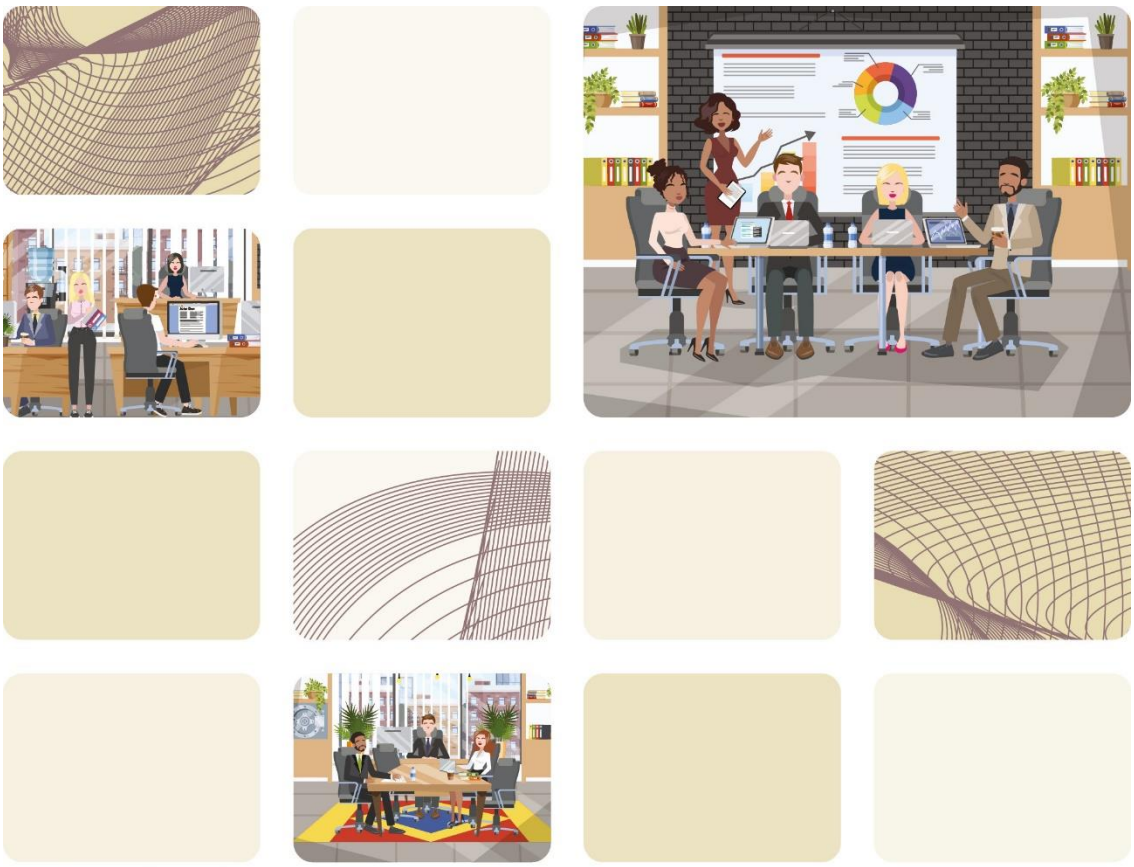
UK Health Security Agency

UK Standards for Microbiology Investigations

Review of users' comments received by Working group for microbiology standards in clinical virology/serology

V 44 Laboratory diagnosis of syphilis



National Institute for Health and Care Excellence (NICE) has renewed accreditation of the process used by the **UK Health Security Agency** to produce **UK Standards for Microbiology Investigations (UK SMIs)**. The renewed accreditation is valid until **30 June 2026** and applies to guidance produced using the processes described in '**UK Standards for Microbiology Investigations Development Process' (2021)**. The original accreditation term began on 1 July 2011.

This publication was created by UK Health Security Agency (UKHSA) in partnership with the partner organisations.

Recommendations are listed as ACCEPT/ PARTIAL ACCEPT/DEFER/ NONE or PENDING

Issued by the Standards Unit, Specialised Microbiology and Laboratories, UKHSA

Consultation: 22/08/2023 – 05/09/2023
Version of document consulted on: V 44 dj+

Amendment table

Comment number: 1

Date received: 05/07/2023
Laboratory or organisation name: IBMS

Date received: 29/08/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

Title is written as tile in title row within the amendment table

Recommended action

Accept. Changed to title.

