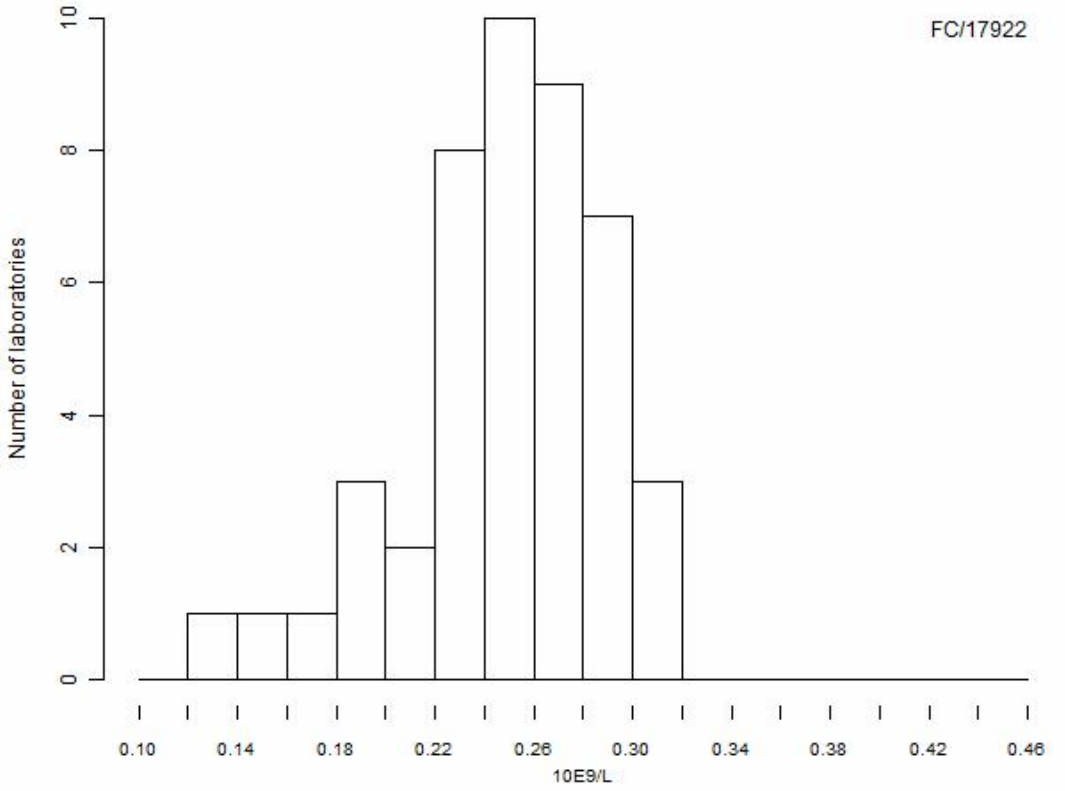
CD19 %


FC/17921
Number of laboratories
0
5
10
15
20
25
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
%

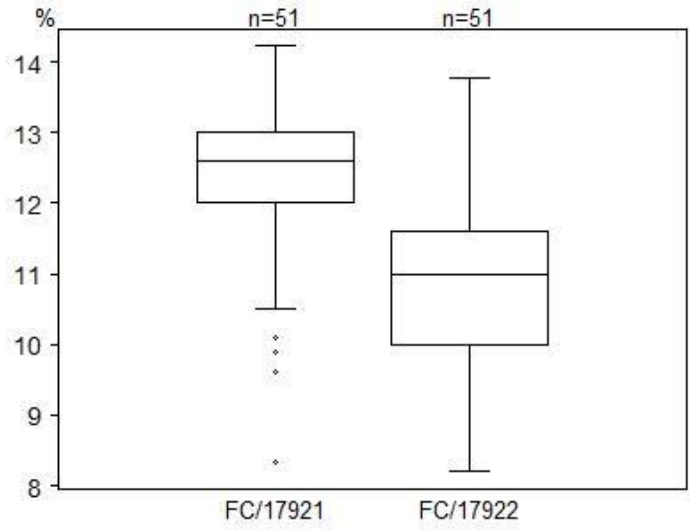

FC/17922
Number of laboratories
0
5
10
15
20
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
%

CD19 10E9/L


FC/17921
Number of laboratories
0
2
4
6
8
10
12
0.10
0.14
0.18
0.22
0.26
0.30
0.34
0.38
0.42
0.46
10E9/L


FC/17922
Number of laboratories
0
2
4
6
8
10
0.10
0.14
0.18
0.22
0.26
0.30
0.34
0.38
0.42
0.46
10E9/L

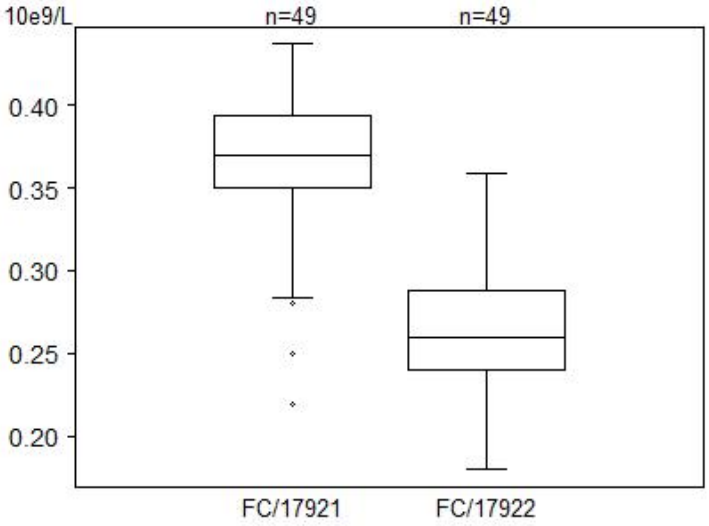
CD19 %



Results not represented on the graph

FC/17921 = 6.7 %
FC/17921 = 14.7 %
FC/17921 = 16.5 %
FC/17922 = 6.3 %
FC/17922 = 6.3 %
FC/17922 = 7.5 %
FC/17922 = 14.6 %
FC/17922 = 22.6 %

