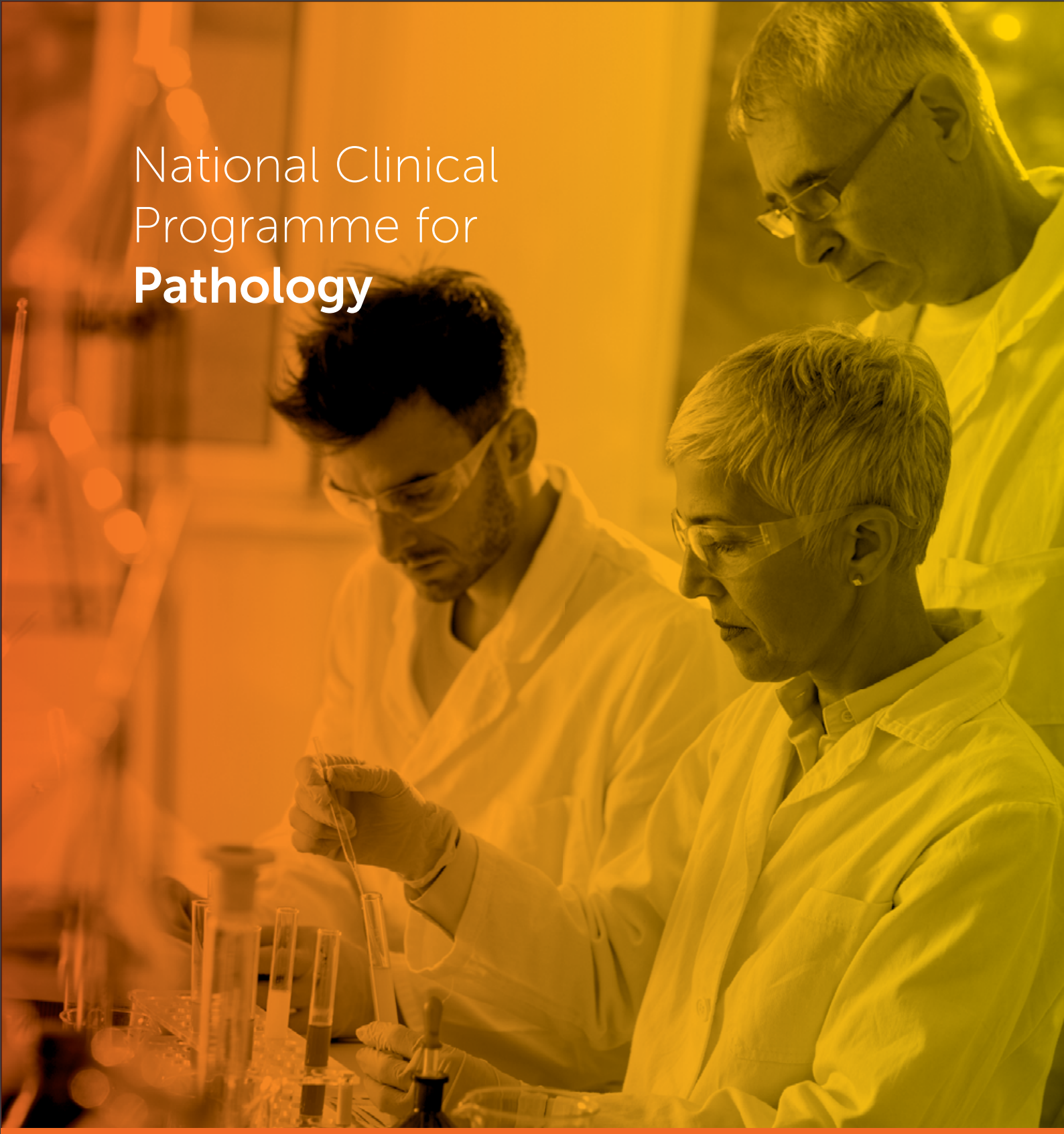

National Clinical Programme for **Pathology**

National Laboratory Handbook | **Volume 1**

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

PATHOLOGY

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

National Clinical Programme for Pathology
HSE Clinical Strategy and Programmes Division
and the Royal College of Physicians of Ireland
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Foreword

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The National Clinical Programme for Pathology (NCPP) identified the need to develop a National Pathology Handbook which would provide a set of concise national guidelines and order sets for common clinical diagnostic problems particularly those which were associated with either high volumes or potential over-usage of laboratory medicine investigations. This focus was designed to assist with appropriate use of the clinical laboratory and in demand management, in accordance with Principle 4 of the *Ten Principles for Laboratory Medicine Modernisation* (see appendix I). A multidisciplinary working group was established in March 2014 to support this project.

An outline table of contents was developed which was divided into sections for clinical users and laboratory use, and includes proposals to develop agreed test panels and reference ranges, clinical guidelines for common laboratory medicine problems and consensus standard operating procedures for common investigations.

The Handbook will be developed in stages with the initial plan of developing a bundle of ten guidelines and reports in Volume 1. A team usually consisting of a pathologist and a scientist were invited to develop a guideline and a standard template was agreed (see appendix II). Each guideline development group was encouraged to consult with experts in their field for review before submission of their drafts. Dr. Gerard Boran contributed to and edited the document. It was considered appropriate to include reports on research regarding harmonisation and references intervals which has been conducted in Ireland.

A three week consultation process including the Handbook Working Group, the Faculty of Pathology, the professional bodies (Academy of Clinical Science and Laboratory Medicine (ACSLM), Association of Clinical Biochemists in Ireland (ACBI), Haematology Association of Ireland (HAI), Irish Society of Clinical Microbiologists (ISCM) the Health Products Regulatory Authority (HPRA)), Irish National Accreditation Board (INAB), Irish External Quality Assessment Scheme (IEQAS) was conducted in August- September 2015 before the final draft Volume 1 of the handbook was submitted for approval to the Clinical Advisory Group and the National Clinical Advisor and Group Lead of the Acute Hospitals Division in October 2015. The final step was submission to the Senior Management team of the Clinical Strategy and Programmes Division.

The Programme has commenced preparation for Volume 2 of the National Laboratory Handbook and looks forward to engaging with colleagues across the specialities to ensure that the guidelines are developed by subject experts and meet the needs of the healthcare system.

Acknowledgements

A huge debt of gratitude is owed to each author and co-author of these guidelines and reports for their dedication and commitment to the process. Also we acknowledge the contribution of those who reviewed the guidelines and provided constructive comments.

The National Clinical Programme for Pathology gratefully acknowledges support and advice received from the *Faculty of Pathology*, other professional bodies including *The Academy of Clinical Science and Laboratory Medicine*, *The Association of Clinical Biochemists in Ireland*, *The Irish Haematology Society*, *The Irish Society of Clinical Microbiologists*, the Chemical Pathologists SubGroup of the Faculty of Pathology and a number of individuals including consultant immunologists.

We wish to thank the National Cancer Control Programme and Eileen Nolan in particular for permission to include the report on PSA harmonisation. We offer sincere thanks to Dr. Niamh Moran, General Practitioner, Project Officer Irish Collage of General Practitioners (ICGP) Quality in Practice (QIP) Committee and the QIP Committee for their input into the Thyroid Function Tests Guideline.

Finally we acknowledge the support Dr. Aine Carroll, National Director of the Health Service Executive (HSE) Clinical Strategy and Programmes Division, Dr. Colm Henry, HSE Clinical Advisor and Group Lead, Acute Hospitals and Dr. Barry White, Director of Quality and Clinical Care, Royal College of Physicians of Ireland.

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Standardisation of Reporting Units for extended Full Blood Count in Haematology

Author
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Date
23rd December 2015

Introduction and background

The full blood count (FBC) is the most frequently requested test in laboratory haematology worldwide. Reporting units used for the FBC currently vary around the world, from country to country and also within countries between laboratories. This variation is perceived to be a potential problem in the era of rationalisation of pathology services, re-structuring of pathology providers, and increase in point-of-care provision. There has been an agreement in the United Kingdom (UK) to standardise the reporting units used for the extended FBC nationwide using the accepted SI (International System) units from April 2013[1]. In addition there is a current international project under the auspices of the International Committee for Standardization on Haematology (ICSH) to address this issue worldwide and make a recommendation for standardization. A standardization exercise similar to that carried out in the UK was previously completed among five Scandinavian countries (Norway, Sweden, Finland, Denmark and Iceland) by the Nordic Reference Interval Project (NORIP) group[2]. The SI reporting units adopted in the UK are the same as those adopted by NORIP.

In the Republic of Ireland (RoI), a survey of all haematology laboratories conducted by the ACSLM jointly with IEQAS in 2012, revealed some variation in the reporting units in use for the extended FBC. It also surveyed opinion of laboratory professionals in regard to standardization along the line adopted in the UK, and found that the majority were in favour, subject to the project being supervised nationally and to include advance notification to service users. The issue was also discussed with representatives of Irish professional bodies in 2013 as described below.

The planned introduction of a national laboratory information system (MedLIS) for the Republic of Ireland beginning in 2015 will require the adoption of single reporting units for all laboratory tests. This therefore represents an opportunity to standardize the reporting units for the FBC in line with the International Committee for Standardization on Haematology (ICSH) recommendations which are expected to be published in early 2016.

The following reporting units for the extended blood count, which follows the original ICSH guideline[3] were agreed and adopted in the UK from March 2013[1]:

Table 1: SI Reporting units for the Blood Count adopted in the United Kingdom which are the same as those used in Scandinavia

Pathology Harmony Proposal Analyte	Units
White blood cell (WBC) count	$x10^9/L$
Neutrophil count	$x10^9/L$
Lymphocyte count	$x10^9/L$
Monocyte count	$x10^9/L$
Eosinophil count	$x10^9/L$
Basophil count	$x10^9/L$
Nucleated red blood cell (NRBC) count	$x10^9/L$
Red blood cell (RBC) count	$x10^{12}/L$
Haemoglobin (Hb)	g/L
Haematocrit (Hct)	L/L
Mean cell volume (MCV)	fL
Mean cell haemoglobin (MCH)	pg
Mean cell haemoglobin concentration (MCHC)	g/L
Red cell distribution width (RDW)	%
Platelet (PLT) count	$x10^9/L$
Reticulocyte count	$x10^9/L$

Results of the survey of Republic of Ireland Laboratories 2012

The results of this survey, which gathered information both on reporting units used and opinion on the merits of standardisation, are summarised as follows:

- A wide range of cell counting instrumentation for the FBC is used (all major manufacturers are represented).
- 43 laboratories responded of which 96% (41 laboratories) currently report haemoglobin and MCHC as g/dL which is not a true SI unit, while 4% (2 laboratories) already report these parameters as g/L.
- All laboratories already report total RBC count as $x10^{12}/L$ and total WBC count as $x10^9/L$ as per the UK and Scandinavian adopted units.
- 79% of laboratories (34) report the WBC differential as $x10^9/L$ while 21% (9 laboratories) report as both $x10^9/L$ and as a percentage.
- Reticulocyte reporting is more mixed, but the majority (63%) already report as x $10^9/L$ or both (28%) with only 9% reporting as percentage.
- Nucleated red blood cell (NRBC) reporting is the most mixed, with 26% of respondents reporting as x $10^9/L$, 58% as "number per 100 WBCs" and 16% as both.
- Despite the finding that the majority of laboratories report Hb as g/dL along with some perceived disadvantages and issues to be addressed, a clear majority of 93% (39 labs) are in favour of harmonising to SI units in principle, with only 7% selecting "Don't know". No laboratories answered that they would be opposed to standardization.
- The majority of perceived disadvantages and issues to be addressed concern IT systems, Point-of-Care testing devices and related costs of change for both, advance notification and education of users. They include managing the change and impact on delta checking and archived results.
- Those laboratories that already report haemoglobin as g/L, reported that there had never been any incident where the haemoglobin level was misinterpreted and that the clinicians who had rotated from other hospitals adapted with no problem to the different reporting units.

Discussion at National Laboratory Handbook Meeting 2013

A meeting was arranged between all the relevant Irish professional bodies to form a national view. This was chaired by Dr. Gerard Boran, Clinical Lead of the HSE National Clinical Programme in Pathology, as part of a meeting on the National Laboratory Handbook in April 2013. The meeting included representatives of the ACSLM, IEQAS, the Faculty of Pathology of the Royal College of Physicians of Ireland (RCPI), and the ICGP. The Irish Haematology Society (IHS) was invited but unable to attend. This meeting concluded that there was merit in principle in adopting the UK reporting units in the interests of harmonisation. It was not felt that the change would pose any difficulty to clinicians, provided that sufficient advance notification was given. The meeting also recognised however, that the necessary inclusion of point-of-care devices and IT systems in the change may well have resource issues and also that the change would have to be managed carefully as a national project. It was concluded these aspects needed to be explored further and that we must also take account of the new National MedLIS project. Funding issues for a national change would be a matter for the HSE. Subsequently the chair of the Haematology Advisory Body of the ACSLM made contact with the Quality & Change manager of the National MedLIS project to report the conclusions of this meeting.

International Dimension

A survey of international practice was conducted by the ICSH in 2013, to which the Republic of Ireland survey data was submitted. This international survey revealed quite a great diversity in reporting units being used around the world. It showed that only two countries, the Netherlands and now the UK, have nationally agreed units of measurement, although Australia reported a very good consensus and the NORIP data from Scandinavia was later obtained. The ICSH adopted a formal project to agree and publish a recommendation for standardisation of reporting units to be used for the extended blood count in October 2013. This was led by Michelle Brereton, Manchester and the project team included Richard McCafferty, Republic of Ireland and contributors from Australia, Spain, Korea, China, Japan, Germany, France, the Netherlands and USA. This paper has now been finalised and agreed at the last ICSH General Assembly held in Shenzen, China in October 2015. It has been submitted for publication in the International Journal of Laboratory Haematology which is expected in early 2016. The paper recommends that the original ICSH guidelines for use of SI reporting units for the blood count from the 1970s and 1980s[3,4], which the UK and Scandinavian groups have followed in their recent national and network standardisations, should be used internationally where possible to improve standardisation.

Current Position and Conclusion

Harmonisation of reporting units in pathology is an issue currently being addressed worldwide. Reporting units for the full blood count have been standardised in Ireland's nearest neighbour the UK and also in Scandinavia. A new international recommendation for standardisation by the ICSH has been finalised and is currently in press as described above. Experience in Ireland, the UK (where there has been a long transition phase to the agreed units) and in Europe has shown that the use of different reporting units can co-exist within countries without adverse clinical consequences. However, the merits of standardization are well described and accepted. These include, for example, the ability to directly compare laboratory results for the purposes of clinical trials and when patients travel between jurisdictions. It may well also be the case that laboratory equipment, point-of-care devices and cell counter analysers supplied to the Republic of Ireland in the future by UK-based suppliers, will express results by default in the UK-adopted units and may require resetting to express results in other units. This will have particular relevance for reporting of haemoglobin concentration which is now expressed in g/L in the UK and Northern Ireland but as g/dL by the majority of Republic of Ireland laboratories. The view of the Irish professional bodies arising from the joint meeting of 2013 is that adoption of the reporting units used in the UK, now also endorsed internationally by the ICSH, would be advantageous for the reasons described above. However the implementation of such a national change will be dependent on logistical and cost issues. These must include the availability of HSE funding for any resource issues identified, such as the need for administrative support for national change management, advance notification of service users, and conversion of cell counters (if needed), point-of-care devices and IT systems. The latter will include hospital IT and Electronic Patient Record (EPR) systems as well as Laboratory information systems. The survey of Irish laboratories has shown that FBC reporting is already mixed within the country so this is a pertinent issue. The work already done by the ACSLM, IEQAS and consideration of the issue by the Irish professional bodies, in addition to the anticipated international recommendation, all serve as resources available to the HSE and the MedLIS project to move forward on this issue.

Proposal

It seems logical to synchronise the potential change in reporting units to the timescale for the National MedLIS project roll-out, which represents both an opportunity to introduce standardisation of reporting units for the FBC and an obligation to make a choice regarding which reporting units to adopt, since only one type of unit can be used for each parameter of the FBC. The ICSH published recommendation will shortly be available to support this proposed strategy from the scientific point of view. This will bring the advantages of adoption of an international recommendation already used by Ireland's nearest neighbour the UK as described above, thus providing future-proofing for Irish pathology practice in this area. Finally, given that it is already the case that different reporting units are used by different hospitals within Ireland; the change could in fact be implemented on a hospital-by-hospital basis according to the timescale for implementation of MedLIS. This would make the changeover more manageable in the first instance and allow each hospital in turn to benefit from the experience of those who are the first to implement MedLIS. The resources of the HSE, MedLIS project group and the Irish professional bodies who have already contributed to this project could all be used and co-ordinated towards ensuring a successful implementation of this important development.

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The Irish Reference Interval Harmonisation Project

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Background

It is well recognised that having different reference intervals for the same analyte measured in different laboratories is a source of confusion and annoyance for users of laboratory services and could constitute a risk for misdiagnosis. For some analytes there are valid technical reasons for different ranges but for others that does not apply.

International efforts to achieve common reference intervals (RIs) have not been particularly successful, but in recent years a project in the UK, Pathology Harmony (PH), has adopted a pragmatic approach. It started with ten standard clinical chemistry analytes and, with subsequent UK Dept. of Health endorsement, the proposed common RIs are being widely adopted across the UK.