4. Definitions

Comment number: 2

Date received: 01/09/2023
Laboratory or organisation name: Wye Valley NHS Trust

Small typo: RPR: rapid plasma reagin (not regain)

Recommended action

Accept.

Comment number: 3

Date received: 29/08/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

RPR- Rapid plasma regain; should be reagin.

Recommended action

Accept.

5. Introduction

Comment number: 4

Date received: 29/08/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

1. Syphilis is transmitted by direct contact with an infectious lesion through genital or extra genital sites (anal, rectal and oral). Transmission occurs during pregnancy, where T. pallidum crosses the placenta. This can occur at any stage of pregnancy (1). Might be better to state ‘Transmission can occur in utero at any stage of pregnancy, and at the time of birth through contact with maternal lesions in the birth canal (1).’

2. Suggest minor change to ‘Primary stage- ulcer or chancre found at the inoculation site usually located on the genitals, rectum, tongue, or lips, which occurs 10-90 days after exposure (1)’

3. Secondary stage signs- could add mucous patches, condylomata lata, alopecia.

4. Latent stage- early is defined as within 1 year in some guidelines, such as USA and Canada, so consider stating that and also that the 2 years is UK and WHO. States latent syphilis ‘ends with the development of tertiary disease’- it doesn’t in everyone, only about a third.

5. Add tertiary stage includes skin signs- gummata. So as guideline stands the test of time, suggest not stating ‘infectious syphilis is increasing’….' unless add 'currently' or at time of writing'.

Recommended action

Accept all comments. Document has been updated.

Comment number: 5

Date received: 01/09/2023
Laboratory or organisation name: Wye Valley NHS Trust

Primary Stage- Good to mention that the ulcer is painless?

Recommended action

Accept.

Comment number: 6

Date received: 01/09/2023
Laboratory or organisation name: Wye Valley NHS Trust

Secondary stage- Add in sore throat as a symptom?

Recommended action

Accept.

Comment number: 7

Date received: 01/09/2023
Laboratory or organisation name: Wye Valley NHS Trust

Tertiary stage- I am unclear where this section ends (presumably at the end of the 2 lines), and the 'background' general info starts. Maybe a section header for the background info would be helpful.

Recommended action

None: The layout in the HTML version was changed by GOV.UK. Please refer to the PDF version which has a clear distinction.

Comment number: 8

Date received: 05/07/2023
Laboratory or organisation name: IBMS

Is GBMSM the accepted nomenclature now rather than just MSM?

Recommended action

None. The term GBMSM is stated in the UKHSA report which is referenced.

Comment number: 9

Date received: 07/09/2023
Laboratory or organisation name: Bristol Clinical Research Facility

Laboratory staff should consider syphilis testing on samples where syphilis has not been requested but the clinical details would be consistent with syphilis. Examples of this could be acute hepatitis with negative results on initial virological screening or genital wounds swabs

Recommended action

None. Not required for this UK SMI. The title of this document is Laboratory diagnosis of syphilis.

Comment number: 10

Date received: 07/09/2023
Laboratory or organisation name: Bristol Clinical Research Facility

Does MSM covers everything without attaching further specific labels?

Recommended action

None. The term GBMSM is stated in the UKHSA report which is referenced

6 Treponemal serology

Comment number: 11

Date received: 29/08/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

Footnote d- a second assay is not used just to exclude false positives but to confirm true positives.

Recommended action

Accept. Wording added to clarify- A second treponemal test is used to confirm screen positive results and exclude false positives

Comment number: 12

Date received: 30/08/2023
Laboratory or organisation name: Nottingham University Hospitals

1. Paragraph 3 – 'If the treponemal test 1 gives a negative result (refer to footnote b) then report treponemal antibody as not detected'. Should this read 'If the treponemal test 2 gives a negative result'
2. Should we be cautious that treponemal test 2 could be TPHA, which we have seen to be considerably less sensitive than EIA. Therefore, there would be a risk of missing a very early infection if repeat samples were not sent. Would it be better to advocate either EIA or CLIA as the second treponemal test and not TPHA/TPLA?