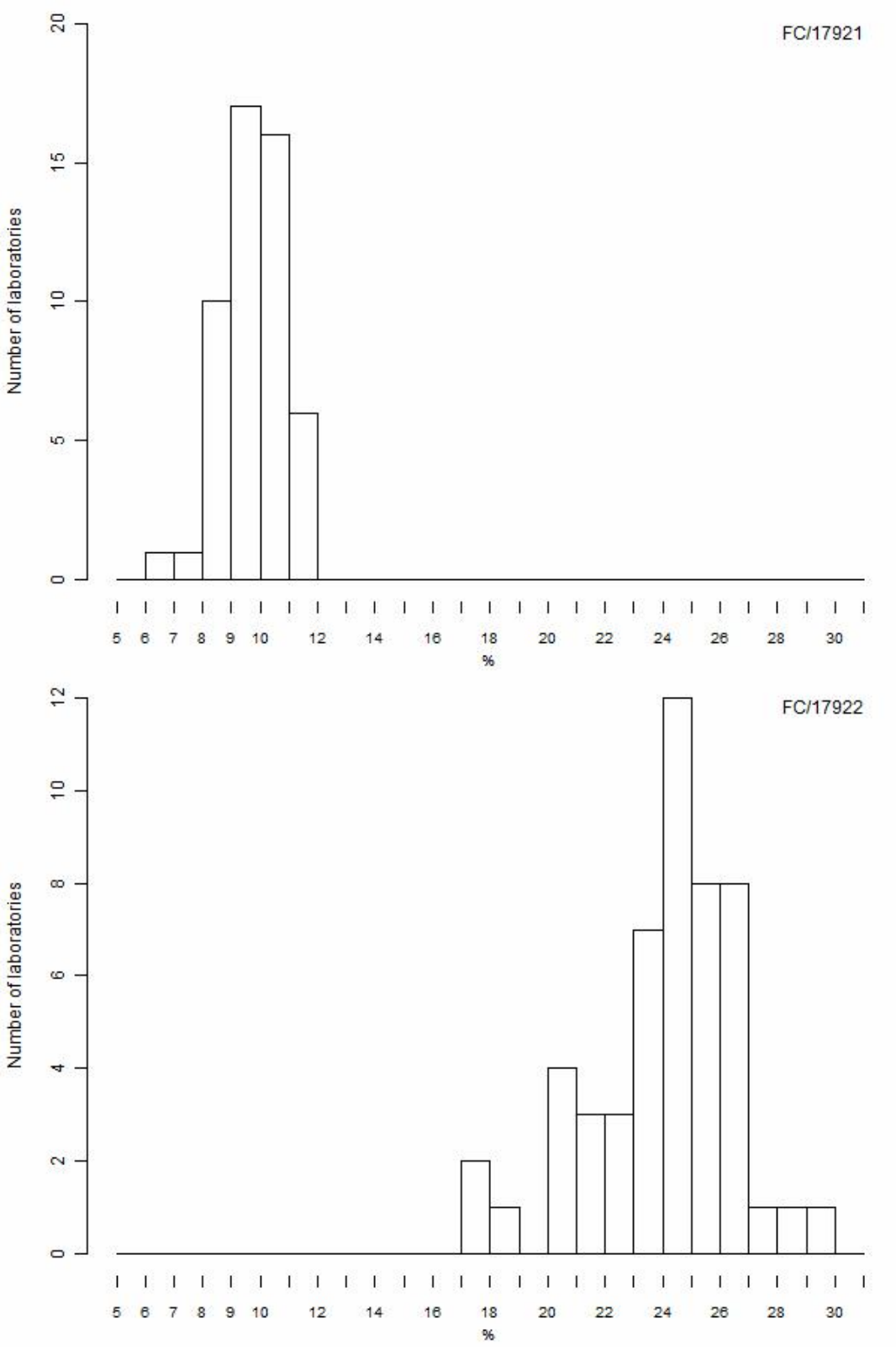
CD19 10E9/L



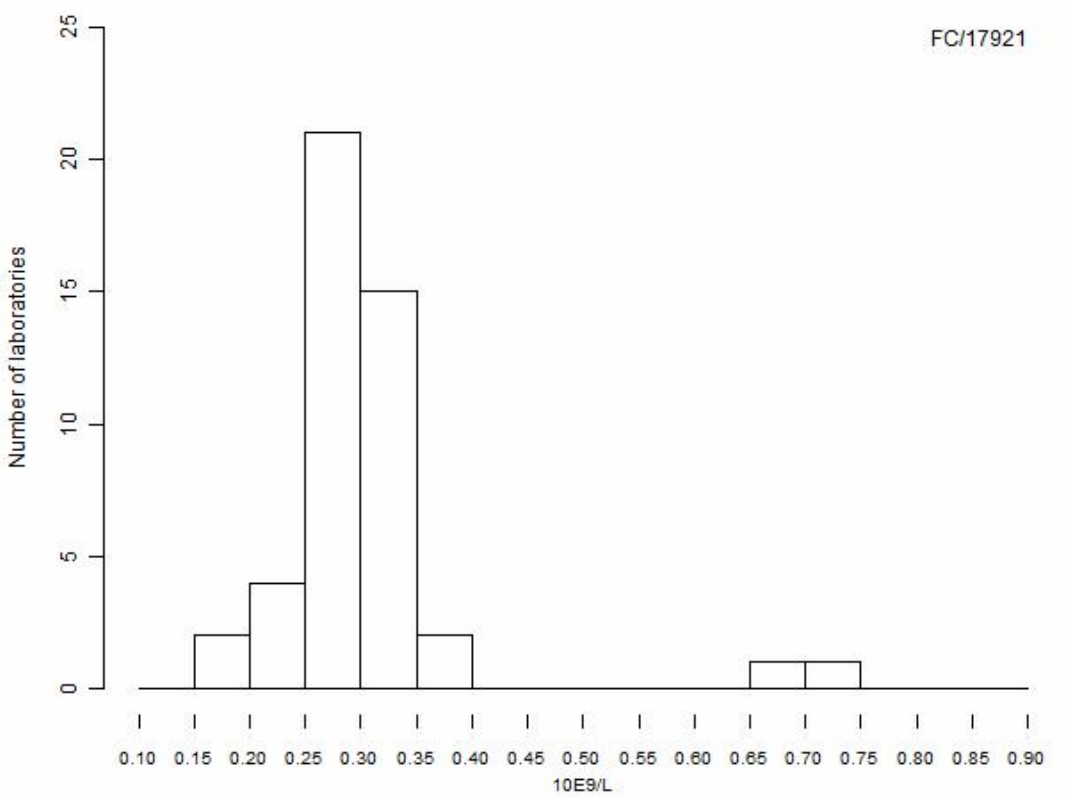
Results not represented on the graph

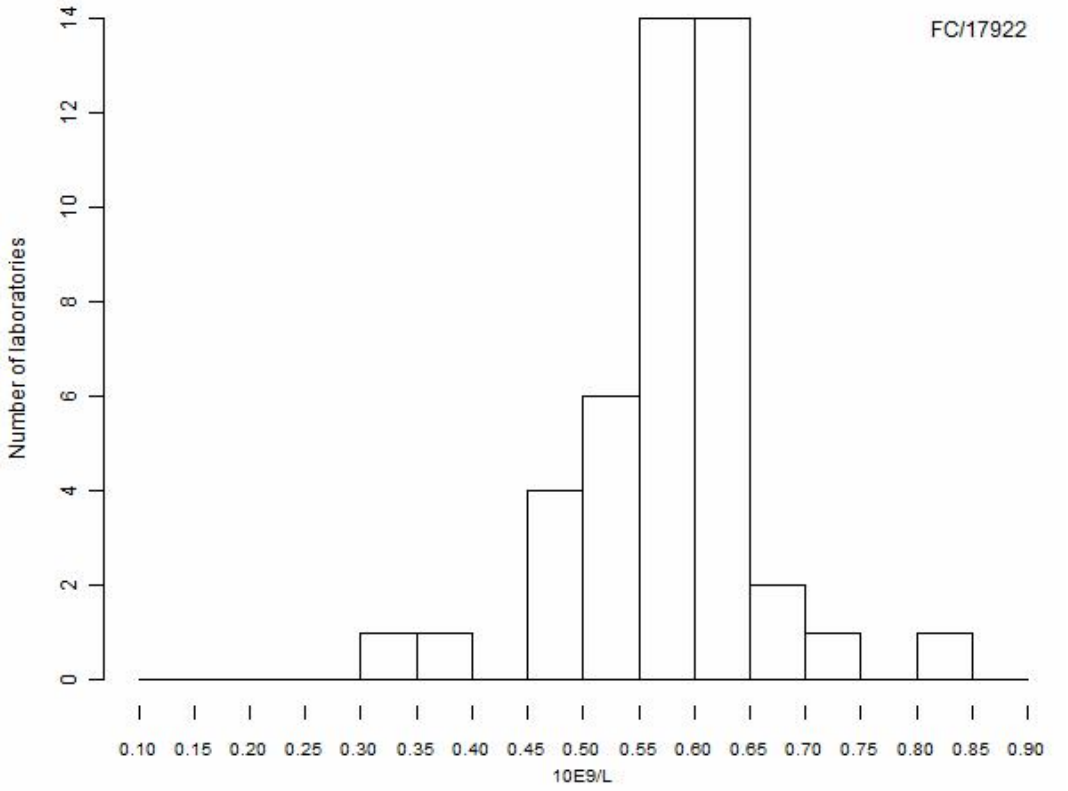
FC/17921 = 0.163 10e9
FC/17921 = 1.14 10e9/l
FC/17921 = 257 10e9/L
FC/17921 = 340 10e9/L
FC/17921 = 503 10e9/L
FC/17922 = 0.13 10e9/l
FC/17922 = 0.142 10e9