A working group, representing ACBI, ACSLM, IEQAS, and RCPI (Faculty of Pathology), investigated the possibility of producing similar common RIs for the Republic of Ireland for the ten analytes initially covered by PH. A survey was used to collect data on methods, RIs, and source of RIs. With very active follow-up of non-responders, responses were achieved for a total of 50 labs, including all major hospitals and private labs.

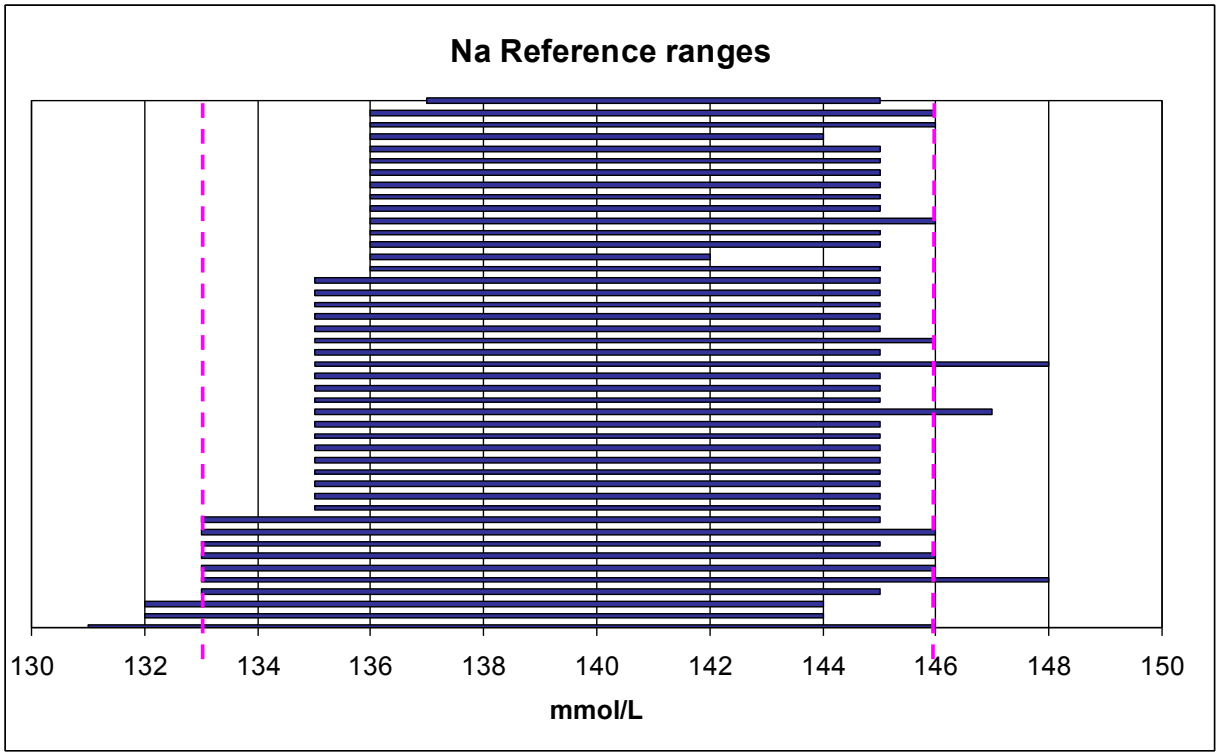
Review of RIs

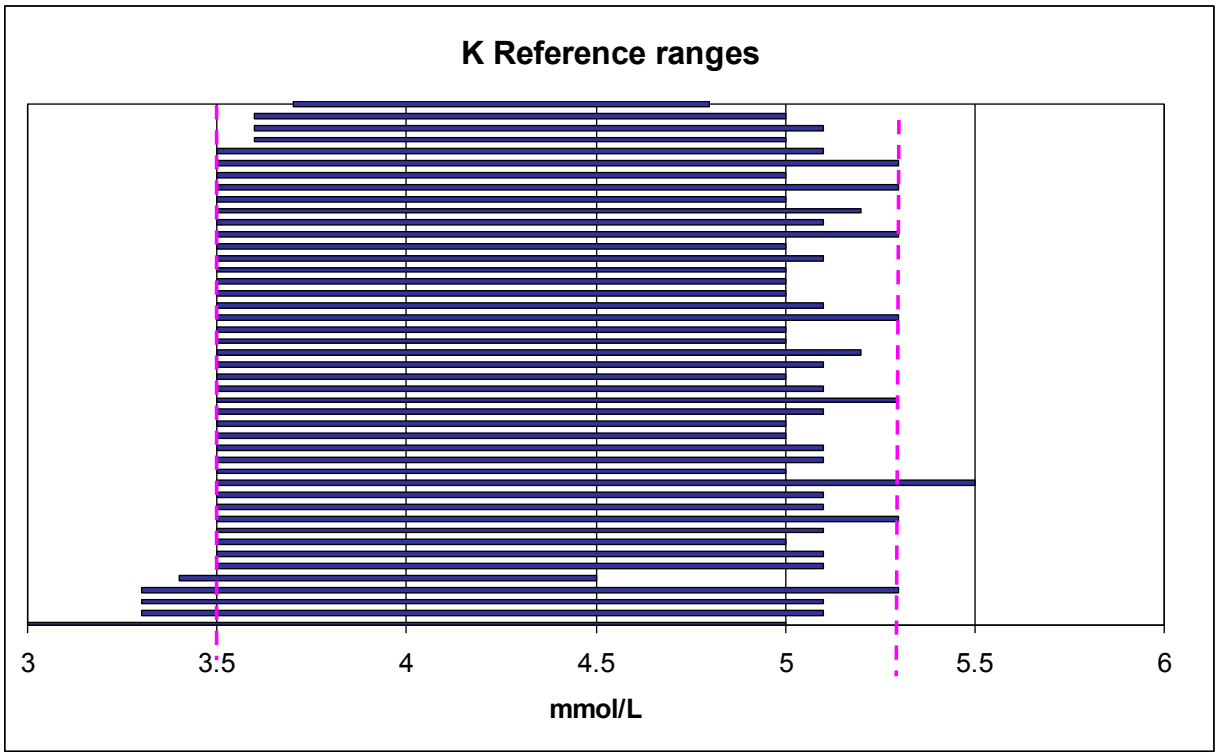
RIs in use were reviewed and compared to harmonised RIs in use in the UK and New Zealand / Australia (NZ/Aus). RIs were agreed and subjected to verification (below). These intervals are the same as those of PH UK except for Sodium where the lower limit of 133 was considered inappropriately low. The NZ / Aus RI of 135-145 was chosen.

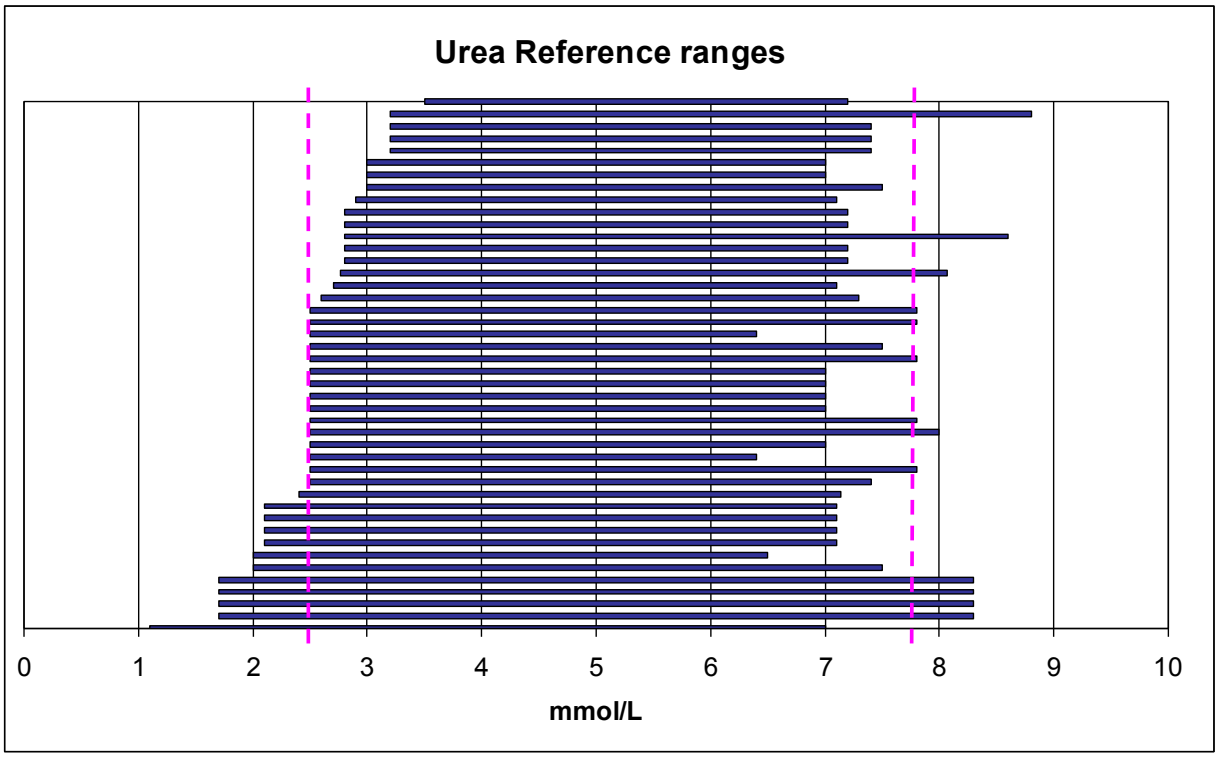
Overview of Survey Results

Figure 1 shows the different range of reference intervals reported from the various laboratories (not all laboratories provided a service for all analytes). The PH range is marked on each graph.

Figure 1: Spread of reference intervals for 10 common clinical chemistry analytes



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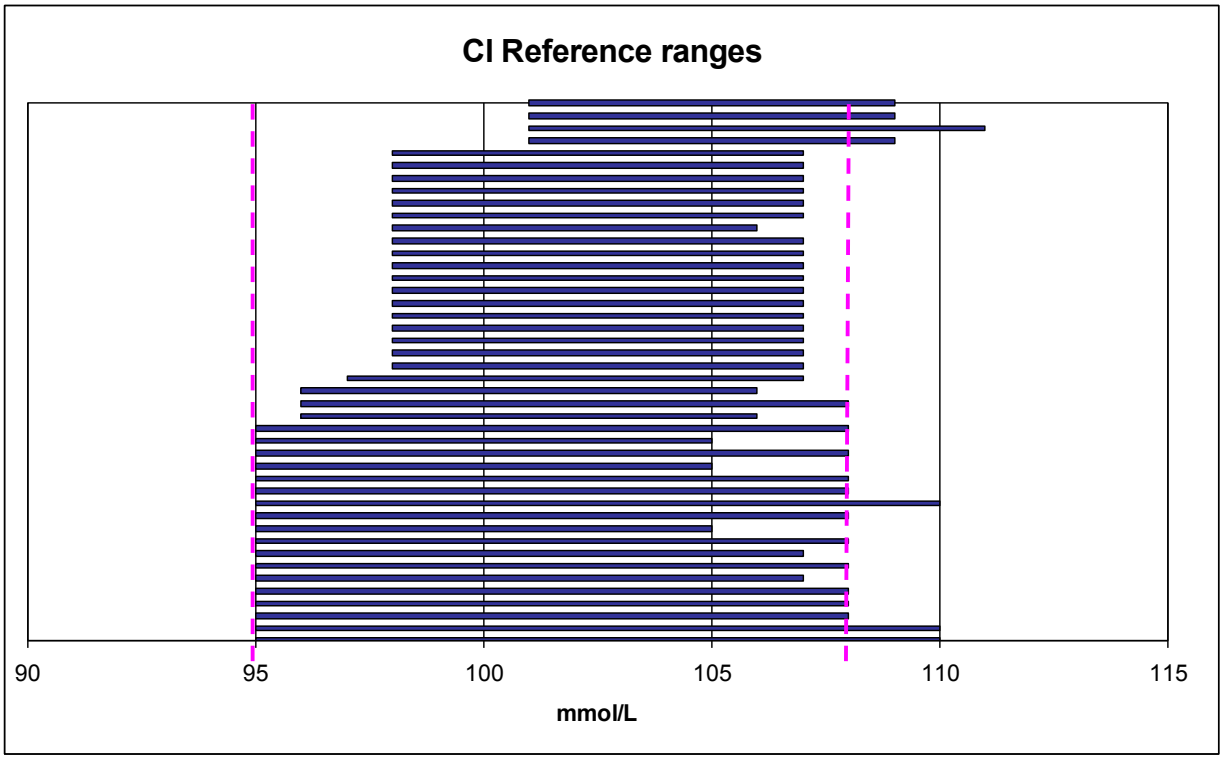
1
2
3
4
5
6
7
8
9
10
mmol/L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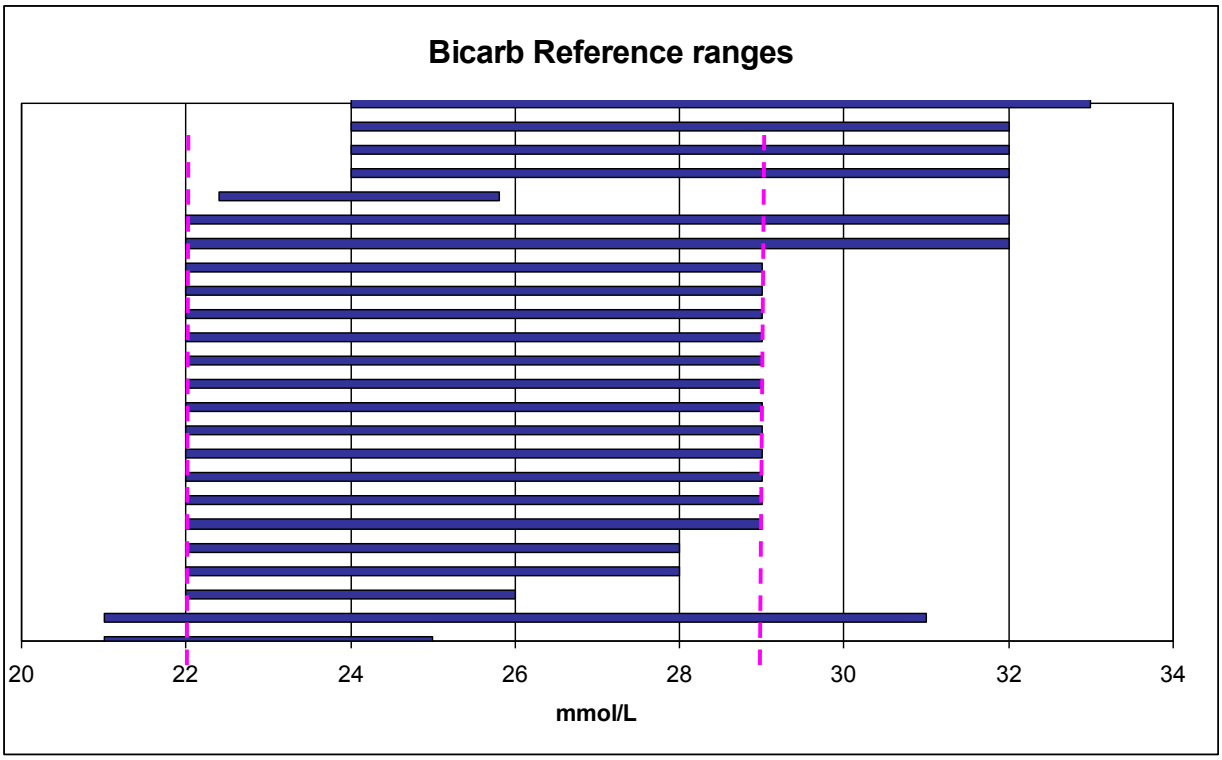
100
105
110
115
mmol/L


