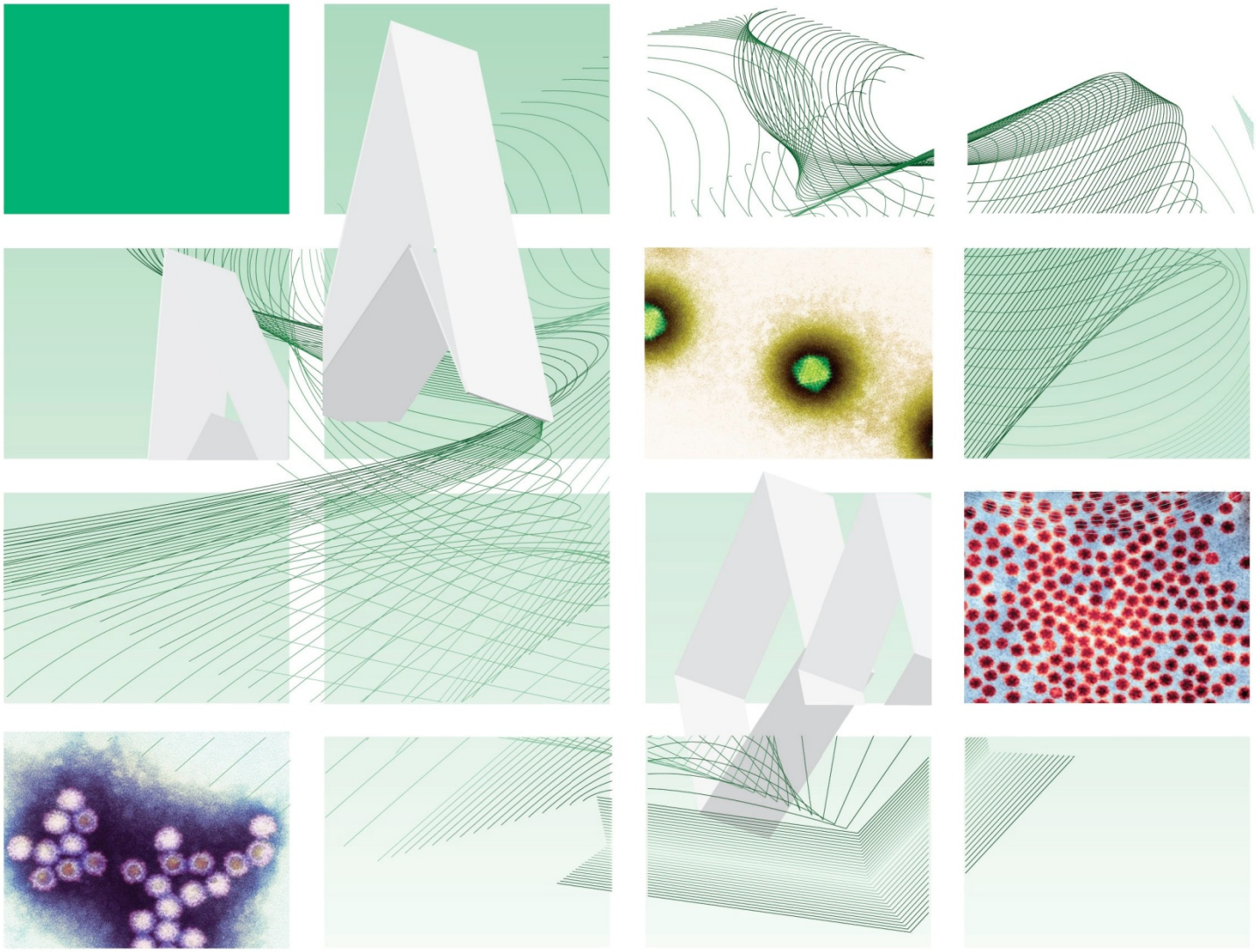
Public Health England

NHS

UK Standards for Microbiology Investigations

Syphilis serology



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Acknowledgments

UK Standards for Microbiology Investigations (SMIs) are developed under the auspices of Public Health England (PHE) working in partnership with the National Health Service (NHS), Public Health Wales and with the professional organisations whose logos are displayed below and listed on the website https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories. SMIs are developed, reviewed and revised by various working groups which are overseen by a steering committee (see https://www.gov.uk/government/groups/standards-for-microbiology-investigations-steering-committee).

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Contents

Amendment table

Each SMI method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@phe.gov.uk.