FC/17922 = 1.66 10e9/l
FC/17922 = 178 10e9/L
FC/17922 = 276 10e9/L
FC/17922 = 290 10e9/L
FC/17922 = 347 10e9/L

NKcells %

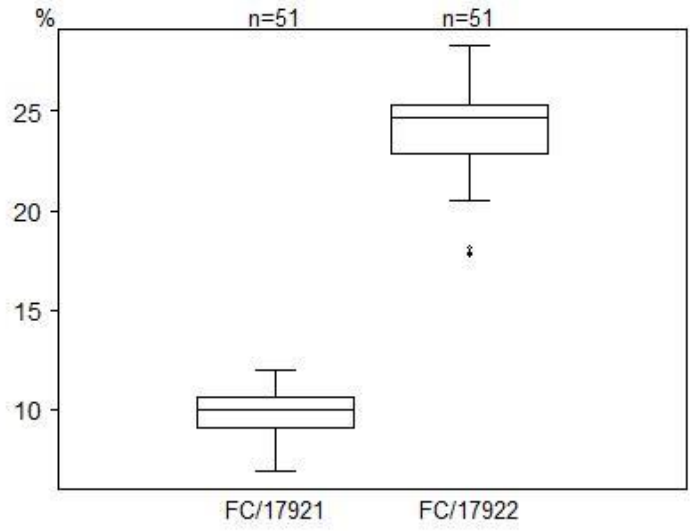

FC/17921
Number of laboratories
0
5
10
15
20
5 6 7 8 9 10 12 14 16 18 20 22 24 26 28 30
%
FC/17922
Number of laboratories
0
2
4
6
8
10
12
5 6 7 8 9 10 12 14 16 18 20 22 24 26 28 30
%