Bicarb Reference ranges
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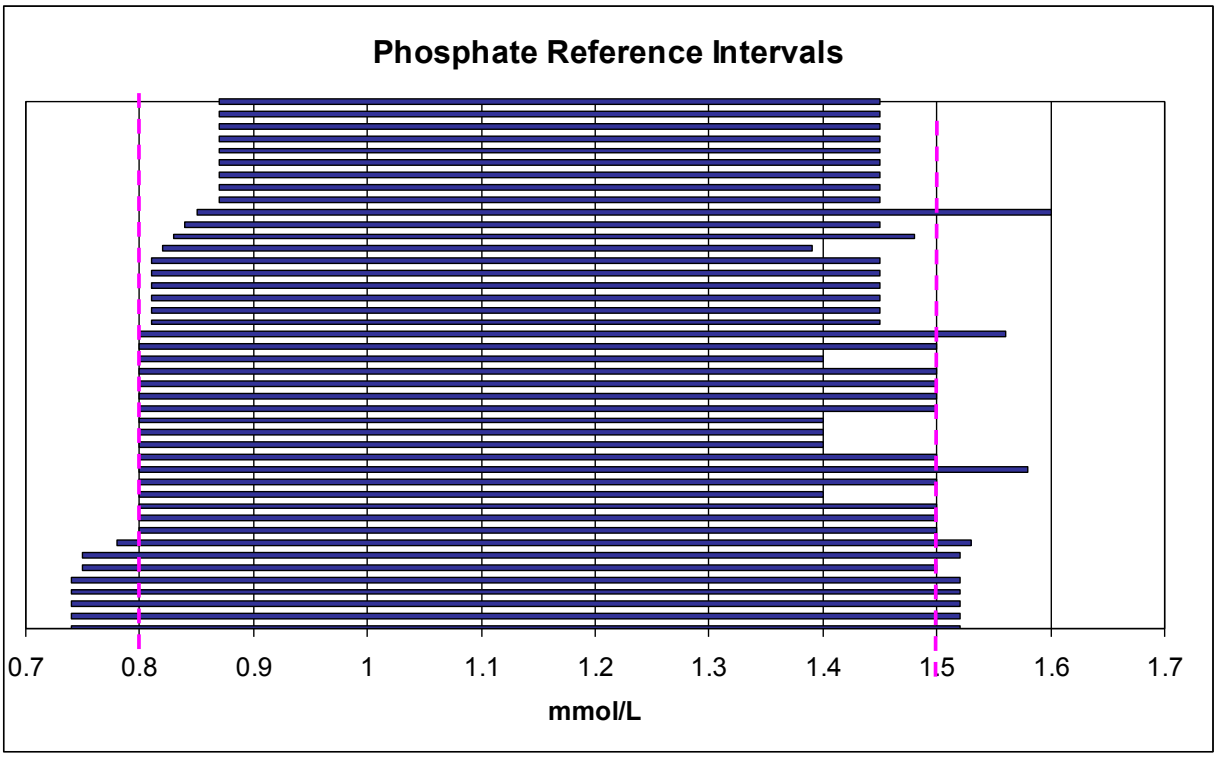
22
24
26
28
30
32
34
mmol/L


Phosphate Reference Intervals
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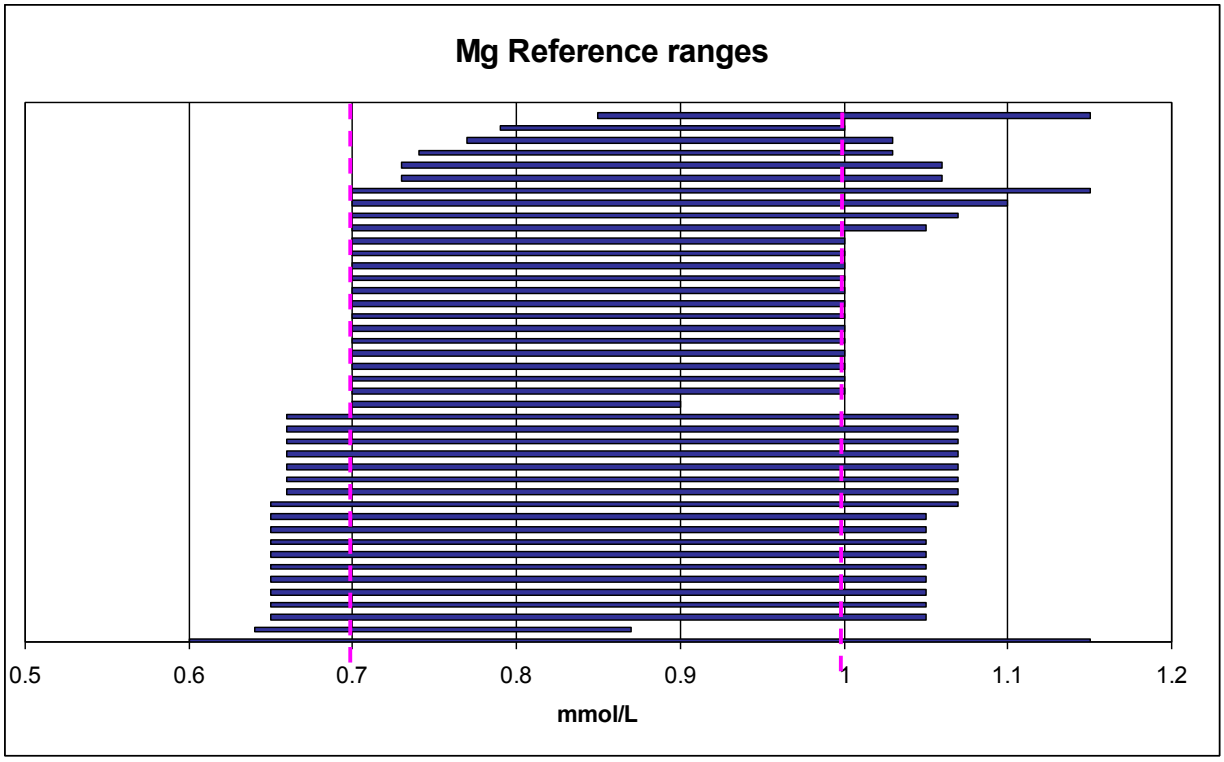
0.8
0.9
1
1.1
1.2
1.3
1.4
1.5
1.6
1.7
mmol/L


Mg Reference ranges
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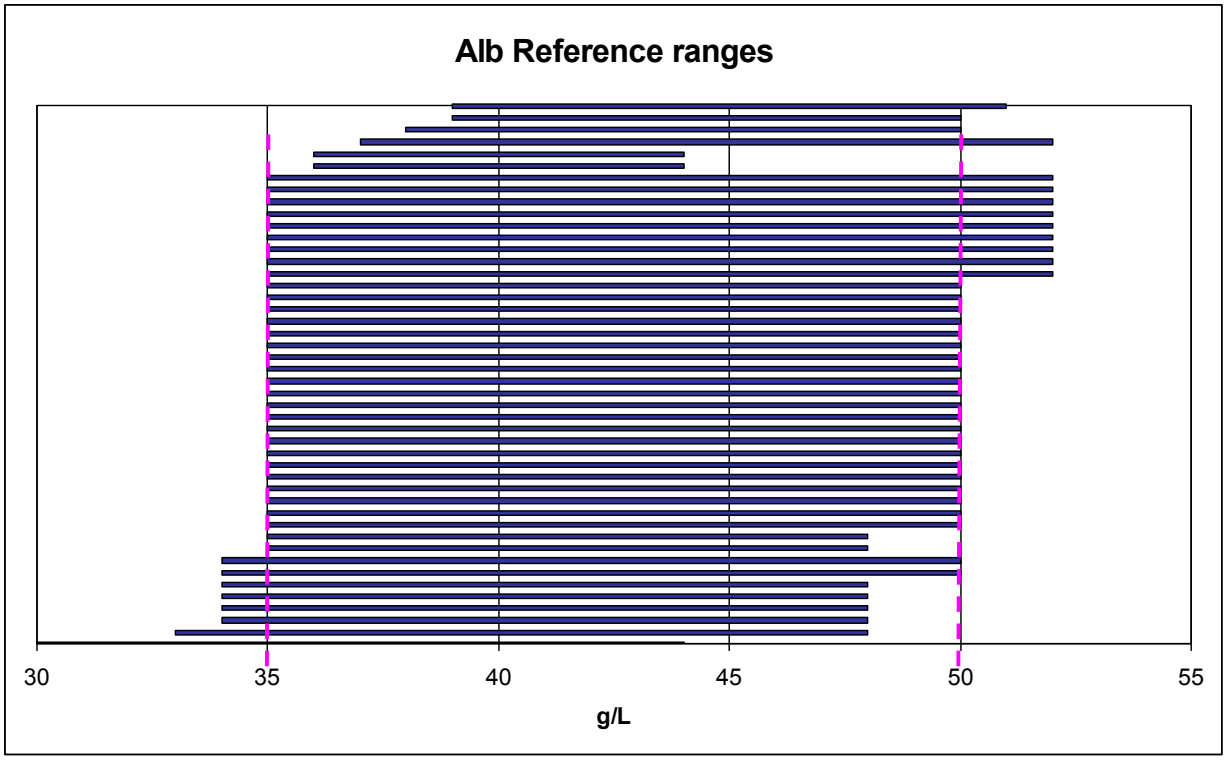
0.6
0.7
0.8
0.9
1
1.1
1.2
mmol/L


Alb Reference ranges
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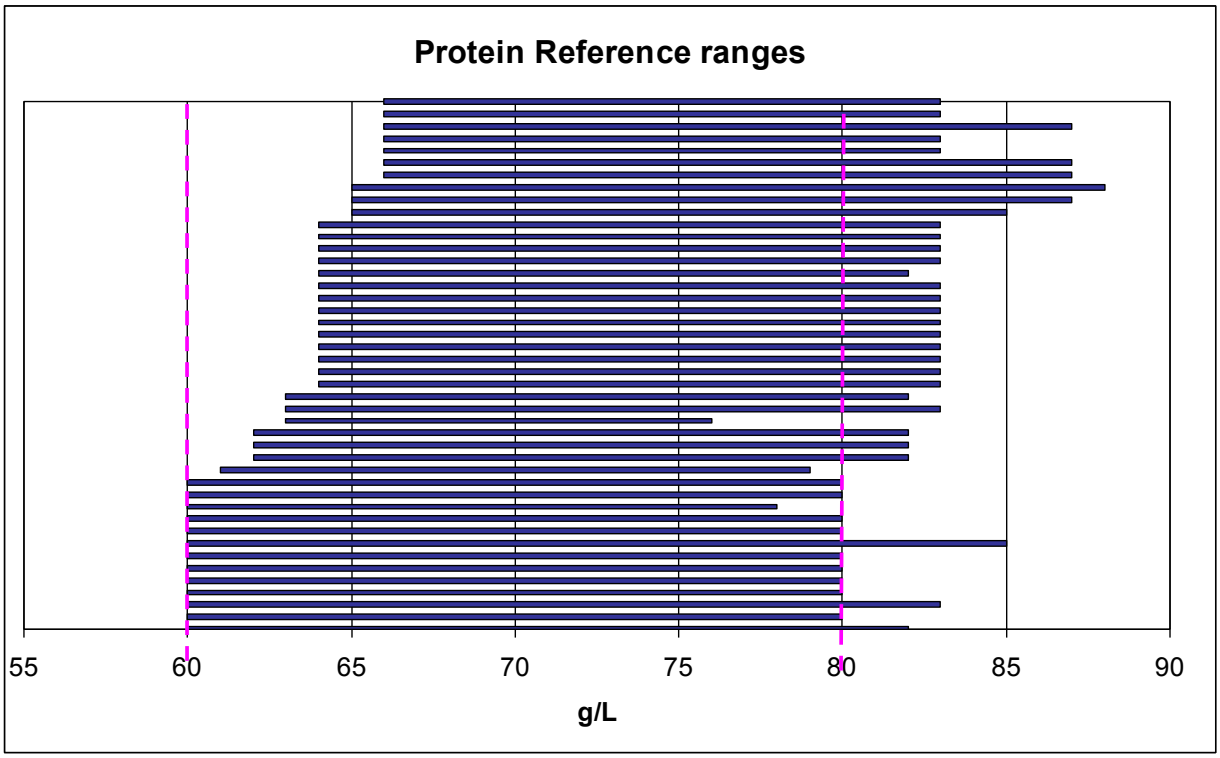
35
40
45
50
55
g/L


Protein Reference ranges
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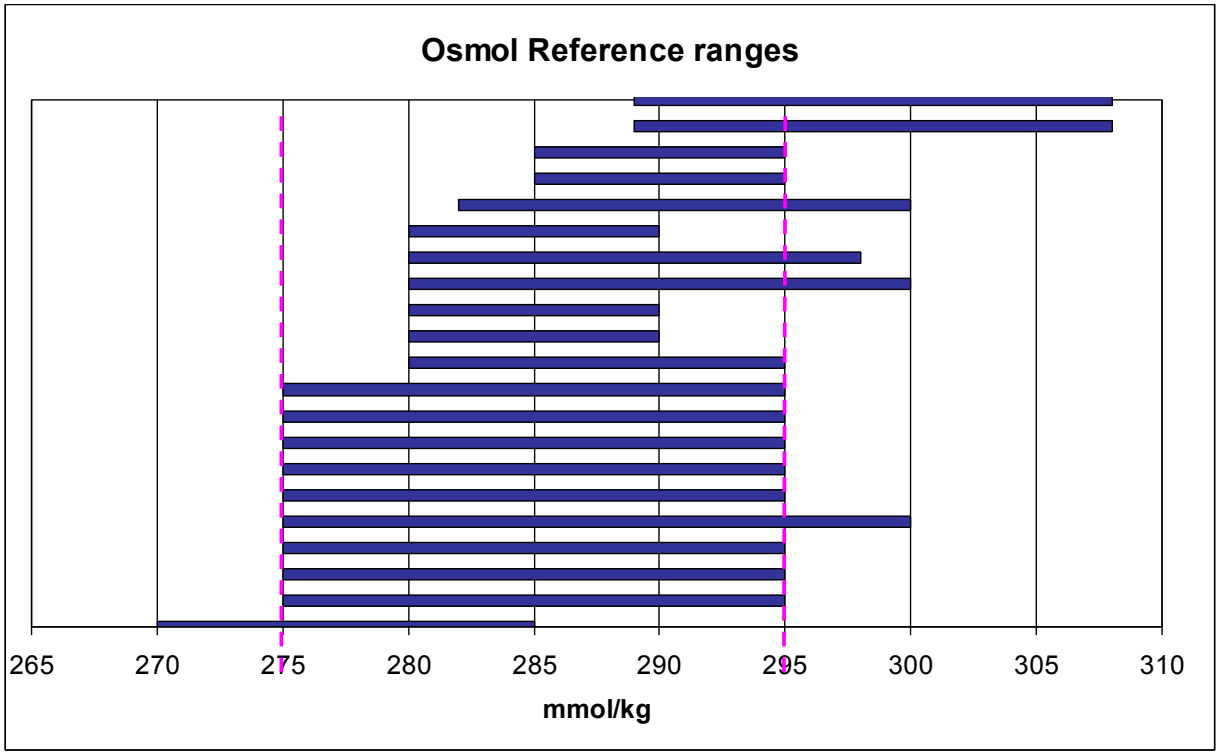
60
65
70
75
80
85
90
g/L


Osmol Reference ranges
265
270
275
280
285
290
295
300
305
310
mmol/kg

Key findings

A number of key findings emerged from review of this data.

- A wide variety of RIs are in use for some of the analytes, without any clear reason why.
- For most analytes there is no single range that would be identical to the current reference intervals in use in a majority of hospitals.
- Many laboratories have different RIs despite using the same method on the same analyser and stating they have adopted the manufacturer's recommended reference range. Table 1 shows an example of this in respect of urea (an analyte with no issues in relation to gender or plasma versus serum).
- Only some laboratories appear to have taken into consideration known differences between serum and plasma for Potassium and Total Protein, and between BCG and BCP methods for albumin.
- A number of laboratories are already using PH ranges for particular analytes.
- Only three laboratories had derived their own reference intervals; these RIs covered a number of the analytes (but not all).
- Some smaller hospitals grouped with larger hospitals had achieved a degree of common reference intervals through agreement following purchase of similar analysers.

Table 1: Variation in Urea Reference Intervals and their sources in Irish Clinical Laboratories (data collected 2012)

	Total [1]	Kit [1]	Other [1]
Abbott Architect	11 (9)	8 (6)	3 (3)
Beckman AU	9 (3)	3 (1)	6 (2)
Beckman Synchron	8 (5)	4 (3)	4 (3)
Roche Modular	11 (7)	8 (6)	3 (3)
Other	5 (5)	4 (4)	1 (1)
Total	44 (25)	27 (18)	17 (10)

[[1]Total number of laboratories (number different ranges)]

Verification

To support laboratories in adopting the proposed ranges the group undertook to perform verification studies according to CLSI / IFCC criteria. An RI is deemed valid for transfer if two or less samples from twenty healthy individuals fall outside the proposed interval.

Of the 20 samples distributed to each laboratory just ≤ 1 result outside the proposed RI was obtained for serum and plasma for Na, K, Urea, Cl, PO4, Mg, BCG Albumin, and Total Protein. For BCP Albumin 2/4 laboratories reported 2 results (33-34 g/L) outside RI.

For Bicarbonate only one result outside the RI was obtained at the primary laboratory and at one laboratory nearby. Laboratories further away (>1hour transport time) reported 4 to 9 results outside range.
For Osmolality only one laboratory (1 result outside RI) complied with CLSI requirement for verification. Five other laboratories which measured Osmolality reported 3 to 5 outliers. A second set of 20 samples at one laboratory gave a similar result. Additionally the mean Osmolality for 127 measurements from the 6 labs was 292 mmol/kg (SD=5), not consistent with an RI of 275-295 mmol/kg.

Expected differences were verified for serum versus plasma (K, PO4, Total Protein) and BCG versus BCP Albumin.

Survey Results (Analytes) and Recommendations

Recommendations are summarised in Table 3, a table which also includes UK and New Zealand current practice as well as proposed Australasian recommendations for agreed RIs.