Recommended action

1. None. This is the text description reading the algorithm from Treponemal test 1 to the negative box.
2. Accept. There are disadvantages of both approaches. Many laboratories can not access a 2nd EIA/CLIA, so we need to leave laboratories with either option. Update footnote d to say TPHA is known to be less sensitive.

Comment number: 13

Date received: 31/08/2023
Laboratory or organisation name: Portsmouth Hospitals NHS Trust

Is it acceptable if you have a positive Syphilis PCR, to not undertake the second line T. pallidum antibody test (TPHA/TPLA, CLIA etc)? The chart alludes to this but seems to suggest that second line testing is still indicated.

Recommended action

It is not acceptable in this scenario because we need to complete the serological pathway.

Comment number: 14

Date received: 04/09/2023
Laboratory or organisation name: STI Reference Lab

1. If the treponemal test 1 gives a positive or equivocal test, then perform a treponemal test 2 using either EIA, CLIA, TPHA, TPLA (refer to footnote d) or perform an RPR… should be ....and perform an RPR? For this text‘’ "Or if the negative result is suspected in early primary infection, then consider swabs of lesions for PCR, treponemal test 2 (EIA or CLIA or TPHA or TPL’’." Do you need an or/an in between PCR, treponemal test 2”?

2. Consider mentioning EIA false positives in pregnancy

Recommended action

1. Text description has been amended.
2. None. This has been mentioned in 6.2 interpreting and reporting laboratory results for treponemal serology and NAAT testing.

Comment number: 15

Date received: 05/09/2023
Laboratory or organisation name: Microbiology Dept, Watford General Hospital

1. Please specify the type of swab (e.g. chlamydia, UTM, dry etc) to use for PCR from the lesions.
2. 6.1b Consider PCR on EDTA whole blood if syphilis is suspected in immunocompromised individuals.

Recommended action

1. None. This box has been updated and swabs has been removed.
2. None. This is not usually clinically indicated. Decision of local laboratory.

6.2 Interpreting and reporting laboratory results for treponemal serology and NAAT testing

Comment number: 16

Date received: 21/08/2023
Laboratory or organisation name: NHS Lothian

1. The table is confusing particularly on the HTML version where the layout is different from the PDF.
2. I am puzzled as to how by following the algorithm in Table 6 you can get the following results described in the table: Treponemal test 1 EIA/CLIA negative- Treponemal test 2 positive or equivocal. If the screening test is negative you should not be doing Treponemal test 2

Recommended action

1. None. GOV.UK have displayed the table in a different way. Going forward we can hopefully resolve this issue. Refer to the PDF version of the document as it is more accurate.
2. The algorithm is correct in a step wise scenario but you can come across other scenarios which are listed in the table.

Comment number: 17

Date received: 29/08/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

1. Test 1 and 2 positive, RPR pos <16- if low level EIA in test 1 and 2 but RPR positive, is the no-specific or early comment appropriate? The default comment should probably be infection at some time but EIA levels low, therefore send a further sample to confirm.
2. ' Test 1 and 2 positive, RPR >16- advisory note states 'report changes in RPR titre' - what does this mean? Only report if it has changed titre 4 fold; state no change in titre; should it always be tested in parallel, or should parallel testing be done only if the comparative titres are significantly different on firs testing?
3. Clearly and reasonable the table does not cover all result profiles, please state that.

Recommended action

1. None. Comments have been reviewed appropriate for the test scenario. The test results profile is consistent with treponemal infection at some time but early infection should also be considered as a second sample is requested.
2. None. It is self-explanatory.
3. None. It is stated above the table ‘The table cannot cover all serological profiles but should cover most of those encountered in clinical practice’.

Comment number: 18

Date received: 01/09/2023
Laboratory or organisation name: Wye Valley NHS Trust

1. The test 1 and 2 negative and RPR negative profile attracts a different comment to that for a simple screen negative.
2. Test 1 negative, test 2 positive or equivocal- surely that only arises if the situation is regarded as high risk for infection or pre-screened elsewhere- shouldn't that be mentioned? Also, for notes, consider simply stating '....consider treponemal IgG immunoblot testing'.

Recommended action

1. None. there was probably a higher index of suspicion if all 3 tests were done.
2. None. Its mentions above the table that this is just a guide and should depend on the laboratory.