NKcells 10E9/L





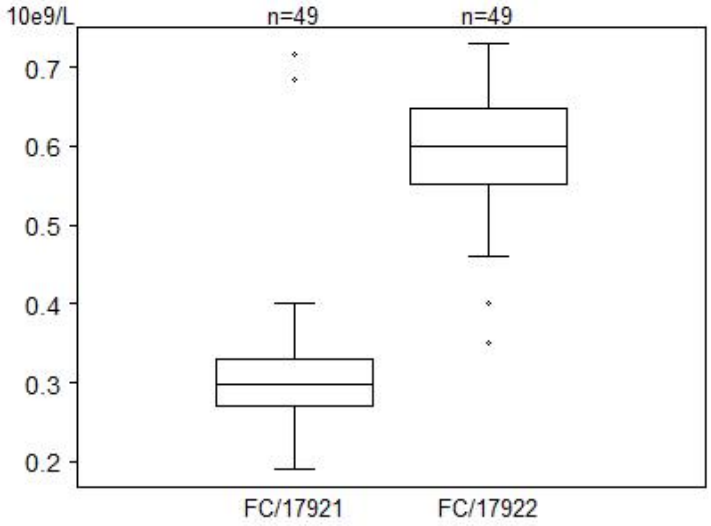
NKcells %



Results not represented on the graph

FC/17922 = 29.3 %

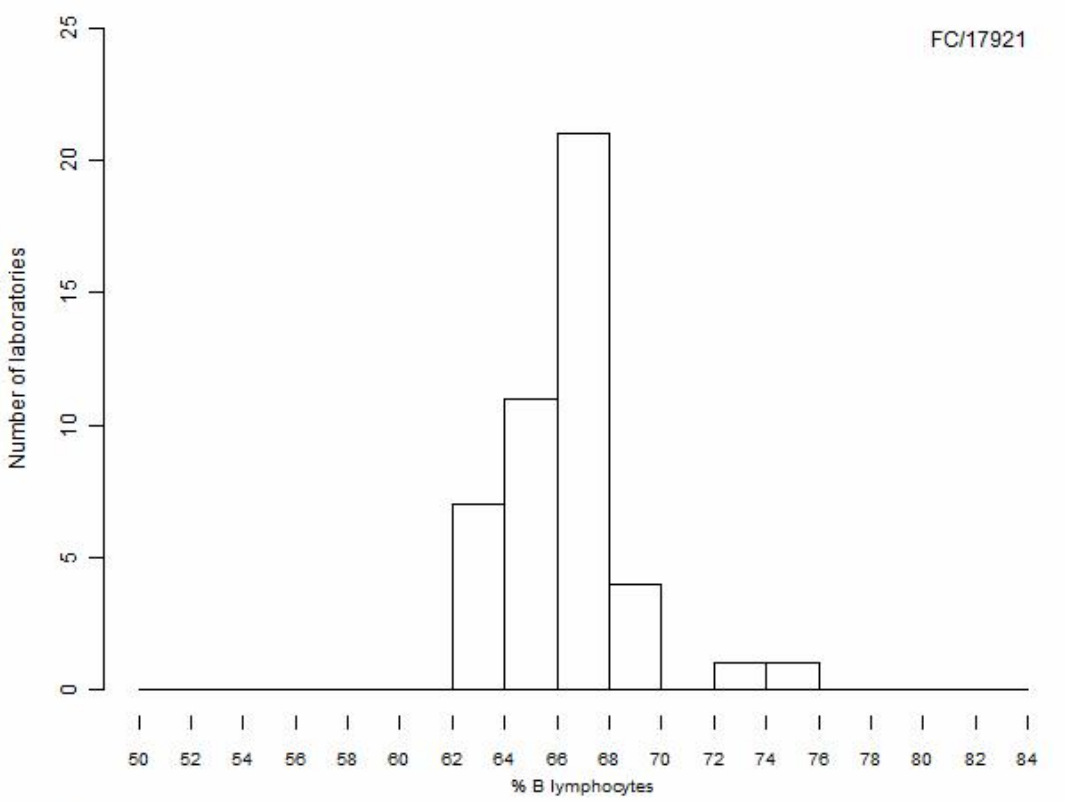
NKcells 10E9/L

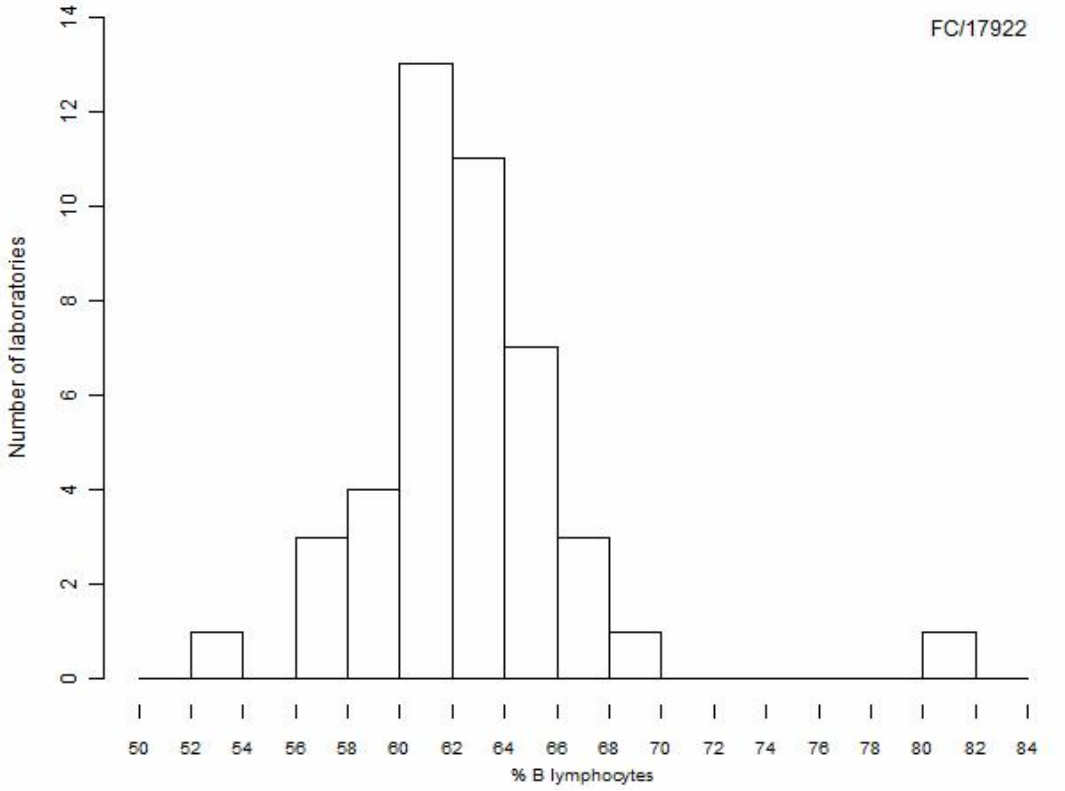


Results not represented on the graph

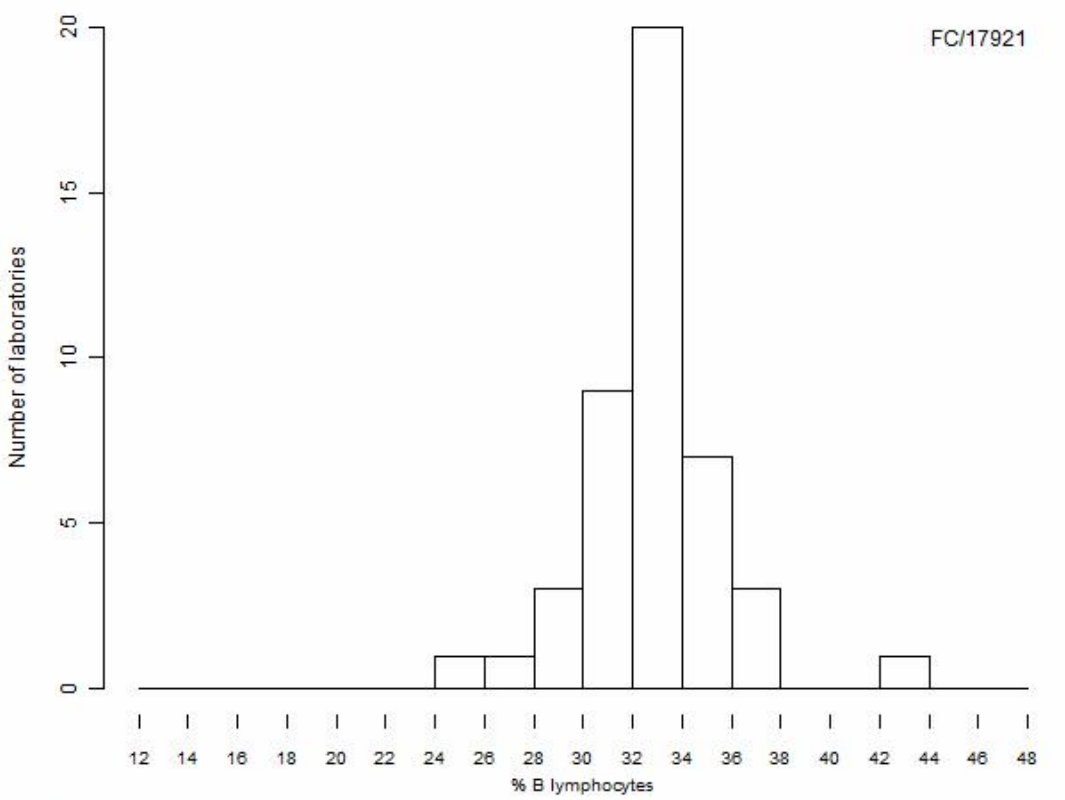
FC/17921 = 184 10e9/L
FC/17921 = 290 10e9/L
FC/17921 = 310 10e9/L
FC/17921 = 329 10e9/L
FC/17922 = 0.803 10e9
FC/17922 = 1.33 10e9/l
FC/17922 = 1.826 10e9
FC/17922 = 344 10e9/L
FC/17922 = 426 10e9/L
FC/17922 = 598 10e9/L
FC/17922 = 642 10e9/L