Table 2: Survey results and recommendations for 10 analytes

Analyte	Recommendation
Sodium:	The group recommends not adopting the PH range, as it was felt that the lower limit (LL) of 133 was too low. A range of 135-145 is proposed as being more in keeping with our survey findings, with clinical limit and target values in European and US guidelines[1-3], and ranges agreed for New Zealand (NZ).
Potassium:	The group recommends 3.5-5.3, as per PH, but for serum only. LL should apply to plasma, but more work is needed before a recommendation can be made on this.
Urea:	The PH range offers a reasonable compromise if an agreed range is to be introduced. The LL of 2.5 is also an average for our Irish labs. The upper limit (UL) of 7.8 is higher than the average from our survey but less than the UL derived in-house by three labs and is in agreement with NZ ranges.
Chloride:	Adopt PH range.
Bicarbonate / Total CO_2:	Adopt the PH interval. Majority of labs already use this RI.
Phosphate:	Adopt PH. The PH interval is close to the RIs currently used in RoI.
Magnesium:	Either 0.65 or 0.70 would agree with equal proportions of RIs in our survey but the group felt that the 0.70 was a better guide clinically. At the higher level the differences in UL of RI were not felt to be important and therefore we recommend the PH range of 0.7-1.0.
Albumin:	Of 45 labs who reported their RIs to us 31 used BCG and 14 BCP. No account seemed to be taken, by most labs and manufacturers, of differences in these methods. We recommend 35-50 for labs using BCG. More work is needed before making a recommendation on BCP.
Total Protein:	There is an equal weight of evidence behind the PH interval of 60-80 and a range of 63-83. The group is recommending the PH interval due to advantage of agreeing with UK practice.
Osmolality:	We recommended the PH interval as being in use by around half of labs reporting osmolality and being clinically valid. We have concerns about some of the higher ULs in use. However, the verification process did not support this range.

Discussion

Lack of sample stability is likely to have affected bicarbonate in the study. The verification studies have shown that the other proposed RIs are valid except for Osmolality. Based on our study findings, we do not support a harmonised RI for Osmolality.

Review of the impact on proposed RIs of plasma versus serum and BCP versus BCG is nearing completion.

Adopting the proposed Bicarbonate interval, which is the same as the PH interval, seems the most appropriate choice and remains our recommendation.

Conclusion

This study confirms significant variation in RIs quoted by Irish Clinical Chemistry laboratories. Proposed harmonised RIs have been tested for serum and plasma in 8 laboratories using 7 analyser platforms covering the major analysers in current use. From this study we propose national adoption of harmonised RIs for 9 of 10 analytes studied and we encourage all clinical laboratories to adopt these intervals.

We recommend that Irish laboratories adopt these common ranges and that the process be coordinated centrally.

Table 3: Proposed Reference Intervals for Republic of Ireland and Comparable International RIs

Analyte	Units	IRIH Proposal (Ireland)	Pathology Harmony (UK)	SIQAG (NZ)	ARQAG (NZ)	AACB proposal (Aus+NZ)
Sodium	mmol/L	135 - 145	133 - 146	135 - 145	135 – 145	135 - 145
Potassium	mmol/L	3.5 - 5.3 (serum)	3.5 - 5.3	3.5 - 5.2 (serum & plasma)	3.5 - 5.2	3.5 - 5.2
Urea	mmol/L	2.5 - 7.8	2.5 - 7.8	3.2 - 7.7	3.2 - 7.7	
Chloride	mmol/L	95 - 108	95 - 108	95 - 110	95 – 110	95 - 110
Bicarbonate	mmol/L	22 – 29	22 - 29		22 – 31	22 - 32
Phosphate	mmol/L	0.8 - 1.5	0.8 - 1.5	0.8 - 1.5	0.7 - 1.5	0.75 - 1.50
Magnesium	mmol/L	0.7 - 1.0	0.7 - 1.0	0.8 - 1.5	0.7 - 1.0	0.7 - 1.1
Albumin	g/L	35 - 50 (BCG)	35 - 50	35 - 50 (BCG)	38 – 52	
Total Protein	g/L	60 - 80 (serum)	60 - 80	64 - 83	66 – 84	60 - 80
Osmolality	*mmol/kg*	*275 – 295 Rejected*	*275 - 295*			

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Prostate Specific Antigen (PSA) Test Harmonisation

Outcomes Agreed at the National Cancer Control Program PSA Harmonisation Board Workshop

Authors

Developed by the NCCP PSA Harmonisation Board:
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Effective date

December 2014

The following is a summary of the PSA harmonisation outcomes and the full report can be accessed by clicking on this link:

The full report *PSA Test Harmonisation Outcomes Agreed at the NCCP PSA Harmonisation Board Workshop 3rd of December 2014.*

The following PSA test harmonisation outcomes were agreed by the laboratories of the NCCP-designated cancer centres:

1. The unit of measurement of PSA concentration in serum or plasma shall be µg/L and at least one decimal point is required.

2. Assay details (calibration followed by manufacturer) shall be specified with the test name on PSA reports.

3. Whole blood specimens for PSA measurement shall be drawn, transported, logged-in, and serum / plasma separated and ready for analysis in less than 24 hours. Requesting doctors shall be advised of this requirement. A warning shall accompany results on specimens exceeding this agreed time limit.

   PSA testing shall not be performed on an un-centrifuged blood specimen received more than 48 hours after it was drawn, unless conclusive evidence indicates that longer contact times do not contribute to result error.

4. Only PSA assays calibrated to the WHO International Standard for Prostate-Specific Antigen (NIBSC Code 96/670) shall be used.

5. All NCCP-designated cancer centres shall participate in an ongoing external quality assessment (EQA) scheme for PSA operated by IEQAS. The types of EQA samples used in the scheme will include pooled residual serum and occasionally donor serum samples. EQA results shall be returned for each analytical system from which patient PSA results are generated.

6. Each NCCP-designated cancer centre shall:
   a) Set internal quality control (IQC) limits for PSA using existing IQC material so as to achieve realistic concordance with coefficients of variation currently attained.
   b) Run a common IQC two-level product for the intensive quality management of PSA measurement. The common IQC material is not intended to replace or displace a centre's existing IQC material.
   c) Set agreed common acceptance / rejection criteria for this material with the aim of improving the quality of results reported across all the centres.

See the full report for more information on approaches to achieving harmonisation of clinical laboratory results.

A Quick Reference Guide for **Use of Thyroid Function Tests in Primary Care**

Authors

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Effective date

January 2016

Scope

The guideline aims to provide guidance regarding appropriate use of Thyroid Function Testing (TFTs) in adults in Primary Care. The guideline applies to adults (greater than 16 years) and does not apply to preconception / pregnancy monitoring or children.

Key recommendations

Recommendations are grouped under the following headings:

1. Use of TFTs when Thyroid Dysfunction is suspected
2. Discordant TFTs
3. Use of TFTs for Primary Hypothyroidism Monitoring
4. Use of TFTs in Secondary Hypothyroidism
5. Use of TFTs for Hyperthyroidism Monitoring
6. Use of TFTs to monitor subclinical hypothyroidism in adults
7. Use of TFTs to monitor subclinical hyperthyroidism in adults

Process of development and review

The guideline was developed by Dr. Gerard Boran, in collaboration with Dr. Niamh Moran, ICGP in response to a request from the ICGP. The guideline was reviewed by the Quality in Practice Committee of the ICGP, Dr. Anne McGowan, Dr. Mark Sherlock, and Dr. James Gibney and feedback was incorporated.

1. Use of TFTs when Thyroid Dysfunction is suspected	
1 When to test	• **Symptoms suggestive of Hypothyroidism** Especially in women of menopausal age (or > 50 years old [1,2,3]). Symptoms are often nonspecific and include weight gain, fatigue, poor concentration, depression, diffuse muscle pain, and menstrual irregularities. Symptoms with a higher specificity for hypothyroidism include constipation, cold intolerance, dry skin, proximal muscle weakness, and hair thinning or loss.[4] • **Hyperthyroid symptoms** Symptoms include heat intolerance, palpitations, anxiety, fatigue, weight loss, muscle weakness, and menstrual irregularities. Clinical signs may include tremor, tachycardia or atrial fibrillation, lid lag, and warm moist skin.
2 When not to test	• Healthy asymptomatic individuals under 50. • *Screening for thyroid dysfunction in a healthy adult population is not warranted.*[3]
3 When to re-test in healthy individuals with previously normal TFTS	• Not less than 3 years since a previous normal test in healthy asymptomatic individuals.[5]
4 When not to do imaging	• Don't routinely order a thyroid ultrasound in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland.[6]
2. Discordant TFTs	
5 T4 High or T4 Low in the presence of a normal TSH in a patient with suspected thyroid dysfunction	• Discuss these cases with your local laboratory consultant or endocrinologist before commencing any treatment. This is because further laboratory and / or endocrinologist evaluation is usually necessary.
3. Use of TFTs for PRIMARY Hypothyroidism Monitoring	
6 When to test	• Check TFTs annually in patients stabilised on long-term T4 therapy. [3]
7 When not to test	• Don't check TFTs in a stable patient more often than annually. [3] • After a change in thyroxine dosage, do not re-check TFTs for at least 3 months. In stable patients, there may be no need to alter thyroxine dosage for very minor abnormalities in TFTs. Instead enquire about non-compliance and whether there was an intercurrent illness.[3]
8 When to test for Thyroid Peroxidase Autoantibodies (TPO Ab)	• Measure TPO Ab on one occasion for diagnosis of autoimmune thyroiditis, but not for monitoring.
9 When NOT to test for TPO Ab	• Do not test for TPO Ab when the TFTs are normal.
10 When not to order T3 levels	• Don't order a total T3 or free T3 level when assessing T4 therapy in hypothyroid patients.[6]

4. Use of TFTs in SECONDARY Hypothyroidism.	
11 Suspected new cases	• Please discuss these cases with your local laboratory consultant or endocrinologist before commencing any treatment. This is because further endocrinologist and / or laboratory evaluation is usually necessary.
12 Maintenance	• Perform annual TFTS in patients stabilised on Thyroxine therapy. These patients should be under endocrinologist review. * Note in patients with secondary hypothyroidism due to pituitary disease the TSH level should NOT be used to guide treatment (as it is often low) and therefore the Free T4 level should be used.

5. Use of TFTs for Hyperthyroidism Monitoring	
13 Monitoring Neomercazole therapy	• Perform TFTS every 4-6 weeks after commencement, and at 3 month intervals once maintenance dose is reached.[3]
14 Monitoring after Radioactive iodine (RAI) or thyroidectomy treatment in Graves Disease*	• Follow-up in first 1-2 months after RAI treatment.[6] • If patient remains thyrotoxic then recheck TFTs at 4-6 week intervals. • Following thyroidectomy for Graves disease (and commencement of T4 therapy), measure TFTs 6-8 weeks post-operatively.[3] • In either case: once stabilised, reduce frequency of testing to 3-monthly for one year and then annually for life. *Note these patients are usually under the care of an endocrinologist so this section is provided for information only.
15 Monitoring after RAI or surgical treatment in Toxic Multinodular Goitre and Toxic Adenoma*	• Follow-up in first 1-2 months after RAI treatment for Toxic Multinodular Goitre. Repeat TFTs at 1-2 month intervals until stable, and then annually.[6] • Following surgery for toxic multinodular goitre and start of thyroxine therapy, TSH should be measured 1-2 monthly until stable and annually thereafter. • Following surgery for toxic adenoma TSH and Free T4 levels should be obtained 4-6 weeks post operatively.[3] • In either case: once stabilised, reduce frequency of testing to 3-monthly for one year and then annually for life. * Note these patients are usually under the care of an endocrinologist so this section is provided for information only.

6. Use of TFTs to Monitor Subclinical Hypothyroidism	
16 Definition of Subclinical Hypothyroidism	TSH above the defined upper limit of the reference interval, with a serum free T4 within the reference interval. Patients have few or no symptoms. Pattern should be confirmed on two occasions 3-6 months apart.
17 When to test	• Patients with subclinical hypothyroidism should have the pattern confirmed within 3-6 months to exclude transient causes of elevated TSH.[3] *If treatment is initiated see Use of TFTs for primary hypothyroidism monitoring.* • Patients with subclinical hypothyroidism who are TPO Ab positive should have TFTs checked annually. • Patients with subclinical hypothyroidism who are TPO Ab negative should have TFTs checked every 3 years.

7. Use of TFTs to Monitor Subclinical Hyperthyroidism in adults	
18 Definition of Subclinical Hypothyroidism	Low or undetectable serum TSH levels, with normal free T4 and total or free T3 levels.
19 When to test	• These cases should be discussed with the local laboratory consultant or endocrinologist to decide a monitoring/treatment plan.[3] *If treatment is initiated see Use of TFTs for hyperthyroidism monitoring.* If treatment not undertaken then check TFTs every 6-12 months.

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Laboratory Testing for **Folate Deficiency**

Author
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Background

Folate is found in vegetables, fruit, cereals, and dairy products. Folate deficiency is rare in the era of food fortification. It may be seen with very poor diet, alcoholism and malabsorption. Folate deficiency may lead to megaloblastic anaemia and neural tube defects.

Scope

Folate testing in adults in hospitals and in primary care settings in the Republic of Ireland.

Key recommendations

Limit folate testing to patients with a recognised clinical indication and avoid screening with a folate test. Do not include it as part of a standard admission order set for example. Serum folate is the first-line test of choice.

Testing

Who to test-indications for testing

- Haematological
  - unexplained anaemia / other cytopenias
  - unexplained macrocytosis
  - haemolysis
- Pregnancy
- Malabsorption
- Anticonvulsant therapy
- Methotrexate therapy
- Alcoholism
- Dialysis patients

Who not to test

There is no value in re-testing folate in patients who are already on folic acid unless symptoms or blood counts fail to improve.

Routine screening for folate deficiency is not indicated.

How to test

Serum folate and red cell folate are the commonly available tests. Serum folate reflects recent folate status and intake whereas red cell folate level reflects tissue folate status over the lifetime of the red cells. Serum folate measurement may be better than red cell folate because it is affected by fewer pre-analytical and analytical variables and is the first-line test of choice. Red cell folate may be useful in patients with macrocytosis who have a normal serum folate.

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Laboratory Testing for Vitamin B_{12} Deficiency

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Background

Vitamin B_{12} is found in animal products such as meat, seafood, dairy products and eggs. Dietary deficiency of Vitamin B_{12} is unusual except in strict vegans. Causes of Vitamin B_{12} deficiency include pernicious anaemia, gastric resection and malabsorption. Pregnancy and long term use of Metformin or proton pump inhibitor / H2 receptor antagonist may also lead to low Vitamin B_{12} levels. Vitamin B_{12} deficiency may lead to megaloblastic anaemia and neurological symptoms including peripheral neuropathy, cognitive impairment and sub-acute combined degeneration of the cord.

Scope

Vitamin B_{12} testing in adults in hospitals in the Republic of Ireland.

Key recommendations

Limit Vitamin B_{12} testing to patients with a recognised clinical indication and avoid Vitamin B_{12} testing as part of a routine order set, e.g. for newly admitted patients.

Epidemiology

Vitamin B_{12} is a very commonly requested test. University Hospital Limerick received over 40,000 samples annually prior to the implementation of local guidelines which resulted in a 70% reduction in samples received without any reduction in the number of low Vitamin B_{12} results.

Testing

Who to test-indications for testing

- Hematological
  - unexplained anaemia / other cytopenias
  - unexplained macrocytosis
- Neurological
  - sub acute combined degeneration of the cord
  - peripheral neuropathy
  - dementia
  - unexplained neurology
- glossitis
- pregnancy
- malabsorption
- strict vegans
- previous gastric resection
- metformin therapy
- prolonged proton pump inhibitor or H2 receptor antagonist therapy

Who not to test

There is no value in re-testing Vitamin B_{12} in patients who are already on parenteral Vitamin B_{12} unless FBC parameters or neurological symptoms fail to improve.

Routine screening for Vitamin B_{12} deficiency is not indicated.

How to test

A Vitamin B_{12} immunoassay is currently the standard routine diagnostic test. It is a widely available and low cost test. However, it lacks specificity and sensitivity. The significance of Vitamin B_{12} test results should be assessed in conjunction with the clinical features. If there is strong clinical suspicion of Vitamin B_{12} deficiency despite a normal or borderline Vitamin B_{12} test result, treatment should not be delayed to avoid neurological impairment. Additionally interpretation of the results can be difficult during pregnancy and in patients on combined oral contraceptives.

Second line tests to help assess Vitamin B_{12} status include homocysteine, methylmalonic acid and holotranscobalamin, however these are not as widely available as Vitamin B_{12} immunoassay at present.

Homocysteine is raised in Vitamin B_{12} deficiency. However, homocysteine is not specific to Vitamin B_{12} deficiency and may also be elevated in folate deficiency, Vitamin B_6 deficiency, renal failure and hypothyroidism.

Methylmalonic acid is raised in Vitamin B_{12} deficiency. However, it also may be falsely elevated in patients with renal failure, small bowel bacterial overgrowth and haemoconcentration.

Holotranscobalamin may be more specific than serum Vitamin B_{12} levels. It is also likely to be more accurate in pregnancy and in patients on combined oral contraceptives.

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Use of the D-dimer Test

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Background

D-dimer is a terminal degradation product of cross-linked fibrin that can be easily quantified in the laboratory and may be assessed in venous thrombosis and disseminated intravascular coagulopathy. D-dimer may also be elevated in other situations such as pregnancy, cancer, inflammation and post-operatively.[1]

Scope

D-dimer testing in adults in hospitals in the Republic of Ireland.

Key recommendation

Do not use D-dimer as a screening test in all patients with suspected deep vein thrombosis (DVT) / pulmonary embolism (PE). Restrict initial D-dimer testing in suspected DVT / PE to patients with low clinical probability of DVT / PE.

