15 November 2016

Ms Jeanette Radcliffe
Secretary
Standing Committee on Community Affairs
References Committee
PO Box 6100
Parliament House
CANBERRA ACT 2600

Dear Ms Radcliffe

Inquiry into growing evidence of an emerging tick-borne disease that causes a Lyme like illness for many patients

NATA thanks the Committee for the opportunity to provide evidence to the Public Hearing held on 2 November 2016 in Sydney.

In response to the questions taken on notice and provided in your letter of 11 November, NATA is pleased to provide the following general information to provide context as well as specific responses to each question.

A working definition of "accreditation"

Accreditation is a process of peer assessment that provides formal recognition that a laboratory is competent to carry out specific tasks. As such, it is not blanket recognition of all testing services provided by the laboratory. These specific competencies are described in a scope of accreditation specific for each laboratory site.

The meaning of "mutual recognition"

NATA and DAkkS are signatories to the International Laboratory Accreditation Cooperation (ILAC) Mutual Recognition Arrangement (MRA). Signatory status is achieved through having undergone peer evaluation against the requirements of ISO 17011, the standard applicable to accreditation bodies.

"Mutual recognition" applies to the accreditation processes of each Accreditation Body (AB). This facilitates the recognition of testing performed but conditional upon it being conducted in accordance with the test methods prescribed by the user of the test results in the country of destination, not those of the country of origin.

Hence the ILAC MRA must to be considered an enabling arrangement that facilitates rather than mandates recognition. It most efficiently enables recognition when the requirements of two countries are identical. Where differing requirements apply, the MRA may still facilitate recognition for differing requirements provided the AB in the country where the testing is performed has appropriately assessed the laboratory for the requirements of the second country.

Australian accreditation requirements for medical testing laboratories

In Australia, the National Pathology Accreditation Advisory Council (NPAAC) produces standards additional to ISO 15189 which are mandated for Medicare rebatable tests. Additionally the Therapeutic Goods Administration Under its IVD Regulations, also mandates that laboratories that use in-house developed IVDs (test methods) be NATA accredited for the NPAAC IVD standard. This standard specifies that clinical utility and clinical validity (clinical performance) of a test be demonstrated for any in-house test developed in Australia. Such a process safeguards the Australian public from tests not proven to have clinical benefit.

It must also be noted that under these regulations, any commercial IVD that is listed on the Australian Register of Therapeutic Goods on the basis of having undergone regulatory approval which is either modified or used outside its design parameters by a laboratory, becomes an in-house IVD.

To avoid two levels of accreditation criteria between – or even within a laboratory – NATA applies both ISO 15189 and the NPAAC standards to all medical testing laboratories. This approach has been endorsed by both NPAAC and the RCPA.

Question 1
Are test results provided by German laboratories reliable if these laboratories are accredited with DAkkS?

Reliability of results between laboratories accredited by different ILAC MRA signatories needs to be qualified i.e. what is being compared? Taking into account the introductory information, it is reasonable to assume that DAkkS accredited laboratories:

- meet the requirements of the applicable international standard (ISO 15189 for medical laboratories) for testing services that are within their scopes of accreditation;
- provide testing services that are relevant to the German context and any regulatory expectations; and
- if assessed and accredited to the requirements of foreign countries, can perform testing under their scopes of accreditation that would be equivalent to testing performed by laboratories in that country accredited as per the local requirements.

Hence, for a clinician in Australia to use a DAkkS accredited medical laboratory with the same level of confidence they would have in a NATA accredited laboratory, some additional information should be obtained.

(a) Is the type of test/methodology being requested within the scope of accreditation?

(b) Is the test method approved by the European equivalent of the TGA?

(c) If the test method is an in-house IVD, has the accreditation body assessed against the requirements of the NPAAC IVD standard?

Australia's expectations of medical testing laboratories may be more onerous than in other countries or regions. This does not, however, mean the MRA is not useful or that it is counteracted by the NPAAC Standards.

1. It does provide a basis for recognition which otherwise would have to either be managed by government or the medical profession itself.
2. The NPAAC standards are all public domain documents available free of charge so there is nothing to prevent a NATA MRA partner AB from using these documents as additional criteria if required by a laboratory wishing to service the Australian market.

3. If indeed Australia's requirements are at the more onerous end of the spectrum, NATA accredited laboratories should be able to gain a position of high credibility within the global market for testing services.

Also refer to the response to Question 2.

Question 2

In a hypothetical situation where an accredited Australian laboratory returns a negative test result for suspected Lyme disease, and a sample from the same patient is then sent to a German lab accredited with DAkkS, which returns a positive test result, which result is more reliable and why?

If the same sample was tested, using exactly the same test method, under exactly the same test conditions then one would expect the same results if the integrity of the patient sample can be assured (i.e. there has been no deterioration of the sample when transported to the German laboratory). Again, it would also need to be established if the test method was included in the scope of accreditation for both laboratories.

Differences in results may not necessarily be related to reliability but to individual method performance or method capability e.g. method sensitivity and specificity. As mentioned, results can really only be compared if the test methods adopted are the same i.e. "comparing apples with apples". It is not known what methods the accredited DAkkS laboratories are using compared to the Australian laboratories.