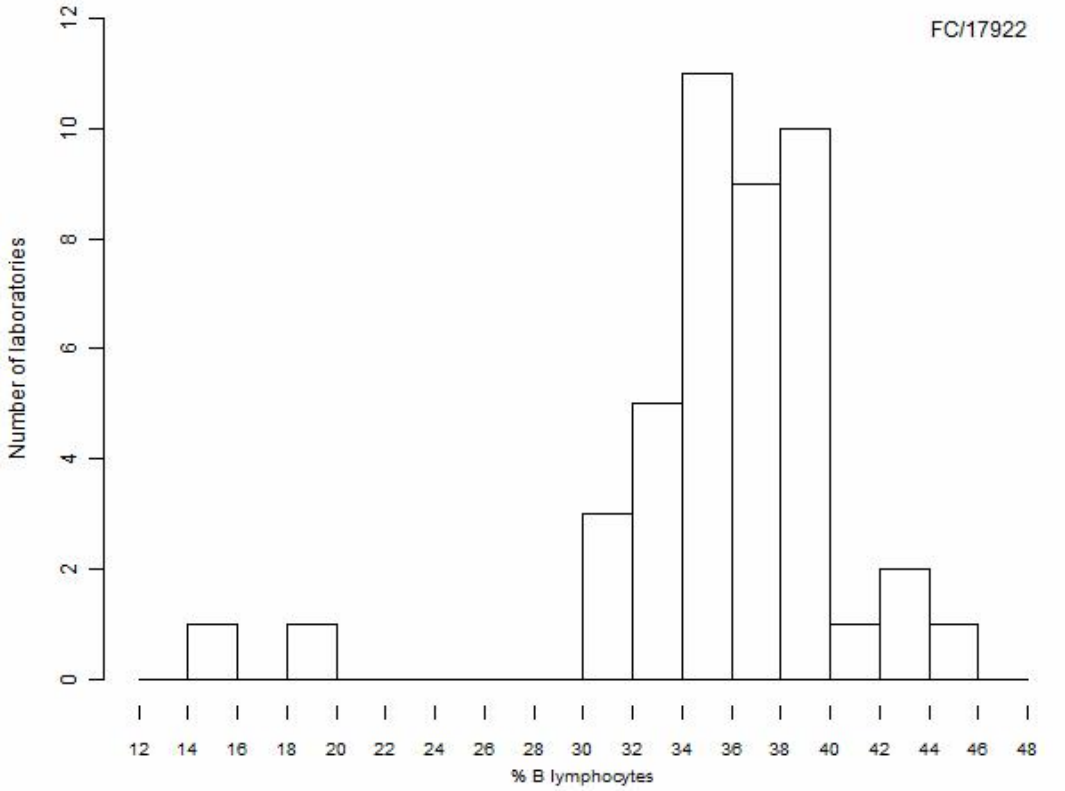
Kappa % B lymphocytes



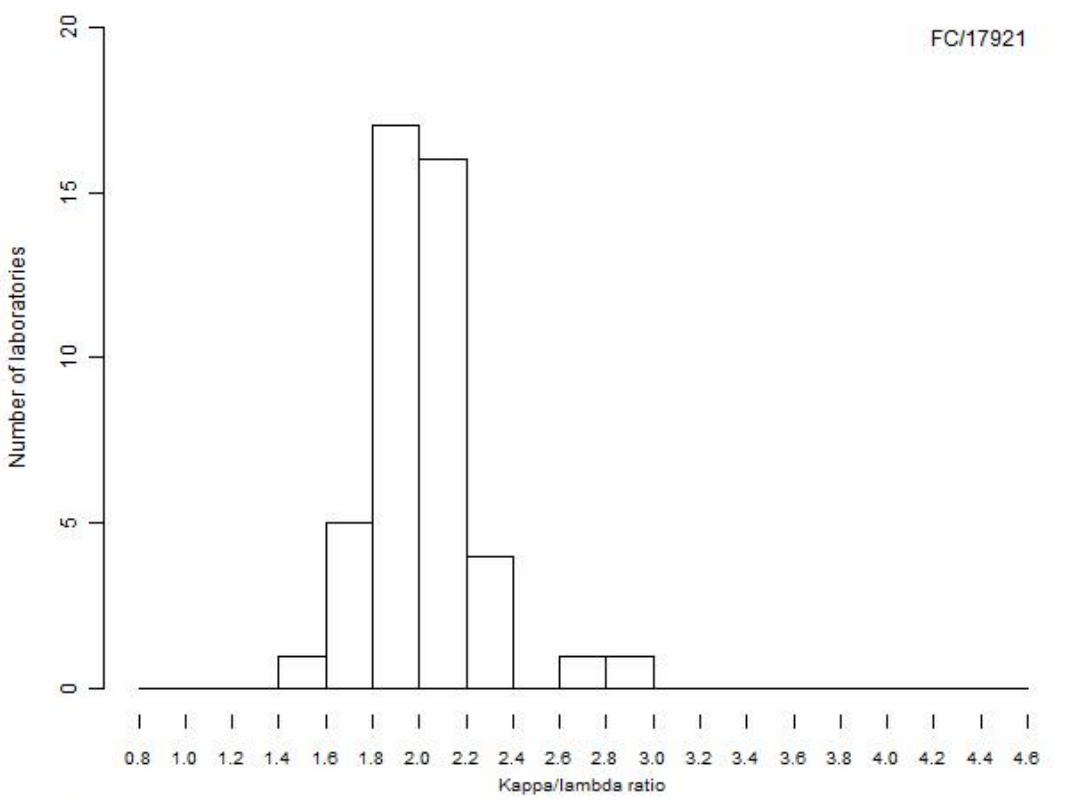


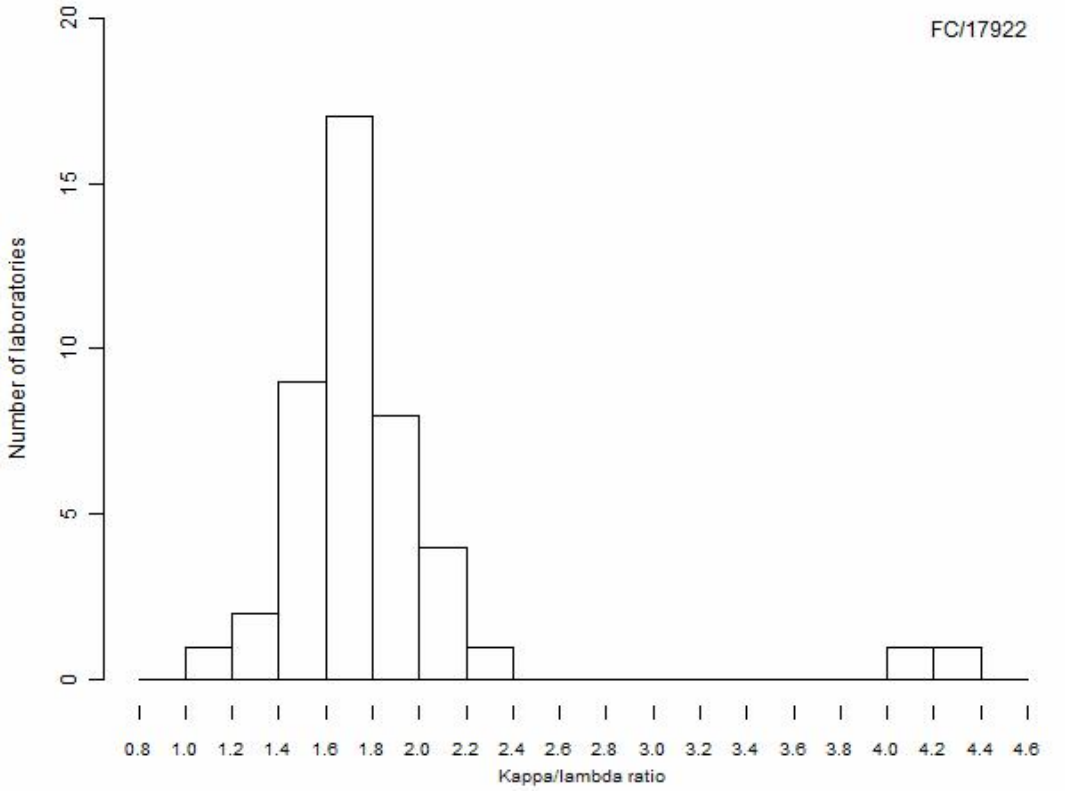
Lambda % B lymphocytes



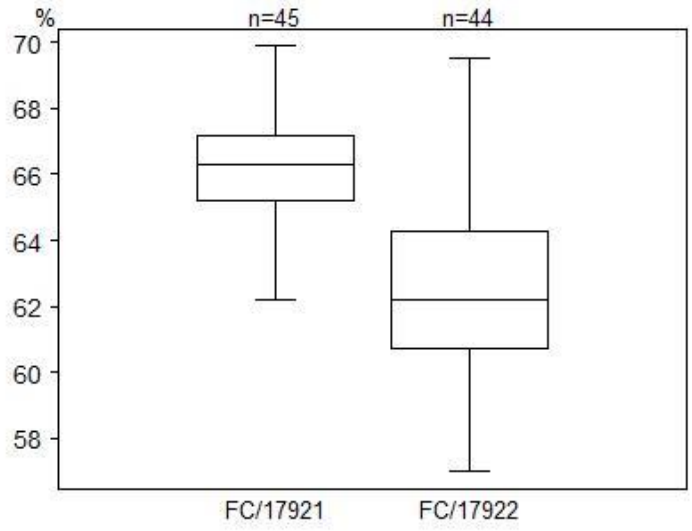


Kappa/lambda





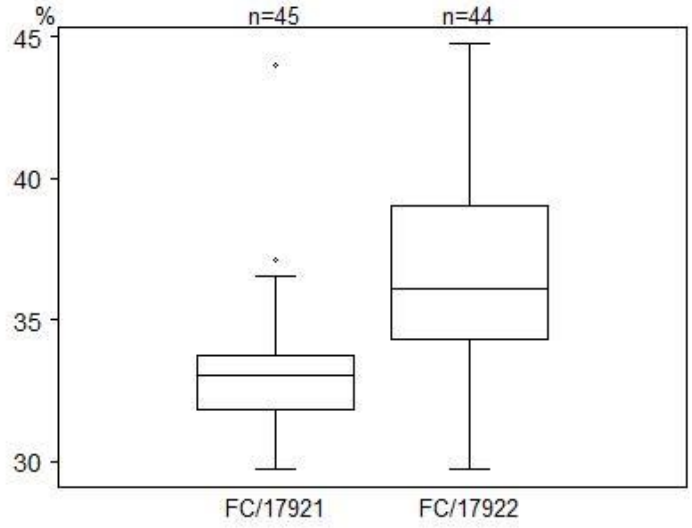