New or revised documents should be controlled within the laboratory in accordance with the local quality management system.

Amendment no/date.	5/20.07.16
Issue no. discarded.	2
Insert issue no.	2.1
Section(s) involved	**Amendment**
Whole document.	Congenital syphilis section of the document updated to bring the UK SMI in line with the "UK national guidelines on the management of syphilis 2015" [1].

Amendment no/date.	4/09.04.15
Issue no. discarded.	1.3
Insert issue no.	2
Section(s) involved	**Amendment**
Whole document.	Hyperlinks updated to gov.uk.
Page 2.	Updated logos added.
Whole document.	Restructured to include scope of document, type of specimen and definition.
Algorithm.	Restructured and colour coding removed. Additional footnotes added and made more comprehensive. A reports comments table added.
Neurosyphilis diagnosis.	Information added on this area.
Congenital syphilis.	Information added on this area.

UK SMI[#]: scope and purpose

Users of SMIs

Primarily, SMIs are intended as a general resource for practising professionals operating in the field of laboratory medicine and infection specialties in the UK. SMIs also provide clinicians with information about the available test repertoire and the standard of laboratory services they should expect for the investigation of infection in their patients, as well as providing information that aids the electronic ordering of appropriate tests. The documents also provide commissioners of healthcare services with the appropriateness and standard of microbiology investigations they should be seeking as part of the clinical and public health care package for their population.

Background to SMIs

SMIs comprise a collection of recommended algorithms and procedures covering all stages of the investigative process in microbiology from the pre-analytical (clinical syndrome) stage to the analytical (laboratory testing) and post analytical (result interpretation and reporting) stages. Syndromic algorithms are supported by more detailed documents containing advice on the investigation of specific diseases and infections. Guidance notes cover the clinical background, differential diagnosis, and appropriate investigation of particular clinical conditions. Quality guidance notes describe laboratory processes which underpin quality, for example assay validation.

Standardisation of the diagnostic process through the application of SMIs helps to assure the equivalence of investigation strategies in different laboratories across the UK and is essential for public health surveillance, research and development activities.

Equal partnership working

SMIs are developed in equal partnership with PHE, NHS, Royal College of Pathologists and professional societies. The list of participating societies may be found at https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories. Inclusion of a logo in an SMI indicates participation of the society in equal partnership and support for the objectives and process of preparing SMIs. Nominees of professional societies are members of the Steering Committee and working groups which develop SMIs. The views of nominees cannot be rigorously representative of the members of their nominating organisations nor the corporate views of their organisations. Nominees act as a conduit for two way reporting and dialogue. Representative views are sought through the consultation process. SMIs are developed, reviewed and updated through a wide consultation process.

Quality assurance

NICE has accredited the process used by the SMI working groups to produce SMIs. The accreditation is applicable to all guidance produced since October 2009. The process for the development of SMIs is certified to ISO 9001:2008. SMIs represent a

[#] Microbiology is used as a generic term to include the two GMC-recognised specialties of Medical Microbiology (which includes Bacteriology, Mycology and Parasitology) and Medical Virology.

good standard of practice to which all clinical and public health microbiology laboratories in the UK are expected to work. SMIs are NICE accredited and represent neither minimum standards of practice nor the highest level of complex laboratory investigation possible. In using SMIs, laboratories should take account of local requirements and undertake additional investigations where appropriate. SMIs help laboratories to meet accreditation requirements by promoting high quality practices which are auditable. SMIs also provide a reference point for method development. The performance of SMIs depends on competent staff and appropriate quality reagents and equipment. Laboratories should ensure that all commercial and in-house tests have been validated and shown to be fit for purpose. Laboratories should participate in external quality assessment schemes and undertake relevant internal quality control procedures.

Patient and public involvement

The SMI working groups are committed to patient and public involvement in the development of SMIs. By involving the public, health professionals, scientists and voluntary organisations the resulting SMI will be robust and meet the needs of the user. An opportunity is given to members of the public to contribute to consultations through our open access website.

Information governance and equality

PHE is a Caldicott compliant organisation. It seeks to take every possible precaution to prevent unauthorised disclosure of patient details and to ensure that patient-related records are kept under secure conditions. The development of SMIs is subject to PHE Equality objectives https://www.gov.uk/government/organisations/public-health-england/about/equality-and-diversity.

The SMI working groups are committed to achieving the equality objectives by effective consultation with members of the public, partners, stakeholders and specialist interest groups.