Comment number: 19

Date received: 01/09/2023
Laboratory or organisation name: Wye Valley NHS Trust

Table for interpretation of NAAT results Detected: 'T. pallidum detected. Consistent with active syphilis infection' PCR will detect viable and non-viable T. pallidum, so saying it will always be 'active' could be misleading? Could you have a resolving ulcer that is still present despite full treatment and that is swabbed and positive?

Recommended action

None. The ulcer heals quickly after treatment so you wouldn't get long detection of residual DNA.

6. Diagnosis of neurosyphilis

Comment number: 20

Date received: 04/09/2023
Laboratory or organisation name: STI Reference Lab

Missing a word after neurological ?
"Testing of CSF should be considered in patients with treponemal infection and neurological (1)."

Recommended action

Accept. Added signs and symptoms.

Comment number: 21

Date received: 29/08/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

4th paragraph- 'considered in patients with treponemal infection and neurological illness.'

Recommended action

Accept. Added signs and symptoms.

7.1 Treponemal serology in neurosyphilis

Comment number: 22

Date received: 29/08/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

CSF tests should be mentioned as not validated.

Recommended action

Accept. Comment added ‘Local validation must be performed for treponemal and non-treponemal serology tests performed on CSF.’

Comment number: 23

Date received: 01/09/2023
Laboratory or organisation name: Wye Valley NHS Trust

A summary table or flow diagram etc would make this easier to interpret

Recommended action

None. Bullet points have been added to break up the text.

8. Congenital syphilis

Comment number: 24

Date received: 05/09/2023
Laboratory or organisation name: Newcastle Hospitals Virology

Footnote b states that maternal syphilis cured prior to pregnancy, does not require clinical evaluation and serological follow up of the baby. In an era of increasing syphilis incidence including in heterosexual woman, the risk of syphilis re-infection after booking cannot be discounted. Some areas of the country have high rates of positive syphilis serology in pregnant woman. Positive syphilis serology in the past may signal ongoing risk factors for infection. This must be acknowledged in the SMI – if the baby is not to be followed up, as a minimum the mother should have a repeat RPR at the time of delivery. (Similar to general advise of rescreening at risk woman later in pregnancy)

Recommended action

Accepted. Reworded the paragraph.

Comment number: 25

Date received: 05/07/2023
Laboratory or organisation name: IBMS

Formatting of the congenital syphilis table (one arrow out of line between interpret combination of and follow up blood)

Recommended action

Accept.

Comment number: 26

Date received: 29/08/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

1. States that a text description of this algorithm is provided with this document- where? I think it means provided online.
2. 8.1- a- Symptomatic baby with risk factors- the baby doesn't need risk factors, symptoms alone are sufficient to raise the possibility of congenital infection.
3. d- second test could also be TPLA.
4. e- last line seems unnecessary- 'if they have these samples already being extracted for other PCRs'
5. 8.2 table heading treponemal test could also be TPLA.
6. 'if mother has acquired syphilis late in pregnancy and is treponemal antibody negative around time of birth'. That doesn't seem biologically likely- if the baby has had time to make IgM surely the mother has? Are there good case examples of this?
7. When the baby tests negative for IgM RPR total EIA it states if baby is over 1 month old at time of testing, then repeat sample is unnecessary- that isn't the longest incubation period. What scenario is being covered here?
8. When comparing maternal and baby results, suggest avoiding interpreted in 'parallel' as it can imply testing in parallel- how about 'in conjunction with' or 'comparison with'.

Recommended action

1. The text description has been added to the HTML version under the algorithm and footnotes. Therefore this has been stated in the PDF. This sentence has been removed in PDF version.
2. Accept. Sentence has been reworded.
3. Accept. Added.
4. Accept. Removed
5. Accept. Added
6. Accept. Section updated
7. Accept. Section updated.
8. Accept. Section updated.

Comment number: 27

Date received: 05/09/2023
Laboratory or organisation name: Newcastle Hospitals Virology

It would also be helpful for guidelines regarding optimal testing for cases of foetal loss in treponemal antibody positive mothers. i.e. what are the best sample types from the foetus for sending for treponemal PCR testing?

Recommended action

Accept. Footnote e updated with - In the case of foetal loss where a post-mortem is performed, suitable samples for PCR (in addition to those above) include liver, lung and spleen tissue samples.