Kappa % B lymphocytes



Results not represented on the graph

FC/17921 = 72.8 %
FC/17921 = 74.5 %
FC/17922 = 52.4 %
FC/17922 = 80.1 %

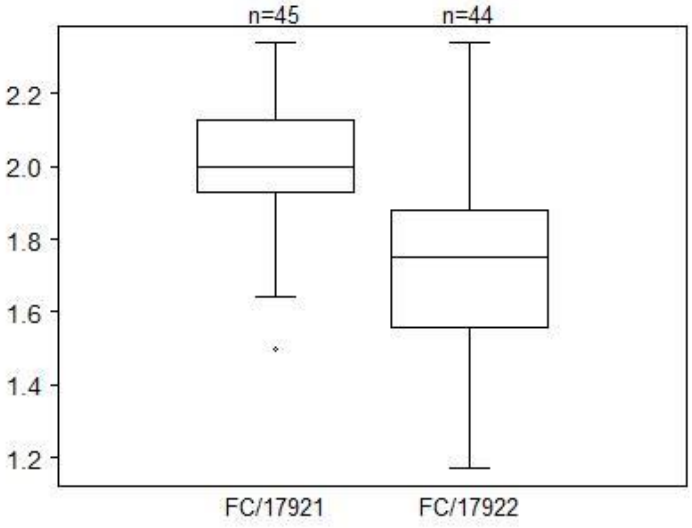
Lambda % B lymphocytes



Results not represented on the graph

FC/17921 = 25.5 %
FC/17921 = 26.7 %