Epidemiology

D-dimer is a commonly requested test. For example, in Tallaght Hospital during 2014, 3,699 requests for D-dimer testing were received. The majority (59%) of the requests were sent from the emergency department.

Testing

Who to test

- Patients with a low clinical probability of venous thromboembolism after assessment of the clinical probability score, e.g.
  - Well's score less than 2 for deep vein thrombosis[2-4,]
  - Well's score of less than or equal to 4 for pulmonary embolism[3-6,]
- Patients with clinically suspected deep vein thrombosis with a high clinical probability score and negative imaging studies,[3]
- Planning duration of anticoagulation in selected patients,[7]
- Diagnosis and monitoring of disseminated intravascular coagulation.[8]

Who not to test

Do not test initially in patients with higher clinical probability scores as they require imaging to assess for venous thrombosis regardless of D-dimer result.[2-6]

Do not test in upper limb DVT as the utility of D-dimer has not been confirmed in this group.[3]

How to test

Sample type: sodium citrate bottle.

Clinical details on request form should include indication for test and clinical probability score if used for acute DVT / PE.

The test should be performed on a quantitative assay and the result reported in SI units, fibrin D-dimer DDU (µg/L) or fibrin D-dimer FEU (µg/L). When used for DVT / PE exclusion, the test should be validated for this purpose and have adequate sensitivity and negative predictive value.[9]

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Laboratory Testing for Thrombophilia

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Effective date
January 2015

Scope

The aim of guidelines on thrombophilia testing is to assist clinicians in identifying patients in whom results of thrombophilia testing would be expected to change clinical management. These guidelines apply to adult, non-pregnant patients only.

Key recommendations

There is a limited role for thrombophilia testing in the management of patients with venous and arterial thrombosis.

Clinical factors, such as the personal and family history of venous thrombosis, are more useful than thrombophilia test results in determining the duration of anticoagulation and risk of recurrence in the majority of patients with venous thrombosis.

Screening of unselected patients is not recommended.

Epidemiology

Venous thrombosis has an incidence of approximately 1/1000 of the general population. Clinical risk factors for venous thrombosis include immobility, surgery, oestrogen containing medications or pregnancy, older age, active cancer, some cancer medicines, central venous catheters, obesity, cigarette smoking, long-haul travel, active IV drug use and medical conditions such as HIV, nephrotic syndrome, inflammatory bowel disease and myeloproliferative disorders.

Testing

Indications for testing and for NOT testing:

Testing for Antithrombin or Protein C or Protein S **is recommended** in the following clinical circumstances:

- Asymptomatic relatives with a family history of Antithrombin, Protein C or Protein S deficiency **AND** a family history of thrombosis,
- Neonates and children with purpura fulminans (severe Protein C or Protein S deficiency).

Thrombophilia testing is **not recommended** in the following clinical circumstances:
- Unselected patients after a first venous thrombosis event,
- Asymptomatic relatives of patients with the Factor V Leiden or Prothrombin gene mutations,
- Asymptomatic relatives of patients with venous thrombosis prior to hormonal treatment,
- Upper limb thrombosis,
- Catheter related thrombosis,
- Retinal vein occlusion,
- Patients prior to assisted conception or patients with ovarian hyperstimulation,
- Hospitalised patients as part of risk assessment for thrombosis,
- Arterial thrombosis.

Thrombophilia testing **may be considered** in the following clinical circumstances:
- First venous thrombosis in a patient with a family history of unprovoked or recurrent venous thrombosis in one or more first degree relatives,
- Asymptomatic relatives of venous thrombosis patients with a known heritable thrombophilia prior to hormonal treatment,
- Cerebral venous sinus thrombosis,
- Splanchnic vein thrombosis,
- Skin necrosis secondary to Vitamin K antagonists.

Antiphospholipid antibody testing (Lupus anticoagulant, antiphospholipid antibodies, anti beta 2 glycoprotein 1 antibodies) **is recommended** in the following clinical circumstances:
- History of recurrent first trimester miscarriage (>/= 3 consecutive miscarriages),
- >/=1 unexplained deaths of a morphologically normal foetus at or beyond 10/40,
- >/=1 premature birth of a morphologically normal neonate before 34/40 because of eclampsia / severe pre-eclampsia or placental insufficiency,
- Young adults (<50 years) with ischaemic stroke,
- Patients with an unprovoked PE or proximal DVT if anticoagulation is discontinued (note that these patients generally warrant long-term anticoagulation and if it has already been decided to continue long-term anticoagulation, then testing is not indicated).

Antiphospholipid testing **may be considered** in the following clinical circumstances:
- History of immune disorders and venous or arterial thrombosis,
- Unusual or extensive venous or arterial thrombosis.

Where testing is done and who does testing

Primary care / Hospital.

Thrombophilia Testing includes any or all of the following laboratory assays:
- Antithrombin,
- Protein C,
- Protein S,
- Factor VIII,
- Fibrinogen,
- Activated protein C resistance,
- Genetic test for the Factor V Leiden gene mutation,
- Genetic test for the Prothrombin gene mutation,
- Lupus anticoagulant,
- Antiphospholipid antibodies,
- Beta 2 glycoprotein 1 antibodies.

Interpretation of tests

The results of thrombophilia tests should be interpreted in the light of the clinical and family history of thrombosis. Advice is available from the Consultant Haematologist locally or from the Consultant Haematologists at the National Centre for Hereditary Coagulation Disorders.

Information required on the referral form

A completed standard laboratory test request form must be sent with all samples (6 Trisodium Citrate samples and 1 EDTA sample) to the Coagulation Laboratory for Thrombophilia Testing. A serum sample should be sent to the Immunology Laboratory for Antiphospholipid antibody / Beta 2 glycoprotein 1 antibody testing. The request form must include detailed patient and clinical information including:

- **Patient demographics**
  - Patient's Name,
  - Patient's Date of Birth,
  - Medical Record Number,
  - Name of Referring Clinician,
  - Name of Referring Hospital,
  - Order number / external laboratory number (if applicable to external agencies only).

- **Request details**
  - Clinical indication for testing,
  - Number of months post partum or pregnancy loss if appropriate,
  - Anticoagulant therapy,
  - Specific tests requested.

Full clinical information should accompany all requests for thrombophilia testing. In the event a request is received which does not have the required data (above) or does not have adequate clinical details the laboratory could:

- Issue a letter to the requesting doctor, requesting additional clinical details and / or advise that the case is discussed with the local Consultant Haematologist,
- Store the sample for up to eight weeks awaiting further communication from the referring clinician,
- Samples can be discarded after eight weeks if the referring clinician has not provided the required details or if it is determined that testing is not indicated.

Samples should not be sent for laboratory thrombophilia testing if patients are being treated with heparin or low molecular weight heparin or with any oral anticoagulants. In specific cases, the patient anticoagulant therapy may be discussed with the local Consultant Haematologist.

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Irish Guideline for the Investigation of **Blood Culture Samples**

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Governance

Report to ISCM executive committee.

Effective date

March 2015

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Executive Summary

The detection of microorganisms in blood using automated blood culture systems continues to be the gold standard in bloodstream infection (BSI) diagnosis. The clinical utility of blood cultures is widely accepted. The detection of significant organisms in blood is helpful in directing further investigations as to the source of an infection. Furthermore, blood culture identification and susceptibility results allow for the rationalisation of antimicrobial therapy to target the organism(s) isolated, thus reducing the emergence of antimicrobial resistance.[1]

Timeliness in the handling, processing and reporting of blood culture samples by the microbiology department is of great importance in the provision of a quality service to users, and to guide effective management of the patient with BSI.[2] The aim of this guideline is to recommend the optimal turnaround times (TATs) for the handling, processing, and reporting of blood culture samples which reflect the clinical needs of the patient.[3]

Summary of Recommendations (See Table 1)

Pre-analytical stage

It is recommended that blood culture bottles are loaded as soon as possible, and ideally within 4 hours from the time the sample is taken.

Analytical stage

Once noted to have a positive reading, the blood culture bottle should be sub-cultured without delay to the appropriate media (with or without direct susceptibility testing), as per local policy.

It is recommended that the Gram stain of a positive blood culture should be performed as soon as is practical or possible, by a scientist equipped with the skills for Gram stain interpretation.

The *clinical significance* of the Gram stain result is interpreted by the doctor to whom the result is communicated.

A TAT of 24-48 hours is recommended for isolate identification, from the time a pure and adequate growth of the isolate is available for further testing.

A specific TAT is not recommended for direct susceptibility results.

A TAT of 24-48 hours is recommended for susceptibility results, from the availability of a pure and adequate growth of the isolate for susceptibility testing.

Post-analytical stage

Results of microscopy should be communicated promptly (within a two-hour period from the time the result is available for reporting) by the laboratory to the physician or other clinical personnel responsible for patient care.

Preliminary positive reports pertaining to isolate identification should be reported verbally or electronically on the same working day the information becomes available.

If the preliminary identification of the organism suggests that a change in antimicrobial therapy may be warranted, the result should be communicated promptly (within a two-hour period) to the clinician or other healthcare personnel responsible for the patient.

Preliminary negative results should be reported at 48 hours (or as per local agreement).

Final written or computer-generated reports should be issued after five days of incubation for standard blood culture investigations.

Direct antimicrobial susceptibility results should be issued according to local policy and under the direction of the microbiologist interpreting the results.

Final susceptibility results should be reported verbally and / or electronically on the same day as the results are confirmed by the laboratory. If final susceptibility results suggest that a change in antimicrobial therapy may be warranted, they should be communicated promptly (within a two-hour period) to the clinician or other healthcare personnel responsible for the patient.

Introduction

The detection of microorganisms in blood using automated blood culture systems continues to be the gold standard in bloodstream infection (BSI) diagnosis. Techniques which allow for the direct detection of microorganisms in blood are not routinely used in Irish laboratories. BSIs are common in Irish communities and hospitals. In 2013, over three and a half thousand E. coli and Staphylococcus aureus bloodstream isolates were reported by Irish laboratories to the European Antimicrobial Resistance Surveillance Network (EARS-Net).[4] The clinical utility of blood cultures is widely accepted. Positive blood culture results are an integral part of diagnostic algorithms such as the Duke criteria for endocarditis.[5] The detection of significant organisms in blood is helpful in directing further investigations as to the source of an infection. Blood culture identification and susceptibility results allow for the rationalisation of antimicrobial therapy to target the organism(s) isolated. Narrowing the spectrum of antimicrobial therapy reduces the emergence of antimicrobial resistance, as well as minimising hospital costs.[1,6] Equally, sterile blood culture results are useful in the assessment of any patient with a febrile illness.

Rationale

Timeliness in the handling, processing and reporting of blood culture samples by the microbiology department is of great importance in the provision of a quality service to users, and to guide effective management of the patient with BSI.[2] The overall mortality associated with true BSI is 17.5%. Mortality is higher if the BSI is acquired in hospital (20.3%) or if the causative organisms are fungi (35.8%). BSI mortality also increases with age and other predisposing factors such as renal failure.[7] Extended-spectrum beta-lactamase- producing *E.coli* and *K.pneumoniae* bloodstream isolates have become increasingly prevalent in Ireland.[4] The emergence of these resistant organisms in hospitals and communities compromises the success of commonly used antimicrobials and adds to the need for their earliest detection by the laboratory. Therefore, blood cultures are recognised as important samples.

Aim

This aim of this guideline is to recommend the optimal TATs for the handling, processing, and reporting of blood culture samples which reflect the clinical needs of the patient.[3]

Guideline Development Group & Methodology

Under the auspices of the NCPP Laboratory Handbook subcommittee, an Irish Society of Clinical Microbiologists (ISCM) Blood Culture sub-group was convened. The purpose of this group was to devise an Irish guideline on the handling, processing and reporting of blood cultures. The Guideline Development group consisted of seven members, including five clinical microbiologists and a representative from each of the ACSLM and the Microbiology Specialist Training Scheme.

Accredited Irish laboratories are compliant with the ISO 15189 standard.[3] This document was the core reference for the group. To this end, the guidance for this document followed the recommendations of Section 5.5.1 of the ISO 15189 document according to the following statement: ''Preferred procedures are those specified in the instructions for use of in vitro medical devices or those that have been published in established / authoritative textbooks, peer-reviewed texts or journals, or in international consensus standards or guidelines, or national or regional regulations.''[3]

The Health Protection Agency UK Standard for Microbiology Investigations (SMI), "Investigation of Blood Cultures (for organisms other than Mycobacterium species)," was available to the group as a document under review.[8] This document and its references were reviewed in detail. As a result of this review, the group conducted a wider literature search, the references for which are cited in the text.

Review Process

The consultation process involved distribution of the guidance, as agreed by the Guideline Development Group, to clinical microbiologists and clinical microbiology scientists via the ISCM and ACSLM, respectively. Submissions made during the consultation process were reviewed and the relevant changes were incorporated into the final document submitted to the NCPP Clinical Advisory Group in 2015. This guidance will be reviewed every three years. Interim guidance will be issued in the intervening period, if necessary.

Definitions

Infection is defined as a pathological process caused by invasion of normally sterile tissue or fluid (e.g. blood) or body cavity by pathogenic or potentially pathogenic micro-organisms. It is important to point out that frequently, infection is strongly suspected without being microbiologically confirmed.[9]

Bloodstream Infections are caused by the entry of micro-organisms into the blood. BSIs may be primary or secondary in origin and transient, intermittent or continuous in nature.[10] Detailed case definitions can be found at *http://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf*.

Sepsis is the clinical syndrome defined by the presence of both infection and the systemic inflammatory response syndrome (SIRS). However, since infection cannot always be microbiologically confirmed, the diagnostic criteria are infection, suspected or confirmed and the presence of any two or more of the modified SIRS criteria.[9]

Caveats considered by the ISCM Blood Culture sub-group in the formulation of the guideline

Evaluation of the usefulness and limitations of blood culture results, particularly in the setting of the ongoing management of sepsis, led to the following conclusions which influenced the recommendations of this guideline:

Owing to time taken for current conventional methods to detect organism growth in blood, blood culture results do not facilitate the initial management of the septic patient. In this time-dependent critical situation the kernel of effective management is early recognition of sepsis, escalation of care as appropriate and prompt initiation of bundles of care such as the 'Sepsis Six', one element of which involves the taking of blood cultures. The Guideline Development Group recommends that patients with sepsis should be managed as outlined in the National Clinical Guideline.[9]

It was noted by the group that the recognition of sepsis has been greatly facilitated by institution of the National Early Warning Score (NEWS) tool, which is now in use in most acute hospitals in Ireland.[9,11]

Although the usefulness of blood culture results should not be under-estimated; timely appropriate empiric antimicrobial therapy and source control are the cornerstones of sepsis management as outlined in the National Clinical Guideline.[9] 'Awaiting' culture results is not appropriate in this context.

The institution of appropriate broad-spectrum antimicrobials has been shown to reduce mortality in the setting of sepsis.[12] Therefore, it was noted by the group that the availability to clinicians of up-to-date empiric antimicrobial guidelines, which take national and local microbiological data into account, is essential.

Timeliness in the initiation of antimicrobial therapy was also noted to be a critical component of sepsis management. Prompt administration of antimicrobials particularly within the first hour of recognition of sepsis leads to increased patient survival.[13]

The availability of an expert in infection at all times is essential in order to provide expert opinion on the management of patients with sepsis.

The group recognised that the clinical utility of positive blood culture results is negatively affected by contamination with skin-type or environmental flora. Up to 50% of positive blood culture results represent pseudobacteraemia rather than true BSI.[1] In one study, only 12.4% of coagulase-negative staphylococcal (CoNS) isolates were found to be clinically significant.[7] In the initial stages these results can be harmful, particularly in the out-of-hours setting when the patients' clinical team are not available to make an informed decision regarding appropriate further action. This may lead to the initiation of unnecessary antimicrobial therapy and investigations, as well as lengthier hospital stays and costs. Efforts to reduce blood culture contamination rates in excess of 3% should be a consideration for the quality-improvement process in Irish microbiology departments in conjunction with their relevant clinical directorates or units.[14]

Where specific TATs are recommended in this document, they represent the optimal TAT for that process as agreed by the Guideline Development group. The group recognises there are differences in microbiology services in Ireland with regard to the funding and resources available to them. Implementation of this guidance may require augmentation of personnel and other resources. These resources may not be available in the short to medium term. Therefore, audit and risk assessment should form part of the implementation of this guideline, to ensure the timeliness and clinical utility of blood culture results in the context of patient safety.

Scope

Standard operating procedures relating to microscopy, culture, choice of media, incubation conditions, identification, susceptibility testing, patient selection and venesection method are found elsewhere.[15,16] The document does not describe the detection of viruses, parasites or *Mycobacterium* species, the processing of post-mortem blood cultures or the significance of individual organisms.

Unless otherwise stated, the document refers to commercial, automated, continuous monitoring blood culture systems as the instrument for detection of microbial growth. Individual instruments are not critically appraised. Manual or semi-automated blood culture processes are not considered in this document.

Type of specimen

Blood.

Please refer to local laboratory policy for the investigation of fluids from normally sterile sites.

Recommendations

A. Pre-analytical stage

The pre-analytical stage involves the time from collection of blood culture samples to the loading of blood culture bottles onto the analyser.

Recommended Loading Time (LT) for Blood Culture samples.