Legal statement

While every care has been taken in the preparation of SMIs, PHE and any supporting organisation, shall, to the greatest extent possible under any applicable law, exclude liability for all losses, costs, claims, damages or expenses arising out of or connected with the use of an SMI or any information contained therein. If alterations are made to an SMI, it must be made clear where and by whom such changes have been made.

The evidence base and microbial taxonomy for the SMI is as complete as possible at the time of issue. Any omissions and new material will be considered at the next review. These standards can only be superseded by revisions of the standard, legislative action, or by NICE accredited guidance.

SMIs are Crown copyright which should be acknowledged where appropriate.

Suggested citation for this document

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Scope of document

Type of specimen

Blood, CSF, swab

This algorithm outlines laboratory testing for diagnosis of *Treponema pallidum* infection. It is concerned with diagnosis of syphilis including primary, secondary, late syphilis including CNS and congenital infections.

Refer to S 6 – Sexually transmitted infections for further information regarding clinical presentations of sexually transmitted infections, and associated tests.

This SMI should be used in conjunction with other SMIs.

Definitions

TPPA – *Treponema pallidum* particle agglutination assay

TPHA – *Treponema pallidum* haemagglutination assay

TPLA – *Treponema pallidum* latex agglutination test automated turbidimetric assay

EIA – Enzyme immunoassay

CLIA – Chemiluminescent immunoassay

RPR – Rapid plasma regain

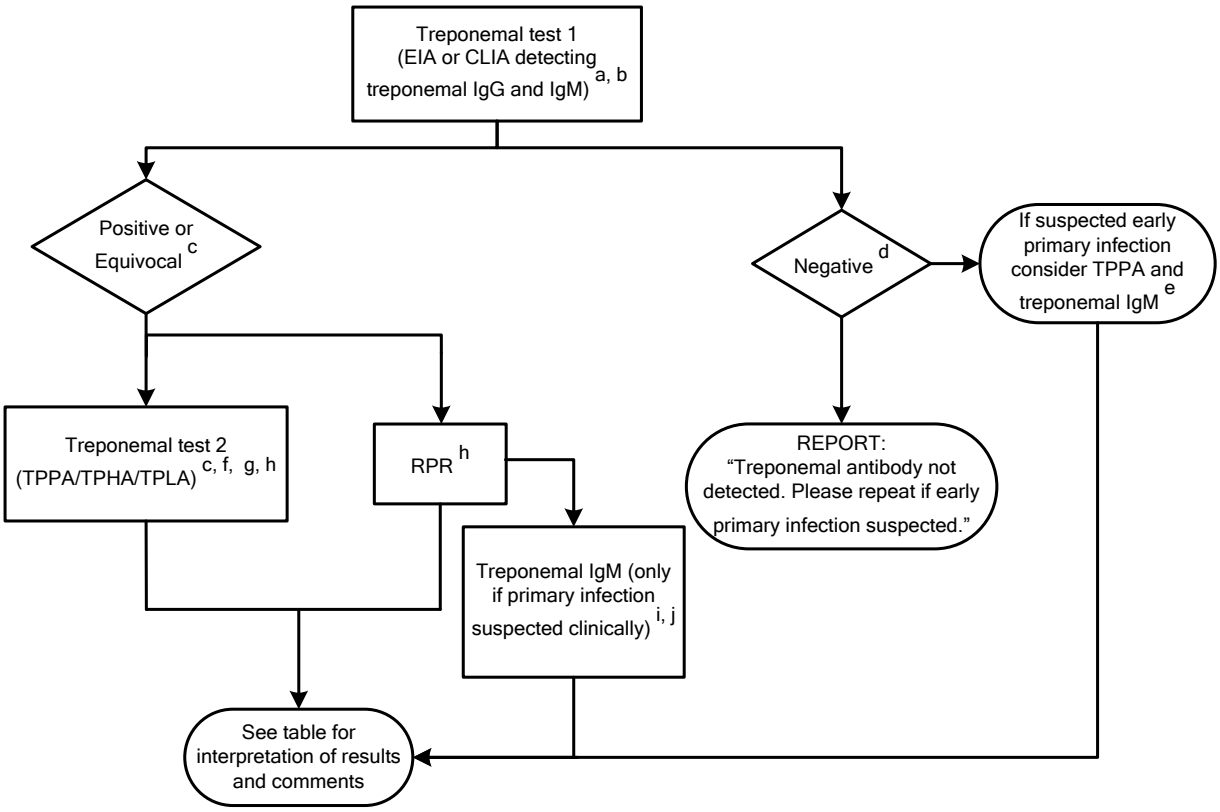
VDRL - Veneral disease research laboratory carbon antigen test.