FC/17922 = 14.8 %
FC/17922 = 18.4 %

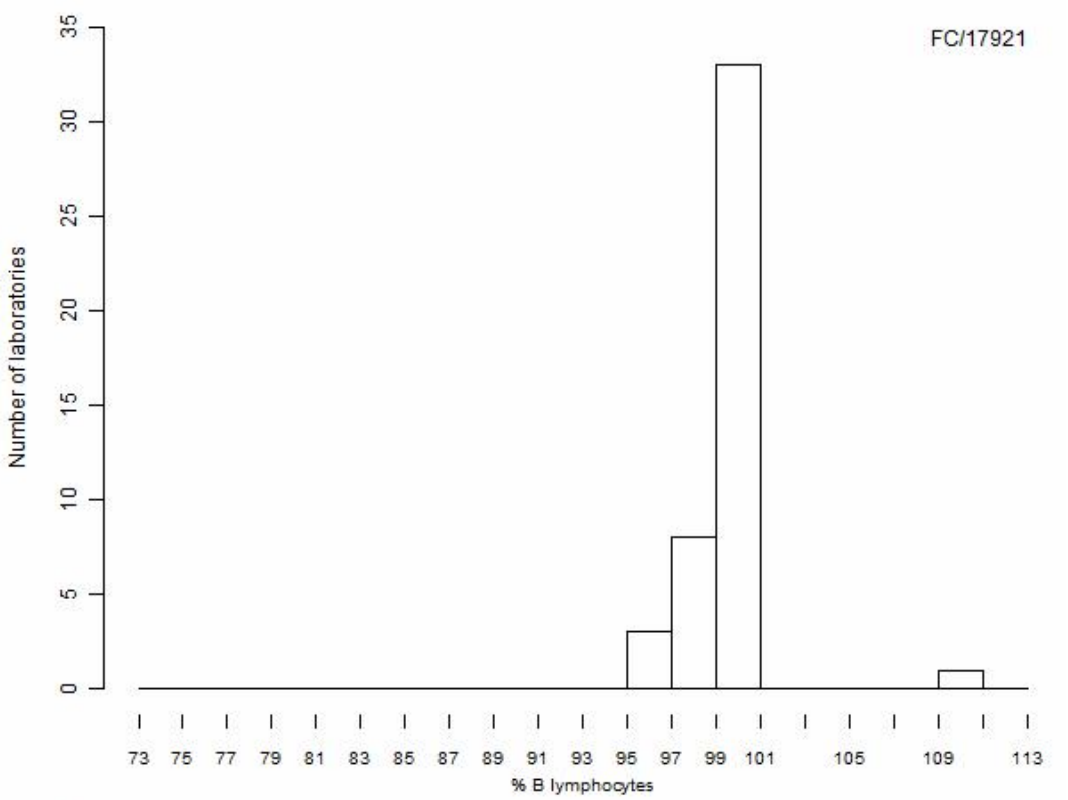
Kappa/lambda

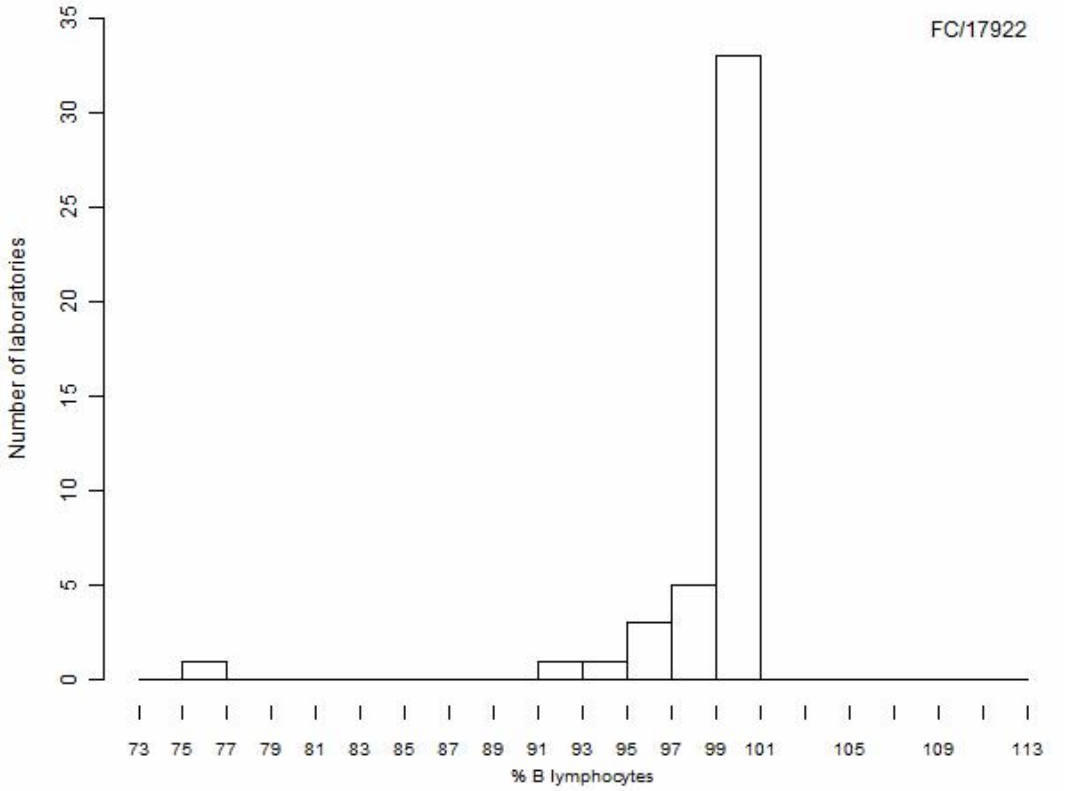


Results not represented on the graph

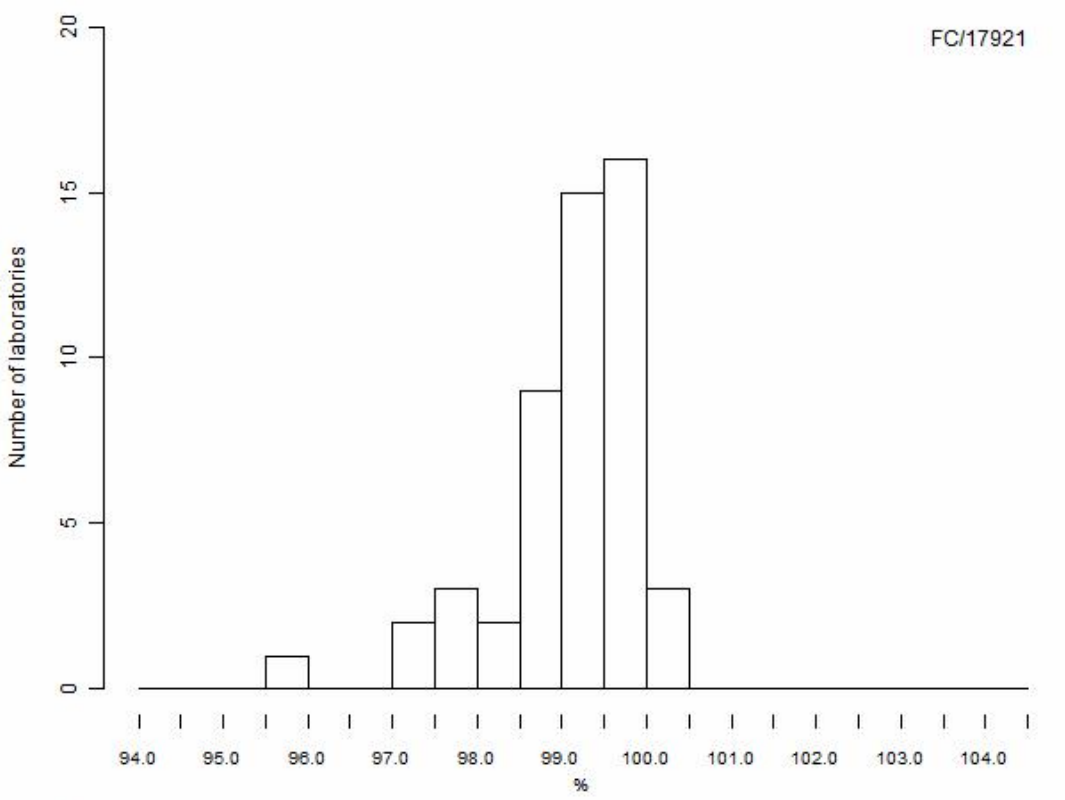
FC/17921 = 2.73
FC/17921 = 2.92
FC/17922 = 4.12
FC/17922 = 4.35