It is recommended that blood culture bottles are loaded as soon as possible, and ideally within 4 hours from the time the sample is taken.

Prompt incubation of blood culture bottles leads to reduced time to detection of positive growth (TTD).[17,18] Conversely, delays in the loading of blood cultures can result in false negative results.[18] Whilst a LT of 4 hours or less has been shown to be achievable,[19] it must be noted that factors such as internal and external transport facilities and out-of-hours staffing levels can have a significant impact on LT. Therefore, out-of-hours arrangements should be in place to facilitate the timely loading of blood culture bottles. This may involve setting up local transport arrangements between satellite hospitals or laboratories and the recipient laboratory, and / or the training of non-microbiological staff to load the bottles onto the instrument out-of-hours. A ≤ 4 hours TAT for the loading of blood culture bottles was considered to be the optimal TAT by the group. It is recommended that the LT is audited. Healthcare workers should be encouraged to document the time of venesection in order to facilitate this process. Factors identified by the audit process which result in systematic delays in the transport or loading of blood culture bottles should prompt remedial actions. Local risk assessment and audit may identify LTs outside of the range recommended here, which may also allow for the timely and successful recovery of microorganisms.

B. Analytical stage

The analytical stage involves monitoring for microbial growth by the analyser and the subsequent generation of microscopy, identification and susceptibility results from positive blood culture samples.

Recommended TAT for Sub-culture and Gram Stain of Positive Blood Culture samples

Once noted to have a positive reading, the blood culture bottle should be sub-cultured without delay to the appropriate media (with or without direct susceptibility testing) as per local policy.

It is recommended that the Gram stain of a positive blood culture should be performed as soon as is practical or possible, by a scientist equipped with the skills for Gram stain interpretation. The clinical significance of the Gram stain result is interpreted by the doctor to whom the result is communicated.

The availability of a culture / isolate for further testing is essential to guide the further management of a patient with a positive blood culture result. Therefore, it is recommended that once the blood culture sample is noted to have flagged with a positive growth, the bottle should be sub-cultured to the appropriate media (according to local policy) without delay. The decision to include direct susceptibility testing at this stage should be guided by local laboratory policy.

Prompt Gram stain results can result in more rational, cost- effective treatment, reduced length of stay (LOS),[6,20] and facilitate the earlier identification of patients on inadequate or inappropriate antimicrobial therapy. A specific TAT has not been suggested for Gram staining of positive blood cultures, as there is insufficient evidence to recommend a specific TAT. Gram stain interpretation is an important skill requiring extensive training and experience and should only be performed by those individuals competent to deliver consistent accurate results. Inaccurately reported Gram stain results can lead to sub-optimal and inappropriate therapy and represents a patient safety issue.[2] Equally, the reporting of a Gram stain result from a contaminated blood culture, or one that is not in keeping with the culture the following day, has similar adverse consequences.[21] This scenario is further exacerbated if the Gram stain report is inappropriately interpreted by staff who may not be familiar with the patient. Therefore, careful consideration should be used in deciding to whom Gram stain interpretation is entrusted.[2] Efforts should also be made to reduce blood culture contamination rates.[14,21] Local risk assessment or audit is recommended to ensure TATs for Gram stain interpretation and reporting meet the clinical needs of the patient.[3] This may be aided by liaison with laboratory users, which in turn may lead to locally agreed TATs.[3]

Recommended TAT for Isolate Identification

A TAT of 24-48 hours is recommended, from the time a pure and adequate growth of the isolate is available for further testing.

Recommended TAT for Direct Susceptibility Results

It was agreed by the group that direct susceptibility results can be useful for microbiologists in directing early antimicrobial therapy. However, as the direct susceptibility testing method is not a standardised process, a specific TAT is not recommended.

Recommended TAT for Final Susceptibility Results

The recommended TAT for final susceptibility results is 24-48 hours from the availability of a pure and adequate growth of the isolate for susceptibility testing.

C. Post-analytical stage

The post-analytical stage involves the reporting and communication of microscopy and culture results. A medical microbiologist should be available to provide further advice on blood culture results that have been communicated, if required.

Recommended Reporting Procedure for Microscopy Results

Results of microscopy should be communicated promptly (within a two-hour period from the time the result is available for reporting) by the laboratory to the physician or other clinical personnel responsible for patient care.[8]

Requestors have a responsibility to ensure contact details are clear when ordering the test.[22] The laboratory, in conjunction with its users, should establish, define and document local protocols for the effective and standardised communication of results. Criteria to be followed on receipt of such communications should also be considered.[22] Written or computer-generated reports should follow preliminary / verbal reports as soon as practicable.

Recommended Reporting Procedure for Culture Results
Preliminary positive reports pertaining to isolate identification should be reported verbally or electronically on the same working day the information becomes available. If the preliminary identification of the organism suggests that a change in antimicrobial therapy may be warranted, the result should be communicated promptly (within a two-hour period) to the clinician or other healthcare personnel responsible for the patient. If appropriate, it should be stated that a further report will be issued. Final written or computer-generated reports should follow preliminary / verbal reports on the same day as confirmation where possible.[8]

Preliminary negative results should be reported at 48 hours from collection (or as per local agreement).[8] Ideally preliminary negative results should be generated automatically to closely reflect the true incubation time.

Final written or computer-generated reports should be issued after five days of incubation for standard blood culture investigations. Cultures requiring extended incubation or reference laboratory testing may require a greater period of time before generation of a final report.

Recommended Reporting Procedure for Antimicrobial Susceptibility Results
Direct Susceptibility Results.

As direct susceptibility testing is not a standardised process, these results should be issued according to local policy and under the direction of the microbiologist interpreting the results.

Final Susceptibility Results
Final susceptibility results should be reported verbally and / or electronically on the same day as the results are confirmed by the laboratory. If final susceptibility results suggest that a change in antimicrobial therapy is warranted, they should be communicated promptly (within a two-hour period) to the clinician or other healthcare personnel responsible for the patient. Owing to the slow-growing nature of certain organisms, a longer incubation period may be required before susceptibility results can be correctly interpreted and reported.

Notification to the Health Protection Surveillance Centre (HPSC)

The Infectious Diseases Regulations 1981 (and subsequent amendments) require diagnostic laboratories to notify the Medical Officer of Health (MOH) / Director of Public Health (DPH) of certain *diseases*. Immediate preliminary notification is required for a *sub-set of notifiable diseases*. Notifications may be made in writing, by email or by telephone to the MOH / DPH. A comprehensive list of causative agents notifiable to the HPSC under the *Infectious Diseases (Amendment) Regulations 2011 (S.I. No. 452 of 2011)* is available at: *http://www.hpsc.ie/NotifiableDiseases/ListofNotifiableDiseases/File,678,en.pdf*.

Table 1: Summary of Recommendations for Investigation of Blood Culture Samples		
Investigative Stage	**Test/Process**	**Recommended TAT or Reporting Procedure**
	Pre-Analytical	
Collection, transport and loading of samples	TAT for collection to loading	≤ 4 hours
	Analytical	
From Flagging Positive to Microscopy & from availability of an isolate for Identification and Susceptibility results	Sub-culture	Once a positive flag is noted sub-culture without delay
	Gram Stain	As soon as possible, by a scientist with the skills for Gram stain interpretation. See Section: Recommendations B Analytical stage
	Identification	24-48 hours
	Susceptibility testing	24-48 hours
	Post-Analytical	
Negative report (from receipt in lab to negative reporting)	Preliminary Negative Report	48 hours (or as per local policy)
	Final Negative Report	After five days of incubation (greater if extended incubation applied)
Positive report (from positive flag to positive reporting)	Positive Microscopy Report	≤ 2 hours (from the time the result is available for reporting)
	Preliminary Identification Report (e.g. *S.aureus-'presumptive'*)	Report as soon as possible, ≤ 2 hours if result suggests a change in therapy may be warranted
	Direct Susceptibility Results	As per local policy/directed by microbiologist
	Final Identification and Susceptibility Results	Report the same day as confirmation of results ≤ 2 hours if results suggest a change in therapy warranted

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TORCH testing
in Obstetrics and Neonatology

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TORCH* Testing Algorithms in Obstetrics and Neonatology

What is the clinical presentation?

01	02	03	04	05
Pregnant woman exposed to or at risk ** of TORCH infection **(Table 1)**	Previously well pregnant woman with symptoms of TORCH infection **(Table 2)**	Previously well pregnant woman with fetal abnormalities detected on routine ultrasound **(Table 3)**	Findings in the neonate suggestive of congenital infection, identified after birth **(Table 4)**	Unexplained intrauterine death / stillbirth **(Table 5)**

Guidance notes for the use of this document

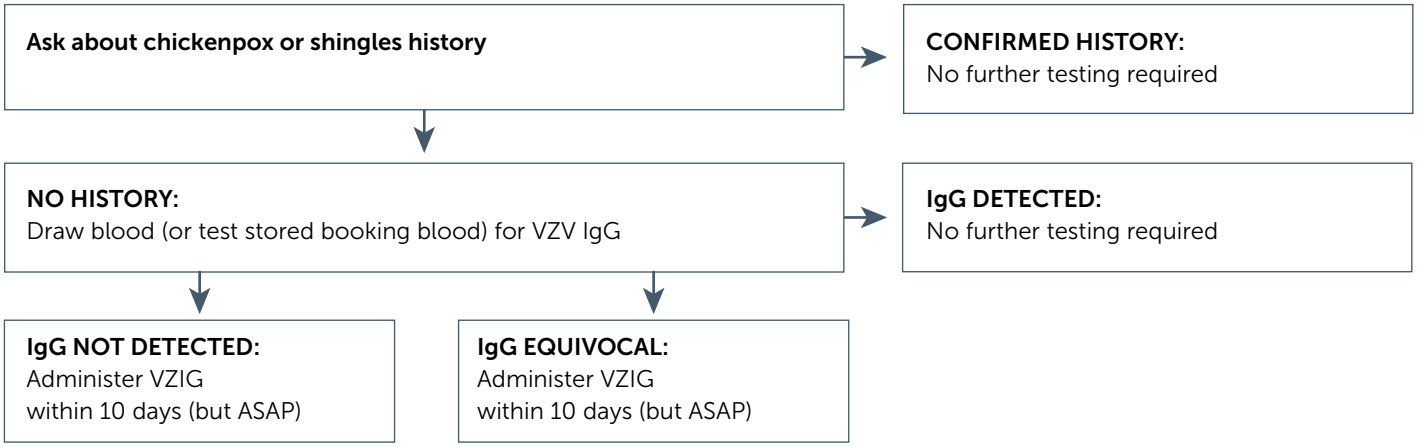
1. *TORCH is a non-exhaustive acronym used to refer to the main pathogens that may cause congenital infection in the fetus and newborn (Toxoplasma, Other [such as parvovirus, syphilis, varicella-zoster virus], Rubella, Cytomegalovirus, Herpes Simplex Virus).
2. **Pregnant women presenting with test results or an existing diagnosis from their GP or overseas should have their serology repeated to confirm the diagnosis before any intervention is considered.
3. This document is not a treatment guideline: it is intended to facilitate the prompt appropriate investigation of common infection-related issues in pregnancy.
4. Positive or unusual results should be discussed promptly with your local infection specialist (Clinical Microbiologist, Infectious Disease Physician (Adult or Paediatric), Clinical Virologist) & maternal-fetal medicine specialist.
5. Infection in the pregnant woman does not necessarily mean that the baby will be infected or affected: therefore, all babies born to mothers with evidence of infection during pregnancy should be screened at birth to confirm or exclude infection in the infant.
6. False positive IgM results are not uncommon in pregnancy: however, no IgM result should be assumed to be a false positive in the absence of confirmatory testing.
7. In the absence of a documented antibody response, a history of immunization against Measles or Varicella does not alter the advice presented below.

This document should be used in conjunction with existing national guidelines
Immunisation Guidelines for Ireland – *www.immunisation.ie*;
Rainbow Clinic guidelines – *www.ssstdi.ie*;
HSE/RCPI National Clinical Programme for Obstetrics and Gynaecology Clinical Practice Guidelines, see *http://www.hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprogramme/guidelines/*

Please note: positive results suggesting recent or active infection should be discussed with your local Infection Specialist

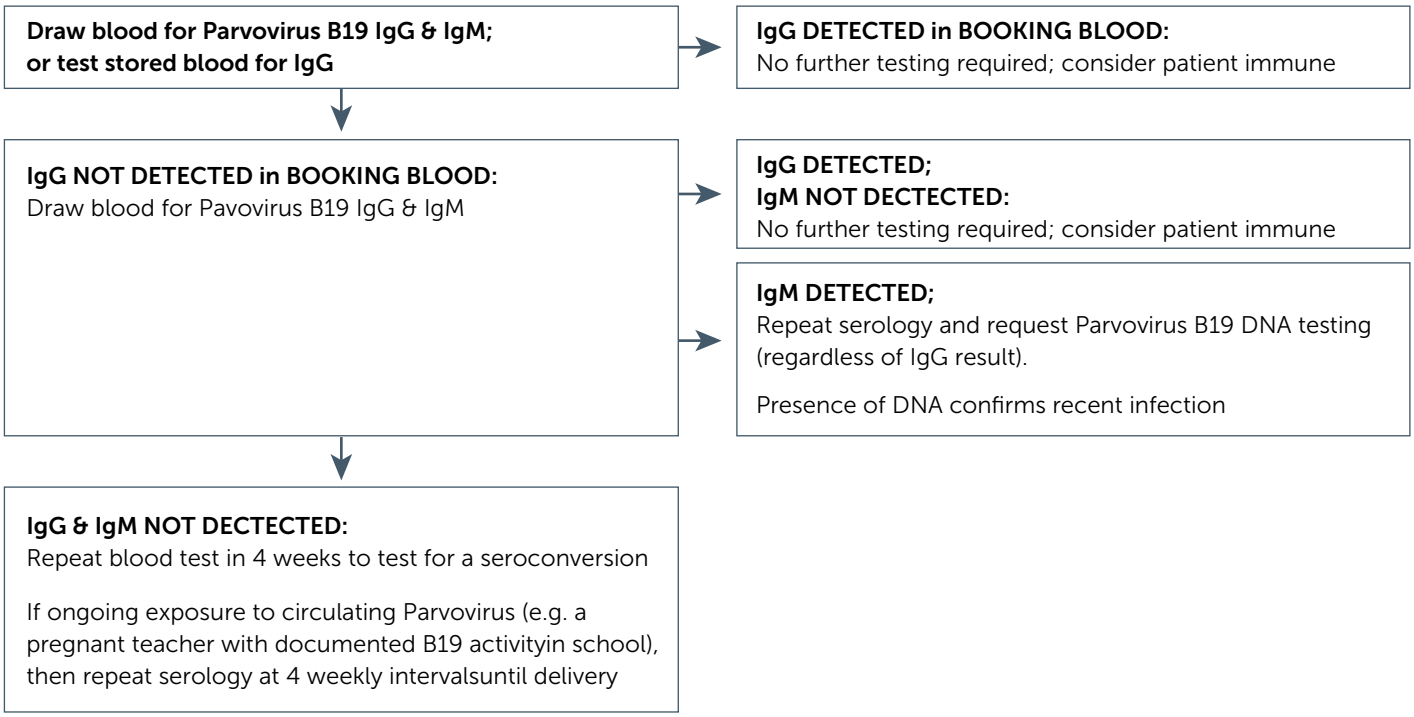
Table 1: Otherwise well pregnant woman exposed to potential TORCH infection

1.1. Varicella Zoster Virus (Chickenpox/Shingles)



NOTES: VZIG is only 50% effective; Consider post-partum vaccination against VZV in non-immune women of childbearing age

1.2. Parvovirus B19 (Slapped Cheek Syndrome)



NOTES: All pregnant women with recent B19 infection should be referred to fetal medicine unit for further assessment

1.3. Measles

Draw blood (or test stored booking blood) for Measles IgG

IgG DETECTED:
No further intervention required

IgG EQUIVOCAL:
Administer Human Normal Immunoglobulin (HNIG) within 6 days.

Please refer to Immunisation Guidelines for Ireland at www.immunisation.ie for additional information

IgG NOT DETECTED:
Administer Human Normal Immunoglobulin (HNIG) within 6 days.

Please refer to Immunisation Guidelines for Ireland at www.immunisation.ie for additional information

NOTES:

1. Measles does not cause a congenital syndrome, but is associated with an increased risk of premature delivery and spontaneous abortion;
2. Morbidity and mortality are increased in pregnant women with measles due to an increased risk of measles pneumonia during the third trimester and peripartum period;
3. Oral fluid should be obtained from the index case and tested for Measles IgM and RNA to confirm the diagnosis;
4. Pregnant women who are not immune to measles should be offered the MMR. vaccine after delivery, and at least 3 months after receiving HNIG.

1.4. Rubella

Draw blood for Rubella IgG (if not already performed on booking blood)

IgG DETECTED:
No further intervention required

IgG EQUIVOCAL:
Immune globulin is NOT recommended for routine post-exposure prophylaxis of rubella in pregnancy.

Oral fluid & blood should be obtained from the index case to confirm the diagnosis and inform further management.

All pregnant women exposed to a case of confirmed rubella should be referred to the fetal medicine unit.

IgG NOT DETECTED:
Immune globulin is NOT recommended for routine post-exposure prophylaxis of rubella in pregnancy.