Introduction

Laboratory test results must be considered together with the clinical and geographical background of the patient because the serological assays used for syphilis testing also detect antibody raised in response to endemic treponematoses such as yaws[2]. As a precaution an individual with positive treponemal serology should be investigated and treated as if for syphilis unless previous treatment can be documented[3].

In suspected early primary syphilis a sample should ideally be taken from the lesion for treponemal PCR[4]. Examination for treponemes by dark ground microscopy should also be undertaken where possible although PCR is preferable when investigating lesions likely to be contaminated with commensal treponemes such as oral lesions[3,5]. Consider requesting herpes simplex PCR as well. *Haemophilus ducreyi* infection is rare in the UK but testing by PCR should be considered where there is a relevant travel or risk history[6]. *Chlamydia trachomatis* PCR testing, to exclude lymphogranuloma venereum, might also be considered in men who have sex with men[7].

Treponemal serology



Footnotes related to treponemal serology

a. TPLA is used by a small number of UK laboratories as an automated assay for syphilis. False results can occur with turbid serum due to high lipid levels[8]. This assay is suitable for use only as a second line test.

b. BASHH/MedFASH Standards for the Management of Sexually Transmitted Infections 2010 specify a turnaround time of no more than 7 days from collection of sample to laboratory report for samples not referred to a reference laboratory, while the UK National Screening Committee standard stipulated in the Infectious Diseases in Pregnancy Screening Programme Handbook for Laboratories 2012 is to have a report despatched from the laboratory within 5 days of receipt of the sample or within 8 days if sent to a reference laboratory[9,10].

c. Positive initial treponemal screening tests must be confirmed by other tests as false reactivity rates can be high. In low prevalence populations, such as pregnant women in the UK, most initial screen reactive results will be false.

d. False negative screening results may be seen in HIV infected patients.

e. Negative results within 2-4 weeks of infection cannot exclude early syphilis, so repeat in 1-2 weeks. RPR should also be repeated when commencing treatment so that the highest titre is documented.

f. At least one test should be performed using the primary tube.

g. TPPA is one of the first tests to become reactive in primary syphilis, together with specific IgM[11]. It is reactive earlier than TPHA. CLIA tests containing TpN47 antigen may be even more sensitive than TPPA in primary syphilis, albeit at the expense of specificity[12].

h. The RPR and confirmatory treponemal antibody test should be done simultaneously if required to meet anticipated turnaround times. With high titres in secondary syphilis or early latent syphilis false negative results due to prozone are sometimes seen.

i. Treponemal IgM results must always be interpreted with care. IgM tests have been shown to have a lack of specificity. IgM results can only be interpreted in association with other treponemal and non-treponemal antibody test results and clinical information. True positive results may reflect recent or active infection but note that IgM reactivity can persist for 12 - 18 months even after adequate treatment of infection[3,13].

j. Where a sample is referred to another laboratory for treponemal IgM testing the other laboratory may need to run additional assays before issuing a report, as IgM serology cannot be interpreted reliably in the absence of additional test results and clinical information. There should be an agreement for such additional testing as required for robust interpretation[3].

Report comments for treponemal serology

Note that the table of comments is a guide, and that clinical details and previous serological results should always be considered when interpreting treponemal serology results. If possible, compare antibody titres (particularly RPR) by testing in parallel.

The table cannot cover all serological profiles but should cover most of those encountered in clinical practice. A full repertoire of tests for final interpretation may include referral tests, depending on the local laboratory test repertoire.

	Immunoassay 1 (EIA, CLIA)	Immunoassay 2 (TPLA, TPHA, TPPA)	RPR ≤16 (RPR titres should always be reported)	RPR >16 (RPR titres should always be reported)	IgM	Comment
a[i]	Positive	Positive	Positive			'Consistent with treponemal infection at some time.' If first sample add: 'Advise repeat to confirm, if clinically indicated.' If treated and this is follow up sample, review previous results and report changes in RPR titre[i]. This would be consistent with a recent infection if seroconversion, or a four-fold rise in RPR titre on parallel testing, were seen in comparison to an earlier sample. RPR titre ≤16 does not exclude active infection especially if there are signs suggesting syphilis or where adequate treatment of previously diagnosed syphilis has not been documented.
b[i]	Positive	Positive		Positive		'Consistent with recent or active treponemal infection.' If first sample add: 'Advise repeat to confirm, if clinically indicated.' Monitor following treatment. If treated and this is follow up sample, review previous results and report changes in RPR titre[i].

