

# 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).

The contributions of many individuals in clinical, specialist and reference laboratories who have provided information and comments during the development of this document are acknowledged. We are grateful to the Medical Editors for editing the medical content.

For further information please contact us at:

Standards Unit
Microbiology Services
Public Health England
61 Colindale Avenue
London NW9 5EQ
E-mail: standards@phe.gov.uk

Website: https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories

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UK Standards for Microbiology Investigations | Issued by the Standards Unit, Public Health England]
Epstein-Barr Virus Serology

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NICE has accredited the process used by Public Health England to produce Standards for Microbiology Investigations. Accreditation is valid for 5 years from July 2011. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

For full details on our accreditation visit: www.nice.org.uk/accreditation.
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.

<table>
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<tr>
<th>Amendment No/Date.</th>
<th>7/03.07.15</th>
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<tr>
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<td>4.1</td>
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<tr>
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</tr>
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<td><strong>Section(s) involved</strong></td>
<td><strong>Amendment</strong></td>
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<tr>
<td>Whole document.</td>
<td>Hyperlinks updated to gov.uk.</td>
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<tr>
<td>Page 2.</td>
<td>Updated logos added.</td>
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<tr>
<td>Type of specimen.</td>
<td>Section added.</td>
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<td>Scope.</td>
<td>Section added.</td>
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<td>Flowchart</td>
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<tr>
<td>Common EBV serological profiles and suggestions for report comments.</td>
<td>Updated and reformatted to separate suggestions for interpretative comments from notes for consideration.</td>
</tr>
<tr>
<td>References.</td>
<td>Reviewed and updated.</td>
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</table>
UK Standards for Microbiology Investigations#: scope and purpose

Users of SMIs

• SMIs are primarily intended as a general resource for practising professionals operating in the field of laboratory medicine and infection specialties in the UK.

• SMIs 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.

• SMIs 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.

#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.
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 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 are 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

Whilst 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.
Scope

Type of specimen
Serum, plasma

Scope
This algorithm considers the interpretation of common Epstein-Barr virus (EBV) serology profiles arising from investigation of acute EBV infection and not those arising from investigation of malaise or persistent lymphadenopathy. Although EBV-specific serology is preferable, properly conducted heterophile antibody tests (eg Paul-Bunnell, Monospot) remain acceptable in appropriate clinical circumstances, as described below. EBV IgG avidity testing may be helpful in distinguishing acute and past infections\(^1,^2\).

Refer to **G 7 – Investigation of red rash** and **G 2 – Microbiological investigation of patients with acute lymphadenopathy and fever** for further information regarding clinical presentations and differential diagnosis.

Refer to **Q 7 - Good laboratory practice when undertaking serology assays for infectious diseases** for information regarding good laboratory practice in serological testing.

This SMI should be used in conjunction with other SMIs.

Definitions
For all antigen, antibody and NAAT testing the following definitions apply:

**Reactive** – Initial internal-stage positive result pending confirmation.

**Not reactive** – Initial internal-stage negative result.

**Detected** – Report-stage confirmed reactive result.

**Not detected** – Report-stage not reactive result.
**Laboratory diagnosis of acute EBV infection**¹,³-⁶

**EBV-specific serology**³⁻⁶

- EBV VCA IgM and EBV VCA IgG
  - Both IgG & IgM Negative
    - REPORT: No evidence of EBV infection at any time
  - Any test Reactive
    - REPORT: Heterophile antibody not detected
    - REPORT: Heterophile antibody detected, consistent with recent acute EBV infection

- EBNA IgG
  - Negative
  - REPORT: EBNA IgG if not already done
  - REPORT: EBV VCA IgM and EBV VCA IgG if not already done
  - REPORT: No evidence of recent EBV infection
  - Reactive
  - REPORT: No evidence of recent EBV infection

**Heterophile antibody testing**³,⁶

- Negative or Non-specific
  - Positive
    - REPORT: No evidence of recent EBV infection

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³ REPORT: Interpret according to table of result profiles and comments

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⁴ REPORT: No evidence of recent EBV infection

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⁵ REPORT: Heterophile antibody not detected

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⁶ REPORT: Heterophile antibody detected, consistent with recent acute EBV infection