When comparing results, some specific issues to take into account include, but are not limited to, the following:

- What organism is being identified by the test method (or in the case of serology, what organism has initiated the immune response in the patient) i.e. method specificity?
- How do different methods react with multiple organisms (cross reactivity)?
- How specific is each method to identify single species of organism (i.e. *Borrelia burgdoferi* compared with *Borrelia anserina?*
- How sensitive is each method to detect "low positivity"?
- Does a method identify the species or genus?
- Has a method been modified (to perhaps increase sensitivity) and has this modification been adequately validated? It should be noted that in some cases an increase in sensitivity may compromise specificity and vice versa.

Differences in the performance characteristics across different test methods may produce different results, which is a limitation of the method and not necessarily the reliability of the laboratory itself.

As heard during the Hearing, the current work being performed by the National Serology Reference Laboratory (NRL) should be able to determine which methods perform better than others. It could be suggested that the method used by the German laboratory is included in the study so as to directly compare it to methods being used in Australia.

Question 3

The testing protocol of Lyme Disease accepted by Australian medical authorities has labs performing the ELISA test, and then, if that comes back positive, the western blot test. Does that mean the Western blot test is reliable as a diagnostic test, and, following on from that, what would be the harm in labs going straight to Western blot?

This is a question to direct to the appropriate experts e.g. RCPA and/or the Australasian Society for Microbiology (ASM).

However, in general tests should not be used outside of their intended purpose. If a test is validated for "screening" and not for "confirmation" it should only be used for such.

It is likely performing Western Blot as a first line test will add significant costs and time.

Question 4
The committee has been told that the two-tiered testing protocol was established for disease surveillance, not diagnosis, and that the Center for Disease Control in the US states that surveillance criteria should not be used for diagnosis. What is your view on this, how can a protocol be designed for screening yet recommended for diagnosis? *[See Dr Peter Dobie, Secretary, Australian Chronic Infectious and Inflammatory Disease Society, Brisbane transcript, p. 19.]?*

NATA cannot form a view on this matter as it is beyond its remit. This question should be directed to the appropriate scientific and professional experts e.g. RCPA or ASM.

Question 5
In Brisbane on 15 April *[Dr Dobie, Brisbane transcript, p. 19]* the committee heard about scientific papers in peer-reviewed literature which discuss seronegativity and Lyme disease, and that evidence may suggest that the presence of chronic Lyme disease cannot be excluded by the absence of antibodies against *Borrelia burgdoferi*. What is your view on this?

NATA cannot form a view on this matter as it is beyond its remit. This question should be directed to the appropriate scientific and professional experts as noted above.

Question 6
What is the false negative rate of the ELISA test where Lyme disease is concerned?

This question is beyond NATA's remit and hence should be directed to the appropriate scientific and professional experts as noted above.

Question 7
To what extent is the fact that different laboratories are using different tests an impediment to establishing beyond doubt whether people are being infected by the *Borrelia burgdorferi* bacterium in Australia? Following on from this, do you have a view on how this impediment might be overcome?

NATA's response is not in relation to people being infected by the *Borrelia burgdorferi* bacterium in Australia, but instead a general response on how impediments on laboratories using different tests can be addressed.

The impediment might be overcome through a number of ways:

- An extensive review of the methodology available (serology and PCR, in-house tests and commercial kits) to be performed (such as that being performed by NRL on behalf of the Department of Health) with this information being made publically available. The TGA could also be involved as they are responsible for the registration of commercially available kits. This would then allow laboratories and clinicians an opportunity to compare test methods in use;
- Laboratories performing in-house testing be encouraged to share their data in order for it to be peer evaluated which would ultimately benefit the Australian public;
- A clear testing strategy to be established in conjunction with the DoH and RCPA.

This question should also be directed to the appropriate scientific / professional experts.

For the Committee's benefit, NATA also offers the following:

Different tests may be in use which may offer different performance characteristics as noted above. In Australia there is no requirement which dictates which methods laboratories must use so long as they are included on the Australian Register of Therapeutic Goods (ARTG) for commercial kits or (from 1 July 2017) the laboratory is accredited for in-house developed tests.

For accreditation purposes all tests must be appropriately verified for commercial kits and appropriately validated as per NPAAC requirements for in-house tests.

Verification is confirmation through objective evidence that a laboratory can obtain the specified performance characteristics as validated by the manufacturer.

Validation is confirmation through objective evidence that the requirements for a specific intended use or application have been fulfilled.

All validated tests must be verified by each user before implementation.

The verification or validation studies would include the accuracy, specificity and sensitivity which should be guided by peer reviewed literature and accepted by the scientific / professional community.

In circumstances whereby NATA comes across a laboratory using tests for which the performance is suboptimal and which are not as specific or sensitive for the analyte / determination in question as compared to other methods, NATA does and has recommended that a more appropriate method be used. Additionally, the laboratory is asked to justify why they are using the method in question.

We thank the Committee again for the opportunity, through the public hearings and in this response, to clarify NATA's role, our accreditation processes and how these fit with international practice.

Should you have any further questions, please do not hesitate to contact me.

Yours sincerely

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