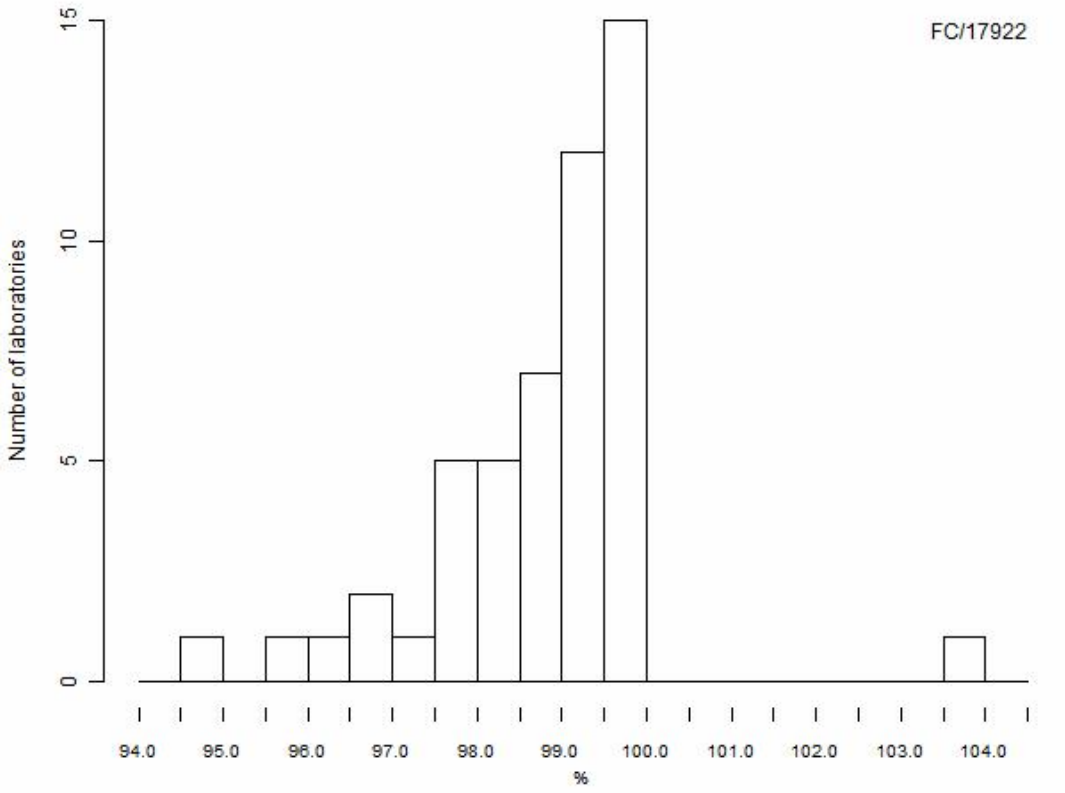
Sum K+L % B lymphocytes



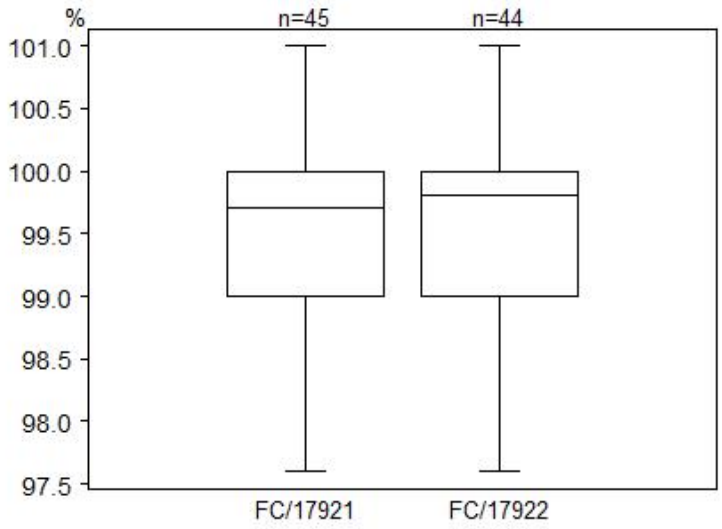


Lymphosum %


FC/17921
Number of laboratories
0
5
10
15
20
94.0
95.0
96.0
97.0
98.0
99.0
100.0
101.0
102.0
103.0
104.0
%


FC/17922
Number of laboratories
0
5
10
15
94.0
95.0
96.0
97.0
98.0
99.0
100.0
101.0
102.0
103.0
104.0
%

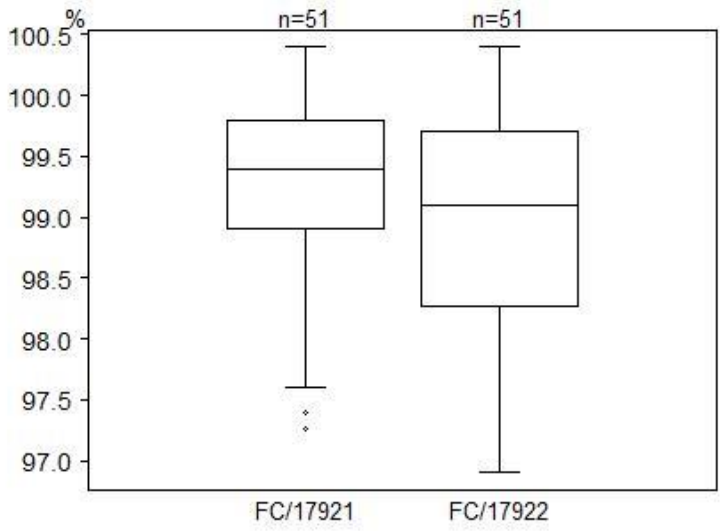
Sum K+L % B lymphocytes



Results not represented on the graph

FC/17921 = 95.5 %
FC/17921 = 95.5 %
FC/17921 = 97 %
FC/17921 = 97.4 %
FC/17921 = 110 %
FC/17922 = 75.8 %
FC/17922 = 91.2 %
FC/17922 = 93.4 %
FC/17922 = 95.3 %
FC/17922 = 95.9 %
FC/17922 = 97 %
FC/17922 = 97.2 %

Lymphosum %



Results not represented on the graph

FC/17921 = 95.7 %
FC/17922 = 94.8 %
FC/17922 = 96 %
FC/17922 = 96 %
FC/17922 = 103.9 %

For technical validation purposes it is worth noting that in non-pathological peripheral blood of adults the sum of kappa and lambda (expressed as a % of CD19+ B-cells) should be between 90 and 110. The lymphosum (sum of $CD3^{+}$% plus $CD19^{+}$% plus $CD3^{-}CD16^{+}$ and/or $CD56^{+}$%) should equal the purity of the lymphocytes in the gate ± 5%, with a maximum variability of ≤ 10%.

END