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UNDER REVIEW
Epstein-Barr Virus Serology

Footnotes

a) Some laboratories choose not to routinely test patients above a specific age as the positive predictive value of any test set will be low for diagnosis of acute infection.

b) Although EBV-specific serology is preferable properly conducted heterophile antibody tests (eg Paul-Bunnell, Monospot) remain acceptable in appropriate clinical circumstances. Heterophile antibody tests are not appropriate for testing children and immunocompromised individuals due to a high false negative rate. False positives are uncommon but have been described in rheumatoid disease, SLE, leukaemia, lymphoma, infections including malaria, HIV, CMV, rubella, viral hepatitis and tularemia, and after administration of anti-thymocyte globulin.

c) Two different approaches to initial screening for EBV are in common use; either initial anti-EBNA-1 or initial VCA (IgG and IgM) testing are equally valid if appropriate algorithms are followed and due care is given to interpretation of results. Anti-EBNA-1 usually appears after 3-4 weeks from onset of illness and appears in 95% or more of individuals; but may not be present in the immunocompromised individuals or in chronic EBV infections. Some laboratories use antibody to early antigen (diffuse) as an additional test in diagnosis of acute infection.

d) EBV DNA PCR must be used to investigate primary or reactivated EBV infection in patients who are immunocompromised and at risk of severe disease as serological tests may be unreliable in the immunocompromised patients.

e) EBV DNA PCR on whole blood (EDTA) or plasma may be useful as a confirmatory assay where antibody test results are inconclusive.

f) EBV IgG avidity testing may be helpful in distinguishing acute and past infections.

g) Interpret with caution as in a small number of cases EBNA IgG may be detectable early, by immunofluorescent antibody testing as early as ten days after the onset of illness in <5%.

h) If haematological parameters consistent with acute EBV infection regard as confirmed. If haematological parameters are not consistent with acute EBV infection or are not available regard as unconfirmed and consider doing confirmatory specific EBV serology.
## Common EBV serological profiles and suggestions for report comments

There are other combinations of results which have not been tabled but which do occur and require individual comments based upon profile and clinical setting, along with a further sample.

<table>
<thead>
<tr>
<th>VCA IgM</th>
<th>VCA IgG</th>
<th>EBNA IgG</th>
<th>Interpretative Comment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>No serological evidence of EBV infection at any time. Re-test if recent onset of illness. Consider testing for HIV³.</td>
</tr>
<tr>
<td>2</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Consistent with past EBV infection. Consider testing for HIV³ if at risk.</td>
</tr>
<tr>
<td>3</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Consistent with recent acute EBV infection. Consider possibility of false negative anti-EBNA-1 when reporting.</td>
</tr>
<tr>
<td>4</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Consistent with but not diagnostic of recent acute EBV infection. Repeat to confirm in 4-6 weeks. IgM result may be false, repeat to clarify. EBV DNA PCR may be useful in this situation.</td>
</tr>
<tr>
<td>5</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>The EBV serological profile may reflect distant past infection, however recent infection cannot be excluded. Repeat in 4-6 weeks if recent EBV infection is suspected. Consider EBV PCR and heterophile antibody testing⁵,⁷</td>
</tr>
<tr>
<td>6</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Evidence of EBV infection at some time, but this profile is difficult to interpret. Although the IgM reactivity might be false, late primary infection or recent EBV reactivation cannot be excluded. Some laboratories may be able to establish a cut off for IgM below which most results are false, and can be reported as such, if EBV VCA IgG and anti-EBNA-1 IgG are positive. Unrelated acute infection can result in the non-specific polyclonal activation of memory cells and the release of VCA IgM. Consider testing for CMV IgM, Parvovirus IgM, HAV IgM and HIV⁵,⁷. EBV PCR and heterophile antibody testing may be helpful. Review in light of clinical details, and the numerical values of the test results and consider repeat to clarify.</td>
</tr>
</tbody>
</table>

**Note:** ‘recent infection’ covers infection in the last 2-4 weeks.
Notification to PHE\textsuperscript{10,11} or equivalent in the devolved administrations\textsuperscript{12-15}

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\textsuperscript{12,13}, Wales\textsuperscript{14} and Northern Ireland\textsuperscript{15}.
References