Oral fluid & blood should be obtained from the index case to confirm the diagnosis and inform further management.

All pregnant women exposed to a case of confirmed rubella should be referred to the fetal medicine unit.

1.5. Cytomegalovirus (CMV)

Draw blood (or test stored booking blood) for CMV IgG

→ **IgG DETECTED in BOOKING BLOOD:**
No further testing required (if single recent exposure)

↓

IgG NOT DETECTED in BOOKING BLOOD:
Draw blood for CMV IgG

→ **IgG NOT DETECTED:**
Repeat CMV serology at 4 and 8 weeks to test for seroconversion (in case of a single exposure)

↓

IgG DETECTED:
Request IgM Testing

→ **IgM NOT DETECTED:**
No further intervention required

↓

IgM DETECTED:
Repeat IgM test to confirm, and request IgG avidity; liaise with local infection specialist

→ **HIGH AVIDITY IgG:**
Consistent with prior infection: no further testing indicated unless clinically indicated (e.g. abnormality on fetal ultrasound)

↓

LOW AVIDITY IgG:
Consistent with recent primary CMV infection

All pregnant women with primary CMV infection should be referred to the fetal medicine unit for further assessment

NOTES: All children born to women with CMV infection in pregnancy should be screened for congenital infection at delivery.

1.6. Toxoplasma gondii

Draw blood (or test stored booking blood) for Toxoplasma IgG

→ **IgG DETECTED in BOOKING BLOOD:** No further testing required (if single recent exposure)

↓

IgG NOT DETECTED in BOOKING BLOOD: Draw blood for Toxoplasma IgG

→ **IgG NOT DETECTED:** Repeat serology at 4 weeks in case of suspected recent exposure

↓

IgG DETECTED: Request IgM Testing

→ **IgM NOT DETECTED:** No further intervention required

↓

IgM DETECTED: Repeat IgM test to confirm, and request IgG avidity; liaise with local infection specialist

→ **HIGH AVIDITY IgG:** Consistent with infection more than 12 weeks previously: no further testing indicated unless clinically indicated (e.g. abnormality on fetal ultrasound)

↓

LOW AVIDITY IgG: Raises the possibility of recent infection (although not a reliable indicator)

All pregnant women with primary Toxoplasma infection should be referred to the fetal medicine unit for further assessment, and to an infection specialist for consideration for treatment

NOTES:

1. All children born to women with Toxoplasma infection in pregnancy should be screened for congenital infection at delivery
2. Toxoplasma gondii is a protozoan parasite for which cats are the definitive hosts, but which can infect most species of mammal. Humans usually become infected by consumption of raw or undercooked meat (that contains cysts) or by accidental ingestion of sporulated oocysts from soil or in contaminated food or water.

1.7. Hand, foot and mouth disease (Coxsackie A / Enterovirus)

- There is no evidence that Enterovirus (EV) infections in pregnancy cause any congenital syndrome: however
  - Infection in early pregnancy can be associated with increased risk of miscarriage
  - Infection near time of delivery may result in transmission of virus to the neonate
- There is no serological test available to confirm prior EV exposure (although the majority of adults are likely to be immune)
- There is no role for post-exposure prophylaxis following EV exposure
  - Pregnant women should be reassured that the risk to the fetus is low

NOTES: Positive results suggesting recent or active infection should be discussed with your local Infection Specialist

Table 2: Previously well pregnant woman with symptoms suggestive of TORCH infection

Previously well pregnant woman with clinical symptoms

2.1. Generalised Rash Illness

Is the rash vesicular?

→ **YES:**
Most likely diagnosis is Varicella Zoster Virus infection (chickenpox)

NO:
Consider Measles, Enterovirus, Rubella, and Parvovirus (MERP)

1. Draw blood for Measles, Rubella, and Parvovirus IgM
2. Send oral fluid for Measles & Rubella IgM & RNA
3. Send nose & throat swab, and stool sample for Enterovirus RNA and culture

MERP Notes:

1. There is no specific antiviral treatment for Measles, but be aware of the increased risk for viral pneumonia in the third trimester.
2. There is no specific antiviral therapy for Enterovirus, nor is treatment typically required.
3. There is no specific antiviral treatment for Rubella, but all confirmed cases should be referred to the fetal medicine unit for further assessment.
4. Parvovirus B19 infection rarely requires treatment for the mother, but all confirmed cases should be referred to the fetal medicine unit for further assessment & monitoring for hydrops fetalis.

NOTES:

1. Antiviral therapy (acyclovir) may be indicated, especially after 20 weeks gestation, or if the pregnant woman is immunosuppressed, but should always be considered in accordance with local guidelines and advice of Consultant Microbiologist or Infectious Diseases physician.
2. Adults are at an increased risk of VZV complications (e.g. pneumonia, with risk greater in later gestations.
3. All women with confirmed VZV infection in pregnancy should be referred to the fetal medicine unit for further assessment.
4. The greatest risk of congenital varicella syndrome is in the first or early second trimester: incidence is approximately 1-2% when infection occurs before 20 weeks.
5. There is no role for VZIG in the treatment of maternal VZV infection in pregnancy.

2.2. Hepatitis

- Draw blood for viral hepatitis screen (Hepatitis A, B, C, E, CMV, & EBV)
  Additional investigations guided by results
  - All primary CMV infections should be referred to fetal medicine unit for further assessment
  - All Hepatitis B & C infections should be referred to hepatology for assessment
  - There is no specific antiviral therapy for Hepatitis A or Hepatitis E, but Hepatitis E is associated with increased mortality in pregnant women (especially in the third trimester) so confirmed cases should be closely monitored
  - There are no specific concerns relating to EBV in pregnancy: severe primary EBV cases should be reviewed by a consultant in Infectious Diseases (ID) or Haematology

NOTES: Positive results suggesting recent or active infection should be discussed with your local Infection Specialist

Table 3: Pregnant woman with abnormalities detected on foetal ultrasound

Recommended investigations for the pregnant woman with abnormalities detected on foetal ultrasound					
	CMV [1]	Parvovirus B19 [2]	Rubella [3]	Toxoplasma [4]	Treponema pallidum (syphilis) [5]
3.1 Micro/ Macrocephaly	X		X	X	
3.2 IUGR	X	X	X	X	X
3.3 Intracranial calcification	X		X	X	
3.4 Echogenic bowel	X				
3.5 Ventriculomegaly	X			X	
3.6 Structural heart defects			X		
3.7 Hydrops		X			X

NOTES:

1. Draw blood for CMV IgG & IgM. If both negative, consider alternative diagnosis. If IgM present, may suggest recent infection. Repeat serology to confirm, and request IgG avidity testing (if not already done): In addition, request retrospective testing (for CMV IgG and IgM) on antenatal booking bloods.
   All confirmed CMV infections in pregnancy should be referred to the fetal medicine unit for further assessment.

2. Draw blood for Parvovirus IgG & IgM. If both negative, consider alternative diagnosis. If IgM present, request Parvovirus B19 DNA testing to confirm recent infection.
   All Parvovirus infections in pregnancy should be referred to fetal medicine unit for further assessment.

3. Draw blood for Rubella IgM. If negative, consider alternative diagnosis. If IgM present, or if patient known to be IgG negative at booking visit, request IgG testing plus IgG avidity to confirm seroconversion in pregnancy and / or recent infection. All confirmed Rubella infections in pregnancy should be referred to the fetal medicine unit for further assessment, and notified to Public Health.
   PLEASE NOTE: positive results suggesting recent or active infection should be discussed with your local Infection Specialist

4. Draw blood for Toxoplasma IgG & IgM. If both negative, consider alternative diagnosis. If IgM present, may suggest recent infection. Repeat serology to confirm, and request IgG avidity testing (if not already done): In addition, request retrospective testing (for Toxoplasma IgG and IgM) on antenatal booking bloods.
   All confirmed Toxoplasma infections in pregnancy should be referred to the fetal medicine unit for further assessment.

5. Draw blood for Treponema pallidum antibodies. If both negative, consider alternative diagnosis. If positive, request RPR to confirm recent / active infection.
   All T. pallidum infections in pregnancy should be referred to consultant in Genitourinary medicine (GUM) or Infectious Diseases for antimicrobial therapy.

Table 4: Neonatal abnormalities at birth

Recommended investigations for the neonate with clinical / laboratory abnormalities at birth								
	CMV [1]	HSV [2]	Parvovirus B19 [3]	Rubella [4]	Toxo [5]	T pallidum [6]	VZV [7]	Other
4.1 Hepatitis / Jaundice / Hepatomegaly	X	X			X	X		
4.2 Rash	X	X				X	X	
4.3 Thrombocytopenia	X		X			X		
4.4 Anaemia	X	X	X			X		
4.5 IUGR	X		X	X		X		
4.6 Microcephaly	X			X	X			
4.7 Hydrocephalus	X				X			
4.8 Failed Newborn Hearing Test	X							
4.9 Patient Ductus Arteriosus (at term)				X				
4.10 Intracranial Calcification	X			X	X			
4.11 Congenital Cataracts or Microphthalmia				X				
4.12 Hydrops			X			X		
4.13 Culture Negative Sepsis not responding to antibiotics in the first month of life[9]		X						X[8]

PLEASE NOTE: Positive results suggesting recent or active infection should be discussed with your local Infection Specialist

NOTES:

1. Send urine sample or salivary (viral) swab from the neonate for CMV DNA testing by PCR.
2. Send vesicular fluid or skin scrapings for HSV DNA testing; oral fluid, conjunctival swabs, EDTA blood, and CSF are also suitable for testing if neonatal HSV suspected.
3. Draw blood from the infant for Parvovirus B19 IgM and DNA testing.
4. Send urine sample and salivary swab from the neonate for Rubella RNA testing.
5. Draw blood from mother and infant for paired Toxoplasma IgM and IgG. If IgM present in either, request IgG avidity and discuss with Infection Specialist.
6. Draw blood from mother and infant for paired T pallidum antibody testing (including RPR). If RPR positive, discuss with Infection Specialist.
7. Send vesicular fluid or skin scrapings for VZV DNA testing.
8. Send NPA, stool, EDTA blood, +/- CSF (as clinically indicated) for Enterovirus RNA, and Adenovirus DNA testing.
9. All cases of culture negative sepsis should be discussed with Consultant Microbiologist or Infectious Diseases physician.

Table 5: Intrauterine death (IUD) / stillbirth

Intrauterine death (IUD) / stillbirth

Please refer to existing HSE / RCPI National Clinical Programme for Obstetrics and Gynaecology Clinical Practice Guidelines and seek advice from Pathologist if post mortem examination is performed and findings are suggestive of infective process.

TORCH Guideline development

A group was established in 2014 including representation from the National Virus Reference Laboratory, the National Clinical Programme for Obstetrics and Gynaecology, the National Clinical Programme for Paediatrics and Neonatology, the National Clinical Programme for Pathology, the Irish Society for Clinical Microbiologists, and the HSE on foot of a request from Dr. Philip Crowley, National Director of Quality Improvement to develop National guidelines for diagnosis and management of viral infections in obstetrics & gynaeocology and neonatology. The draft guideline was developed by the National Director of the NVRL in conjunction with the President of the ICSM. This first draft was circulated to the members of the ICSM and the larger group for feedback, and suggested changes made. The final document was signed off by the group.

Review Date

2017

References

1. American Academy of Pediatrics. Red Book: 2012 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics, 2012.

2. Royal College of Physicians of Ireland National Immunisation Advisory Committee. Immunisation Guidelines for Ireland (2013). *www.hse.ie/portal/eng/health/immunisation/hcpinfo/guidelines/immunisationguidelines.html.*

3. Department of Health, UK (2013). Immunisation against Infectious Diseases (The Green Book.) *www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book*.

4. Royal College of Obstetricians & Gynaecologists. Chickenpox in Pregnancy. RCOG Green-top Guideline No.13 (2015). *https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg13/*.

5. Health Protection Agency UK (2011). Guidance on Viral Rash in Pregnancy. *www.gov.uk/government/uploads/system/uploads/attachment_data/file/322688/Viral_rash_in_pregnancy_guidance.pdf*.

6. Society of Obstetricians and Gynaecologists of Canada Clinical Practice Guideline (2013). Toxoplasmosis in Pregnancy: Prevention, Screening, and Treatment. J Obstet Gynaecol Can 2013;35(1 eSuppl A):S1–S7.

7. Society of Obstetricians and Gynaecologists of Canada Clinical Practice Guideline (2010). Cytomegalovirus Infection in Pregnancy. J Obstet Gynaecol Can 2010;32(4):348–354.

8. Royal College of Obstetricians & Gynaecologists, and the British Association for Sexual Health and HIV (BASHH) Consensus Guideline (2014). Management of Genital Herpes in Pregnancy. *www.rcog.org.uk/en/guidelines-research-services/guidelines/genital-herpes/*.

9. Janier M, Hegyi V, Dupin N, et al. 2014 *European guideline on the management of syphilis*. J Eur Acad Dermatol Venereol. 2014 Dec;28(12):1581-93.

10. Butler K, Ferguson W, Goode M, Lyons F. Preventing Perinatal Transmission: a practical guide to the antenatal and perinatal management of HIV, Hepatitis B, Hepatitis C, Herpes Simplex, and Syphilis (June 2015 Edition). *www.ssstdi.ie* (Accessed August 14, 2015).

11. Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland Clinical Guideline No.31. Parvovirus B19 exposure/ infection during pregnancy (Version 1.0), September 2014.

Choosing Wisely®
Statements

Choosing Wisely® recommendations should not be used to establish coverage decisions or exclusions. Rather, they are meant to spur conversation about what is appropriate and necessary treatment. As each patient situation is unique, providers and patients should use the recommendations as guidelines to determine an appropriate treatment plan together. See *Choosing Wisely website* for more details.

Statements relevant to Pathology as numbered in the Choosing Wisely Guideline and Patient Friendly Resources	Choosing Wisely® Guideline / Patient Friendly Resources
1. Don't order diagnostic tests at regular intervals (such as every day), but rather in response to specific clinical questions.	Critical Care Societies Collaborative - Critical Care *http://www.choosingwisely.org/doctor-patient-lists/critical-care-societies-collaborative-critical-care/*
4. Don't order a total or free T3 level when assessing levothyroxine (T4) dose in hypothyroid patients.	American Association of Clinical Endocrinologists and The Endocrine Society *http://www.choosingwisely.org/doctor-patient-lists/the-endocrine-society-and-american-association-of-clinical-endocrinologists/*
1. Don't do work up for clotting disorder (order hypercoagulable testing) for patients who develop first episode of deep vein thrombosis (DVT) in the setting of a known cause.	Society for Vascular Medicine *http://www.choosingwisely.org/doctor-patient-lists/society-for-vascular-medicine/*
5. Don't perform repetitive CBC and chemistry testing in the face of clinical and lab stability.	Society of Hospital Medicine – Adult Hospital Medicine *http://www.choosingwisely.org/societies/society-of-hospital-medicine-adult/*
Choosing Wisely Patient Friendly Resources	
2. Don't transfuse red blood cells for iron deficiency without hemodynamic instability.	AABB *http://www.choosingwisely.org/doctor-patient-lists/american-association-of-blood-banks/*
1. Don't test ANA sub-serologies without a positive ANA and clinical suspicion of immune-mediated disease.	American College of Rheumatology *http://www.choosingwisely.org/doctor-patient-lists/american-college-of-rheumatology/*
1. Don't order autoantibody panels unless positive antinuclear antibodies (ANA) and evidence of rheumatic disease. 4. Don't perform methotrexate toxicity labs more often than every 12 weeks on stable doses. 5. Don't repeat a confirmed positive ANA in patients with established JIA or systemic lupus erythematosus (SLE).	American College of Rheumatology – Pediatric Rheumatology *http://www.choosingwisely.org/doctor-patient-lists/american-college-of-rheumatology-pediatric-rheumatology/*
5. Don't perform repetitive CBC and chemistry testing in the face of clinical and lab stability.	Society of Hospital Medicine – Adult Hospital Medicine *http://www.choosingwisely.org/doctor-patient-lists/society-of-hospital-medicine-adult-hospital-medicine/*

Appendix I
Laboratory Modernisation – The Ten Principles

The Ten Principles

1. Accreditation of all laboratories
   a) Laboratory Medicine services to support patient and clinician requirements in the context of the ongoing transformation of the Irish health system
   b) Think beyond ISO-15189, - include patient-centred QA and clinical audit
2. Clinical Input in all disciplines – to be increased
   a) Appoint more specialist pathologists in the subspecialties
   b) Provide more clinical audit
   c) Provide more clinical services
3. Networks – develop a network of National, Regional, Local laboratories
   a) Develop a directorate management structure
   b) Incorporate Hot and Cold models
   c) Centralise complex low-volume work to specialised centres, and high volume automated tests to core labs
   d) Include education and training of pathologists and scientists
   e) Include provision for R&D
4. Manage Demand in Primary and Secondary Care
   a) Develop clinical screening programmes with approved investigation strategies (CHD, Diabetes, prostate, thyroid)
   b) Common investigation protocols, standardised test codes and test selection menus, national lab e-handbook
5. IT Connectivity – upgrade to support new network/hot and cold labs, to include:
   a) Unique patient identifier needed
   b) Electronic ordering and reporting
   c) Interlab connectivity (e.g. for referred tests)
   d) Clinical-Laboratory connectivity and GP connectivity
6. Improved work practices
   a) Linked with patient needs, and ongoing clinical / hospital reforms
   b) Extended opening hours, multidisciplinary teams (e.g. lab aides, basic medical scientists staffing core workstations;
   c) Consider an integrated scientific staffing spine
7. Use Core Labs Technology
8. Phlebotomy and Transport Logistics – to be improved
   a) Community phlebotomy centres
   b) Access based on patient need (common waiting list), not ability to pay
9. Develop a charging / cost / workload model using standardised test codes
   a) Is it appropriate to continue to offer pathology testing free of charge at public facilities to all private patients (including those attending private hospitals)?
   b) Which investigations would remain free of charge (e.g. testing as part of an approved clinical programme) and which are chargeable?
   c) Charges for occupational testing, life insurance examinations?, etc.
10. POCT – support implementation of National POCT Guidelines
    a) Including an accreditation scheme for POCT facilities in the community (hospital POCT is covered by hospital accreditation schemes)

Appendix II
Laboratory Testing Template Guideline (Version 1)

Authors
Gerard Boran, Consultant Chemical Pathologist, Tallaght Hospital, Dublin 24, Ireland.
Ideally there will be 2-3 authors, with perhaps one being responsible for the draft.