c	Positive	Positive		Positive	Reactive (at level greater than that regarded as 'low')[iii]	As previous (b). Consider possibility of reinfection if increase in RPR and new IgM reactivity.
d	Positive	Positive		Positive	Reactive (at low or equivocal level)[iii]	As previous (b). Add comment if low IgM level: 'Low level treponemal IgM reactivity is often false and nonspecific, so is of doubtful significance. Consider IgM immunoblot to check IgM specificity.
e	Positive	Positive		Positive	Negative	'Consistent with relatively recent or active treponemal infection.'
f	Positive	Negative	Positive			Confirm specific reactivity using a second EIA or treponemal IgG immunoblot. If confirmed, report as "Consistent with treponemal infection at some time". If not confirmed, request further sample for repeat testing
g[i]	Positive	Negative	Negative			Evaluate clinical details and level of reactivity in immunoassay 1. In **low risk** patient, eg tested as part of antenatal screen, consider reporting as 'No serological evidence of treponemal infection. Initial EIA reactivity not confirmed and is probably non-specific. Please repeat if clinically indicated'. In **high risk** patients eg tested at GU Clinic consider IgG immunoblot and IgM testing before reporting. Request second specimen. If this is a follow up sample in a treated patient, review previous results before reporting[i].

h[ii]	Negative	Negative	Positive			Report as 'RPR reactivity is likely to be biological false positive. Treponemal infection unlikely but please repeat to confirm'.
i[ii]	Negative	Positive	Negative			**Evaluate clinical details if available:** **Low risk** patient: 'TPPA/TPHA reactivity is likely to be false unless early infection is suspected. Please repeat to confirm if clinically indicated. No serological evidence of treponemal infection. **High risk** patient: Test using a second EIA. Consider immunoblot and IgM to investigate for early infection. Report as indicated by further test results. **Consider** performing second EIA or immunoblot to clarify. If specific reactivity confirmed, report as 'Consistent with treponemal infection at some time'. Alternatively, request repeat sample for immunoblot.
j	Negative	Positive	Positive[ii]			Perform second EIA or immunoblot. If specific reactivity confirmed, report as 'Consistent with treponemal infection at some time'. Alternatively, request repeat sample for immunoblot.

Footnotes related to reporting table for treponemal serology

i. For treatment response criteria see 'Serological follow up after treatment for syphilis in Europe (paper nr 3). French P. IUSTI/WHO Europe Workshop on Management of Syphilis: 6 scientific background papers. IUSTi Europe Conference on STI. 2004. Available at http://www.iusti.org/regions/europe/pdf/2012/IUSTI-WHOEuropeWorkshopSyphilisManagement2004-Scientificbgpaper3-French-syphilisserologyfollow-up.pdf

Follow up testing is suggested at 3, 6, 9 and 12 months. RPR titre is expected to decline at least fourfold by 6 months after adequate treatment of primary, secondary and early latent syphilis. Further follow up should be undertaken if necessary at 6-monthly intervals until RPR negative or serofast[1]. Note that around 15% of HIV negative patients, and a higher proportion of HIV positive patients, will not meet these criteria.

There is no clear criterion for serological response in late latent syphilis, although most patients with an RPR ≥32 at baseline will demonstrate some fall in the titre by 1 year after adequate treatment[1].

RPR titre is commonly used in laboratories to help assess whether infection is active, is likely to be recent, or has been adequately treated. A titre of at least 16 is usually found in recent infection (median titre 32 with VDRL[14]). A persisting RPR titre of >16 is seldom seen in patients with adequately treated infection. Failure to achieve a fourfold fall in RPR titre by six months post-treatment, or an eightfold fall by one year post-treatment, raises concerns about treatment failure or reinfection. A significant rise in RPR titre suggests reinfection. In pregnant women, however, non-treponemal test antibody titres can rise non-specifically[5].

ii. Patterns h and i are likely only to be seen in referral laboratories, where initial reactivity reported in a referring laboratory is not confirmed by the referral laboratory.

iii. Laboratories need to establish what constitutes a low reactive result with each particular test in use.