General comments

Comment number: 28

Date received: 04/09/2023
Laboratory or organisation name: Italy

1. I think that it could be useful to add some comment regarding the follow up:

   Clinical and serologic evaluation should be performed at 6 and 12 months after treatment; more frequent evaluation might be prudent if opportunity for follow-up is uncertain or if repeat infection is a clinical concern. Serologic response (i.e., titer) should be compared with the titer at the time of treatment. However, assessing serologic response to treatment can be difficult, and definitive criteria for cure or failure by serologic criteria have not been well established. In addition, nontreponemal test titers might decrease more slowly for persons previously treated for syphilis.

2. Up to now, there is no clinical validation of NAAT/PCR test for the diagnosis of Syphilis. The PCR test has a high diagnostic value when performed on ulcer exudates in patients with primary syphilis. Its most relevant advantages in clinical practice are the possibility of an early diagnosis before serological tests during the window period, the ability to confirm reinfections in patients with persistent positivity of reaginic antibodies and a history of treated syphilis. Nevertheless, given that a negative PCR test may not rule out infection by Treponema pallidum, serologic tests are still necessary for everyday practice. There is the need to better define the specific primer set.

Recommended action

1. None. The document mentions follow as per BASHH guidelines.
2. None.

Financial barriers

Respondents were asked: 'Are there any potential organisational and financial barriers in applying the recommendations or conflict of interest?'.

Comment number: 29

Date received: 29/08/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

No

Comment number: 30

Date received: 30/08/2023
Laboratory or organisation name: Nottingham University Hospitals

No

Comment number: 31

Date received: 31/08/2023
Laboratory or organisation name: Portsmouth Hospitals NHS Trust

No

Comment number: 32

Date received: 01/09/2023
Laboratory or organisation name: Wye Valley NHS Trust

No

Comment number: 33

Date received: 04/09/2023
Laboratory or organisation name: STI Reference Lab

No

Comment number: 34

Date received: 05/09/2023
Laboratory or organisation name: Microbiology Dept, Watford General Hospital

No

Comment number: 35

Date received: 05/09/2023
Laboratory or organisation name: Newcastle Hospitals Virology

No
Laboratory or organisation name:

Health benefits

Respondents were asked: 'Are you aware of any health benefits, side effects and risks that might affect the development of this UK SMI?'.

Comment number: 36

Date received: 21/08/2023
Laboratory or organisation name: NHS Lothian

No

Comment number: 37

Date received: 29/08/2023
Laboratory or organisation name: Severn Infection Sciences and UKHSA SW

Beneficial- makes sure testing is done to a good standard.

Comment number: 38

Date received: 30/08/2023
Laboratory or organisation name: Nottingham University Hospitals

No

Comment number: 39

Date received: 31/08/2023
Laboratory or organisation name: Portsmouth Hospitals NHS Trust

No

Comment number: 40

Date received: 01/09/2023
Laboratory or organisation name: Wye Valley NHS Trust

No

Comment number: 41

Date received: 04/09/2023
Laboratory or organisation name: STI Reference Lab

No

Comment number: 42

Date received: 05/09/2023
Laboratory or organisation name: Microbiology Dept, Watford General Hospital

No

Comment number: 43

Date received: 05/09/2023
Laboratory or organisation name: Newcastle Hospitals Virology

No

Interested parties

Respondents were asked: 'Are you aware of any interested parties we should consider consulting with on the development of this document?'

Comment number: 44

Date received: 21/08/2023

Laboratory or organisation name: NHS Lothian

No

Comment number: 45

Date received: 30/08/2023
Laboratory or organisation name: Nottingham University Hospitals

No

Comment number: 46

Date received: 31/08/2023
Laboratory or organisation name: Portsmouth Hospitals NHS Trust

Sexual health services.

Comment number: 47

Date received: 01/09/2023
Laboratory or organisation name: Wye Valley NHS Trust

No

Comment number: 48

Date received: 04/09/2023
Laboratory or organisation name: STI Reference Lab

No

Comment number: 49

Date received: 05/09/2023
Laboratory or organisation name: Microbiology Dept, Watford General Hospital

No

Respondents indicating they were happy with the contents of the document

Overall number of comments: None			
Date received		**Lab name/Professional body (delete as applicable)**	
Health benefits			