Effective date
March 28 2016

Background

Write a concise section providing useful background information here.

Key recommendations

The aim of this guideline is to provide indications for testing for analyte x which can be used by clinicians and clinical laboratories, including circumstances where testing is not required. These guidelines apply to adult, non-pregnant patients (or state which other groups as appropriate).

Laboratory testing for analyte X (or condition Y) should be reserved for specific patient groups with indications for testing as described below. It is not recommended to use laboratory testing for X/Y as a "screening" test.

Epidemiology

If there is some information on test utilisation in Ireland please include it in a concise section here.

Testing

This section may contain a short preamble followed by subsections on Who to Test, Who Not to Test, Re-Testing, and other appropriate headings.

Who to Test

The indications for Testing should be covered here.
Example: - Testing for Analyte X is recommended in the following clinical circumstances:

- Condition 1, Clinical feature Y, Xray finding Z, Lab finding L, etc.
- Condition 2, Clinical feature Y, Xray finding Z, Lab finding L, etc.
- Condition 3, Clinical feature Y, Xray finding Z, Lab finding L, etc.
- Those on the following medications:
  - Drug 1
  - Drug 2
  - Drug 3

Who to Re-Test

- Routine repeat X/Y testing IS NOT REQUIRED / EVERY YEAR. Etc.

Who Not to Test

Analytes X/Y testing is not recommended in the following circumstances:

- Example - Do not include in "Routine Bloods", health-screening requests, or other forms of screening
- Example - General screening of any patient groups

How to Test

Include a relevant description here. Pre-analytical or other important factors should be included. A completed standard laboratory test request form must be sent with all samples.

Information required on the referral form

The request form must include detailed patient and clinical information including:

- **Patient demographics**
  - Patient's Name
  - Patient's Date of Birth
  - Medical Record Number
  - Name of Referring Clinician
  - Name of Referring Hospital
  - Order number / external laboratory number (if applicable to external agencies only).

- **Request details**
  - Example - Clinical indication for testing (see list above)
  - Example - Details of any medications

Requests received with no clinical details or with inadequate patient demographics will not be analysed

Full clinical information should accompany all requests. In the event a request is received which does not have the required data (above) or does not have adequate clinical details the laboratory could:

- Issue a report to the requesting doctor, requesting additional clinical details and / or advise that the case is discussed with the local Laboratory Medicine Consultant, and advising that the sample will be discarded after 2 weeks if there is no reply
- Store the sample for up to 2 weeks awaiting further communication from the referring clinician
- Samples can be discarded after 2 weeks if the referring clinician has not provided the required details or if it is determined that testing is not indicated.

Interpretation of tests

Include a concise section on basic facts for interpretation here where appropriate.

Implications for ICT Systems

Computer Physician / Provider Order Entry Systems (CPOE) from a number of different suppliers are in use in a number of hospitals nationwide. Few ICT systems are capable of effectively integrating primary / community with secondary care facilities, though there are examples of "bridging" solutions such as Healthlink which is used for laboratory test reporting and other applications (including possibly test ordering). At present in Ireland, there is no national electronic health patient record, and there is no agreed unique national health identifier. In order to make progress on appropriate utilisation of laboratory services in the interim, it is necessary to consider the laboratory test ordering modules that are currently available in these different settings.
It is also likely that paper laboratory request forms will continue (e.g. in primary care) until the provision of effective ICT systems improves. Improved forms in some cases may help to encourage better provision of relevant clinical information.

Laboratory Test Requesting Ordering Modules in Primary Care

It is recommended that user-friendly GP ordering for Analyte X/Y is developed and implemented at the point of ordering in GP Information Systems. The information required for requesting Analyte X/Y is as stated above, and a user-friendly screen should be developed to allow the GP to select one or more of the relevant clinical indications and to indicate relevant drug therapy. This will require discussion with GP system suppliers.

Laboratory Test Requesting Modules in Hospital-based CPOE Systems

CPOE systems from a number of different suppliers are available in several hospitals nationwide. The national MedLIS will also provide an order-entry system. It is recommended that user-friendly screens for ordering Analyte X/Y is developed and implemented at the point of ordering. The information required for requesting Analyte X/Y is as stated above, and a user-friendly screen should be developed to allow the GP to select one or more of the relevant clinical indications and to indicate relevant drug therapy.

National Laboratory Information System (MedLIS)

The recommendations given for Primary Care and Hospital-based CPOE systems would apply to circumstances where MedLIS will be providing the CPOE functionality (e.g. where its test ordering Module is implemented throughout the hospital).

A pre-laboratory Module in MedLIS should check for (1) absence of any clinical details; (2) repeat testing; (3) correct indication for testing provided, and generate an alert and an appropriate laboratory report as described above.

References

We normally recommend citing not more than ten key references using the Vancouver style with use of numbered superscripts within the text. For example:

1. Cashman KD, Muldowney S, McNulty B et al. Vitamin D status of Irish adults: findings from the National Adult Nutrition Survey. Br J Nutr (2013), 109, 1248-1256.

Please use hyperlinks if possible.

Appendix: Quick Reference Card

Optionally, a 1-page Quick Reference Card may be provided that would summarise the Guideline, particularly of your document exceeds about 4 pages. This may be a graphic, a summary Table or other appropriate format with local adaptations, references and acknowledgements as required.

Appendix III
Consultation Feedback

National Clinical Programme for Pathology

National Laboratory Handbook – Volume 1

Consultation Feedback and Response from Authors, September – November 2015

Nine complete responses were received and four incomplete responses. Emails were sent to two individuals inviting a full response; it was not possible to contact two responders due to incomplete contact details.

Irish Guideline for the Investigation of Blood Culture Samples

- I agree with this. The only comment is to say that negative cultures should be issued at 36-48 hours, as with recent NICE guidelines for early onset sepsis it suggests to stop antibiotics at 36 hours and this is the practice in most neonatal services.
  Conclusion is that we addressed the question / suggestion after the first round of consultations for we agreed with the change from 36 to 48 hours for a variety of reasons. The main reason was to avoid placing an onus on satellite and less well resourced laboratories to validate and issue reports at 36 hours, only for the bottle to flag 4 hours later and so on. This is documented in our minutes. Therefore, no changes to document suggested.

- Excellent document. Provides clear and practical guidance on investigation of blood cultures, which will be useful in all routine diagnostic microbiology laboratories. No suggested amendments.

TORCH Testing in Obstetrics and Neonatology

- Pg 41. Section 1.1.1 Should also include history of vaccination.
  1. **Due to a significant non-response rate to VZV vaccination in adults, we have declined to accept this suggestion, but we have added a new Guidance Note (see below).**

- Pg 41. Section1.1.3 Should address how to deal with equivocal result.
  2. **This suggestion has been accepted: please add "or if IgG reported as Equivocal" at the end of line 1.1.3.**

- Pg 41. Section 1.2 Consider mentioning RCPI guidelines for Parvovirus in pregnancy.
  3. **This document is already included in the reference section, so we have declined to accept this suggestion.**

- Pg 41. Section 1.3.1 Should ask about vaccine history.
  4. **Immunisation Guidelines for Ireland recommend that pregnant women have their status checked: in the interests of consistency, this suggestion has been declined.**

- Pg 41. Section 1.4.2 Consider including if patient does NOT have Rubella IgG detected.
  5. **This suggestion has been accepted: please add "If IgG NOT Detected" at the start of line 1.4.2.**

- PG 43. Section 2.1.1.1.1 Consider stating IV Aciclovir should be given to all women with severe varicella irrespective of gestation.
  6. **This suggestion has been accepted in principle, but we are reluctant for this document to become a treatment guideline. Please add "and advice of Consultant Microbiologist or Infectious Diseases physician" at the end of line 2.1.1.1.1.**

  Please also change the spelling of Acyclovir (U.S.) to Aciclovir (Ireland).
  Consider also discriminating between localised vesicular rash (shingles or Enterovirus) against primary varicella.
  7. **This suggestion has been acknowledged: to avoid confusion, please replace "Rash illness" with "Generalised Rash Illness" as the heading of section 2.1.**

- Pg 43. Section 2.2 Consider discussing acute and chronic hepatitis separately.
  8. **This suggestion has been declined as this is a laboratory handbook rather than a clinical manual: initial viral investigations for abnormal liver function (in the absence of a clinical history) are essentially the same.**

- Pg 43. Section 2.3 would it be worth stating that Micro / ID should be contacted to review these cases.
  9. **This suggestion has been accepted, and Susan and I have agreed that it makes more sense to remove Section 2.3 entirely. Fever of Unknown Origin is a distinct medical entity that requires multidisciplinary input and the risk of including here is that other non-TORCH related issues will be overlooked.**

  Also as this is such a difficult area, would it be worth stating that the investigation should be individualised but that CMV, EBV and toxo should be considered.
  10. **As 9 above, please omit Section 2.3 from Guideline completely.**

- Pg 46. Table 4. No 4.13. Should HSV be sent in all these cases? Again I would probably just suggest discussion with Micro / ID and consideration of viral testing.
  11. **We discussed this and agree to retain the recommendation for HSV testing. However, we accept that an additional Note might be useful. Please add Note 9 (superscript 9 after 'life' in box 4.13) "All cases of culture negative sepsis should be discussed with Consultant Microbiologist or Infectious Diseases physician.**

  In Table 4, Row 4.8, can you please also replace 'Deafness' with 'Failed Newborn Hearing Test'.
  In the 'Guidance Notes Box' at the start of the TORCH Section, can you please include a Note 7. In the absence of a documented antibody response, a history of immunization against Measles or Varicella does not alter the advice presented below.

Choosing Wisely Statements

- Very negatively framed. Needs to be linked to IC0-AM an frame as testing algorithms.
- Would like input on ANF & autoantibody testing indications.
- They appear very useful.

The Irish Reference Interval Harmonisation Project

- Initial project restricted to Chemical Pathology & therefore N/A to Immunology. However this harmonisation needs to be extended to all disciplines particularly in light of MedLIS implementation.

A Quick Reference Guide for Use of Thyroid Function Tests In Primary Care

- I think this is a very well laid out clear guide for GPs. I wonder whether it would help to clarify what subclinical hypothyroidism means, for example "normal fT4, high TSH" or for secondary hypothyroidism "low fT4, inappropriately normal TSH.
  ICGP wanted very brief guidelines – their feedback seemed to be positive on wording. Definition of Sub clinical hypothyroidism included.

Thrombophilia

- Suggestion: A complete request form must be sent with all samples (Trisodium citrate samples 3 ml x 6, EDTA 3ml x 1 and Serum sample x 1.) (Serum sample required for Antiphospholipid antibodies and Beta 2 glycoprotein 1 antibodies.)

General Comments

- Very good concept. Need to ensure that INAB will give accreditation to services that follow these guidelines. A concern that I would have is that INAB may not be on board with them leading to labs having to have 2 different systems in place. Should ideally be discussed in advance with INAB to ensure that they agree that these are the standards.
- Great to see this started. Long journey ahead.
- Useful document.
- We would value contributing to the Immunology section of the National Handbook. As part of our requirements for ISO15189 all labs have a User Manual. The Immunology section of the Beaumont User Manual is very detailed about the tests we provide & the indications for testing & repeat intervals & thus we have a lot of experience in this area.
- My only problem with this handbook is that it visually appears as a mixed bag and aimed at different levels and kinds of health practitioners. I believe the recommendations should come first, in bullet points, with references following for those that want to know about the process. The FBC and RI projects, if agreed with, should only have the final recommendations in the Handbook, with reference papers links provided in order for end users to find out about the process which led to the recommendation. TFTs is bullet-point and clear. Also, I think Choosing Wisely pathology recommendations should be incorporated under the appropriate headings (FBC, TFTs...) rather than having them as a separate chapter / heading, with the link to the website provided under all headings.
- Thank you for including the HPRA in the consultation process on the Draft National Laboratory Handbook Volume 1. The HPRA has no comments on this document.
- Further suggested additions to the Pathology Handbook for Immunology were received from a number of individuals.
  The NCPP will engage with Immunologists in drafting guidelines for Volume 2 and reviewing guidelines as above.

Appendix IV
Permission from Choosing Wisely® to adapt statements

Email Sent Thursday 24/09/2015

Hi Sinead,

Thanks so much for your email and getting back in touch with us. I looked over the handbook and I think the manner in which you're using the recommendations looks good, and doesn't need society review / approval. If possible, it would be great if you could include links back to the individual society recommendations so users could see the source material. Also, recommendations do change or undergo occasional updates, so this would help keep your list current.

Thanks again for sharing,

John Held, APR

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Glossary

AABB	American Association of Blood Banks
AACB	Australian Association of Clinical Biochemists
ACBI	Association of Clinical Biochemists in Ireland
ACSLM	Academy of Clinical Science and Laboratory Medicine
ANA	Anti Nuclear Antibody
ARQAG	Auckland Regional Quality Assurance Group
ASAP	As Soon as Possible
BCG	Bromocresol Green
BCP	Bromocresol Purple
BSI	Bloodstream Infection
CBC	Complete Blood Count
CLSI	Clinical and Laboratory Standards Institute
CMV	Cytomegalovirus
CoNS	Coagulase-negative staphylococcal
CSF	Cerebrospinal Fluid
DDU	D-dimer Unit
DPH	Director of Public Health
DVT	Deep Vein Thrombosis
EARS-Net	European Antimicrobial Resistance Surveillance Network
EBV	Epstein-Barr Virus
EDTA	Ethylenediamine-tetraacetic acid
EPR	Electronic Patient Record
EQA	External Quality Assurance
EV	Enterovirus
FBC	Full Blood Count
FEU	Fibrinogen-equivalent Units
GUM	Genitourinary Medicine
HAI	Haematology Association of Ireland
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HNIG	Human Normal Immunoglobulin
HPSC	Health Protection Surveillance Centre
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
ICGP	Irish Collage of General Practitioners
ICSH	International Committee for Standardization on Haematology
ID	Infectious Diseases
IEQAS	Irish External Quality Assessment Scheme
IFCC	International Federation of Clinical Chemistry
IHS	Irish Haematology Society
INAB	Irish National Accreditation Board
IQC	Internal Quality Control
IRIH	Irish Reference Intervals Harmonisation
ISCM	Irish Society of Clinical Microbiologists
IT	Information Technology
IUD	Intrauterine death
IUGR	Intrauterine Growth Restriction
IV	Intravenous
JIA	Juvenile Idiopathic Arthritis
LL	Lower Limit
LOS	Length of Stay
LT	Loading Time
MCHC	Mean Corpuscular Haemoglobin Concentration
MedLIS	National laboratory information system
MMR	Measles, Mumps & Rubella Vaccine
MOH	Medical Officer of Health
NCCP	National Cancer Control Programme
NCPP	National Clinical Programme for Pathology
NEWS	National Early Warning Score
NIBSC	National Institute for Biological Standards & Control
NICE	National Institute for Health and Care Excellence
NORIP	Nordic Reference Interval Project
NPA	Nasopharyngeal Aspirate
NRBC	Nucleated Red Blood Cell
NVRL	National Virus reference Laboratory
NZ / Aus	New Zealand / Australia
PCR	Polymerase Chain Reaction
PE	Pulmonary Embolism
PH	Pathology Harmony
PSA	Prostate Specific Antigen
QIP	Quality in Practice
RAI	Radioactive Iodine
RBC	Red Blood Cell
RCPI	Royal College of Physicians of Ireland
RI	Reference Intervals
RNA	Ribonucleic Acid
RoI	Republic of Ireland
RPR	Rapid Plasma Reagin
SD	Standard Deviation
SI	International System of Units
SIQAG	South Island Quality Assurance Group
SIRS	Systemic Inflammatory Response Syndrome
SLE	Systemic Lupus Erythematosus
SMI	Standard for Microbiology Investigations
T3	Triiodothyronine
T4	Thyroxine
TAT	Turnaround Times
TFT	Thyroid Function Testing
TPO	Thyroid Peroxidase antibodies
TSH	Thyroid-Stimulating Hormone
TTD	Time to Detection
UL	Upper Limit
VZIG	Varicella-Zoster Immune Globulin
VZV	Varicella Zoster Virus
WBC	White Blood Cell

Notes

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