Diagnosis of neurosyphilis

T. pallidum commonly invades the central nervous system at an early stage of infection and may or may not produce symptoms. Symptomatic infection can present early, as aseptic meningitis, or later, as meningovascular syphilis or parenchymal late neurosyphilis including general paresis and tabes dorsalis[15]. In the preantibiotic era some 20% of infected individuals developed symptomatic neurosyphilis. Early treatment with penicillin markedly reduces the risk of progression of asymptomatic to symptomatic CNS infection.

Diagnosis of neurosyphilis requires consideration of the history (including risk factors, treatment history and HIV status), clinical findings, and CSF microscopy and protein, together with blood and CSF treponemal serology results. CSF protein is variably raised in neurosyphilis depending on the stage of infection. CSF pleocytosis, when present, is lymphocytic. An average of 25-75 **cells X 10^6/L** is found in tabes dorsalis and general paresis. However, the CSF is acellular in 10% of cases of tabes.

If the peripheral blood is negative for treponemal antibodies there is no need to test a CSF sample. Testing of CSF should be considered in patients with treponemal infection and neurological or ophthalmological symptoms, or treatment failure[1]. Blood contamination of CSF should be minimised. A matched serum sample should be taken to compare antibody levels with CSF. Non-treponemal test results on peripheral blood can help to predict, or exclude, neurosyphilis: A negative VDRL virtually excludes neurosyphilis, whereas RPR ≥32 increases the likelihood of neurosyphilis (approximately 11-fold in patients without concurrent HIV infection and 6- fold in the HIV-infected individual)[16,17].

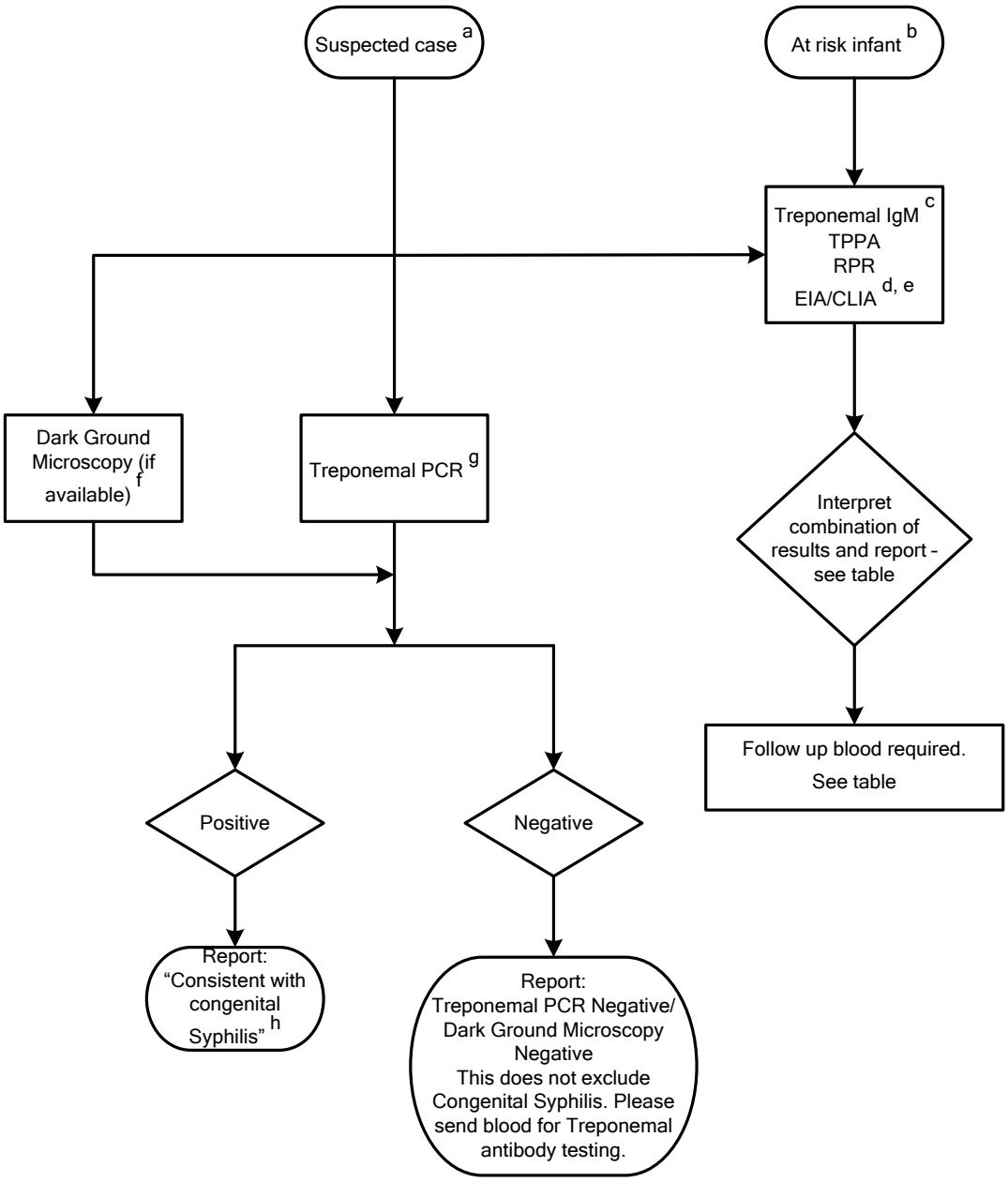
Treponemal serology in neurosyphilis

Much of the original work on serological diagnosis of syphilis was performed using VDRL as the non-treponemal test for CSF. However, changes in practice now mean that RPR is more commonly used. TPPA and RPR on CSF are now the recommended tests for investigating neurosyphilis in the UK.

- CSF RPR is an insensitive test for neurosyphilis being positive in only about 50% of cases[1,18]. Modifying the RPR methodology by diluting the assay antigen, as is performed for CSF VDRL testing to account for the lower concentration of CSF antibody, can improve the sensitivity of RPR in CSF[18]. A positive RPR, in the absence of evidence of blood contamination of the CSF sample, is diagnostic of neurosyphilis[1]
- CSF TPPA is sensitive in the diagnosis of neurosyphilis but lacks specificity. TPPA titre is usually >640 in neurosyphilis[1]. Where there is clinical suspicion however it is doubtful whether a negative TPPA result can exclude neurosyphilis[19]
- treponemal PCR testing has a role in confirming neurosyphilis but is reported to have a sensitivity of less than 50%[20]

Following treatment for neurosyphilis, any CSF pleocytosis should have decreased by six months and CSF should be normal by two years (except for persistent positive treponemal specific antibody tests)[1].

Early congenital syphilis[iv]



Footnotes relating to early congenital syphilis

a. Symptomatic baby with risk factors suggesting possibility of congenital syphilis. Early congenital syphilis manifests within two years of birth. Symptoms might include: snuffles, perioral fissures, hepatomegaly and jaundice, cataracts, growth retardation, rash, mucous patches and condylomata lata. It is advisable to take and compare a contemporaneous blood from the mother when investigating the baby's serum.

b. Mother seropositive for treponemal antibodies, or known to have had syphilis at some time. With the following exceptions;

   - Maternal biological false-positive serology
   - Maternal syphilis cured prior to this pregnancy

   Infants should be tested at birth and then at three monthly intervals until negative[1]. If titres remain stable or increase evaluate and treat for congenital syphilis[1].

   Note that when maternal syphilis is acquired late in the pregnancy antibodies might not be present in mother or baby at birth[21].

c. Serological tests should be performed on baby's blood not cord blood. Treponemal IgM test should be the priority on small volume samples if no maternal sample is available for paired testing.

d. TPPA level can be monitored to look for decline over time in the uninfected.

e. Treponemal EIA or CLIA may be used to confirm presence of maternal antibody.

f. Suitable samples for dark ground microscopy include nasal discharge and lesion swabs. Dark ground microscopy results should be verified by another method (serology or PCR).

g. Treponemal PCR is available in some centres (in some as part of a multiplex PCR), but validation data on samples in congenital syphilis is limited. Suitable samples include lesion swabs, nasal discharge or nasopharyngeal aspirate, EDTA blood and CSF.

h. Contact testing of siblings should be carried out when a maternal or a congenital syphilis diagnosis is made[1].

Report comments for early congenital syphilis[iv]

	IgM[i]	RPR[ii]	TPPA[iii]	Interpretation
A	Positive	Negative	Negative	If mother has acquired syphilis late in pregnancy: 'Suggestive of congenital syphilis. Please repeat to confirm, and send samples for treponemal PCR'. In other situations: 'No conclusive evidence of congenital syphilis. The IgM reactivity is likely to be false. Please repeat to confirm status. Verify maternal treponemal antibody.' Consider treponemal PCR, and/or dark ground microscopy on suitable samples.
B	Positive	Positive with titre ≥4 times higher than mother's RPR titre[iv,v]	Positive at any titre	'Consistent with congenital infection. Please repeat to confirm.' (If confirmed repeat RPR to monitor treatment response). Consider treponemal PCR, and/or dark ground microscopy on suitable samples.
C	Positive	Positive with titre <4 times that of mother[iv]	Positive at any titre	'Suggestive of congenital syphilis but not conclusive. Please send repeat blood for serology.' Consider treponemal PCR, and/or dark ground microscopy on suitable samples.
D	Negative	Negative	Negative	'No serological evidence of congenital syphilis.' Assess likely risk, as the baby could be seronegative if infection in the mother acquired late in pregnancy.
E	Negative	Positive with a titre ≥4 times that of mother[iv,v]	Positive at any titre	'Consistent with congenital syphilis. Please repeat to confirm.' Consider treponemal PCR, and/or dark ground microscopy on suitable samples.

F	Negative	Positive with a titre <4 times that of mother[iv]	Positive at any titre	'This antibody is probably maternal. Advise repeat at intervals to monitor for changes in titres, or until tests become negative. Tests suggested at 3 month intervals until negative.
G	Negative	Positive with a titre <4 times that of mother[iv]	Negative	'No serological evidence of congenital syphilis.' Further interpretation dependent on treponemal total antibody EIA result and/or the mother's serology results: If EIA negative, repeat RPR and if repeat reactive report as "Probable false positive RPR. Repeat at 3 month intervals until negative.' If EIA positive, report as 'This antibody is probably maternal. Advise repeat at intervals to monitor for changes in titres, or until tests become negative. Tests suggested at 3 month intervals until negative.
H	Negative	Negative	Positive	No serological evidence of congenital syphilis. Further interpretation dependent on treponemal total antibody EIA result and/or the mother's serology results: If EIA negative, report as 'Probable false positive TPPA.' If EIA positive report as 'This antibody is probably maternal. Advise repeat at intervals to monitor for changes in titres, or until tests become negative. Tests suggested at 3 month intervals until negative.

Footnotes relating to reporting table for congenital syphilis

i. IgM is usually detected using a μ-capture EIA, but IgM immunoblot or IgM-FTA-abs would also be suitable. Note that all IgM tests are susceptible to false reactivity, as well as false negativity, so results must always be interpreted cautiously and in conjunction with the TPPA/TPHA and RPR results and the maternal serology results.

ii. RPR is the preferred non-treponemal test as it is more sensitive than VDRL for the diagnosis of congenital syphilis.

iii. TPHA may be used as an alternative to TPPA. There are no data available to assess the use of automated agglutination tests such as TPLA.

iv. Sequential and comparative testing of mother and baby should be done in the same laboratory using the same tests.

v. Four-fold (or greater) difference in RPR titre has high sensitivity but poor specificity for the diagnosis of congenital syphilis.

Notification to PHE[22,23] or equivalent in the devolved administrations[24-27]

The Health Protection (Notification) regulations 2010 require diagnostic laboratories to notify Public Health England (PHE) when they identify the causative agents that are listed in Schedule 2 of the Regulations. Notifications must be provided in writing, on paper or electronically, within seven days. Urgent cases should be notified orally and as soon as possible, recommended within 24 hours. These should be followed up by written notification within seven days.

For the purposes of the Notification Regulations, the recipient of laboratory notifications is the local PHE Health Protection Team. If a case has already been notified by a registered medical practitioner, the diagnostic laboratory is still required to notify the case if they identify any evidence of an infection caused by a notifiable causative agent.

Notification under the Health Protection (Notification) Regulations 2010 does not replace voluntary reporting to PHE. The vast majority of NHS laboratories voluntarily report a wide range of laboratory diagnoses of causative agents to PHE and many PHE Health Protection Teams have agreements with local laboratories for urgent reporting of some infections. This should continue.

Note: The Health Protection Legislation Guidance (2010) includes reporting of Human Immunodeficiency Virus (HIV) & Sexually Transmitted Infections (STIs), Healthcare Associated Infections (HCAIs) and Creutzfeldt–Jakob disease (CJD) under 'Notification Duties of Registered Medical Practitioners': it is not noted under 'Notification Duties of Diagnostic Laboratories'.

https://www.gov.uk/government/organisations/public-health-england/about/our-governance#health-protection-regulations-2010

Other arrangements exist in Scotland[24,25], Wales[26] and Northern Ireland[27].

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