UK Standards for Microbiology Investigations

Hepatitis B Diagnostic Serology in the Immunocompetent (including Hepatitis B in Pregnancy)
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 http://www.hpa.org.uk/SMI/Partnerships. SMIs are developed, reviewed and revised by various working groups which are overseen by a steering committee (see http://www.hpa.org.uk/SMI/WorkingGroups).

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: http://www.hpa.org.uk/SMI

UK Standards for Microbiology Investigations are produced in association with:
**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>
<thead>
<tr>
<th>Amendment No/Date.</th>
<th>9/31.03.14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Issue no. discarded.</td>
<td>5.2</td>
</tr>
<tr>
<td>Insert Issue no.</td>
<td>5.3</td>
</tr>
<tr>
<td><strong>Section(s) involved</strong></td>
<td><strong>Amendment</strong></td>
</tr>
<tr>
<td>Whole document.</td>
<td>Document has been transferred to a new template to reflect the Health Protection Agency’s transition to Public Health England.</td>
</tr>
<tr>
<td></td>
<td>Front page has been redesigned.</td>
</tr>
<tr>
<td></td>
<td>Status page has been renamed as Scope and Purpose and updated as appropriate.</td>
</tr>
<tr>
<td></td>
<td>Professional body logos have been reviewed and updated.</td>
</tr>
<tr>
<td></td>
<td>Standard safety and notification references have been reviewed and updated.</td>
</tr>
<tr>
<td></td>
<td>Scientific content remains unchanged.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amendment No/Date.</th>
<th>8/28.06.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Issue no. discarded.</td>
<td>5.1</td>
</tr>
<tr>
<td>Insert Issue no.</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Section(s) involved</strong></td>
<td><strong>Amendment</strong></td>
</tr>
<tr>
<td>Whole document.</td>
<td>Minor formatting amendments.</td>
</tr>
</tbody>
</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 http://www.hpa.org.uk/SMI/Partnerships. 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 or 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 http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317133470313. 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.
Suggested Citation for this Document
Hepatitis B Diagnostic Serology in the Immunocompetent (including Hepatitis B in Pregnancy)

Hepatitis B Surface Antigen (HBsAg) Confirmation by Neutralisation

HBsAg assay
HBsAg minimum target sensitivity level of 0.05 iu / mL

Negative

REPORT: HBsAg not detected

Reactive

Repeat from the original sample

Reactive

Confirm specificity by neutralisation

Not confirmed

REPORT: HBsAg not detected

Confirmed

REPORT: HBsAg detected
Confirmed by neutralisation. Please send a further sample for confirmation
Footnotes

a) It is recommended that only those assays which are able to detect immune / vaccine escape variants should be used.

b) Haemolysed samples (eg, cadaver samples) are prone to give non-neutralisable false reactive results.

c) All newly diagnosed patients with chronic hepatitis should be referred to a hepatologist.
Hepatitis B Virus Serology – HBsAg Confirmation by Alternative Assay

- HBsAg assay
  - HBsAg minimum target sensitivity level of 0.05 iu/mL

  - Negative
    - REPORT: Hepatitis B surface antigen not detected
  - Reactive
    - Confirmatory HBsAg test from original sample using alternative assay of at least equivalent sensitivity
      - Reactive
        - Repeat 1st assay from original sample (if available)
        - Both tests negative
          - REPORT: Hepatitis B surface antigen not detected
        - 1st test reactive
          - 2nd test negative

- Anti-HBc test
  - Anti-HBc negative
    - REPORT: HBsAg equivocal, Anti-HBc negative. Likely to be non specific surface antigen reactivity. Request another sample.
  - Anti-HBc reactive
    - REPORT: HBsAg equivocal, Anti-HBc reactive. Further test results to follow. Please send another sample.

Testing for other markers as appropriate see table.
Footnotes

a) It is recommended that only those assays which are able to detect immune / vaccine escape variants should be used.

b) Haemolysed samples (eg, cadaver samples) are prone to give non-neutralisable false reactive results.

c) All newly diagnosed patients with chronic hepatitis should be referred to a hepatologist.
Hepatitis B Surface Antigen Confirmed Reactives

- **Anti-HBc total**
  - Positive
    - **Core IgM**
      - Positive (\(\leq 50\) PEI/mL)
        - **HBV DNA**
          - Positive
            - Perform HBeAg / Anti Hbe
              - For interpretation: see Table
          - Negative
      - Positive (>50 PEI/mL)
        - Negative
  - Negative

For interpretation: see Table
Footnotes

a) All newly diagnosed patients with chronic hepatitis should be referred to a hepatologist.

b) When interpreting anti-HBc reactivity, consider the possibility of false reactivity if weak.

c) Testing a further sample or doing other Hepatitis B markers may give a useful final status before the HBV DNA result is available.

d) Hepatitis D (delta) virus testing should be considered at presentation of chronic HBV infection, and during any clinical flares or during acute infection, especially if complicated by acute liver failure.
### Hepatitis B Reporting for Immunocompetent Individuals*

<table>
<thead>
<tr>
<th>HBs Ag</th>
<th>Anti HBc (total)</th>
<th>HBC IgM</th>
<th>HBe Ag</th>
<th>Anti HBe</th>
<th>Anti HBs</th>
<th>Hep B DNA</th>
<th>Suggested wording of report comment (see footnotes for further information and actions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
<td>Negative/Not tested</td>
<td>No evidence of current or past hepatitis B infection (see note ii).</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
<td></td>
<td>Positive</td>
<td>Consistent with past hepatitis B infection**.</td>
<td></td>
</tr>
<tr>
<td>3a, b</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
<td></td>
<td>Negative</td>
<td>Consistent with probable past hepatitis B infection** (consider the possibility of false anti-HBc).</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
<td>Positive</td>
<td>No evidence of current or past infection with hepatitis B. Anti HBs is compatible with a vaccine response.</td>
<td></td>
</tr>
<tr>
<td>5b</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative or Low Positive</td>
<td>Suggests relatively recent resolving infection with hepatitis B. Is there a history of infection or recent jaundice? Please send a repeat sample to confirm.</td>
<td></td>
</tr>
<tr>
<td>6c</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Indicates early acute infection with hepatitis B. Please repeat testing in a month’s timevii.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Positive</td>
<td>Negative</td>
<td></td>
<td></td>
<td>Negative</td>
<td>HBsAg detected. No evidence of viral replication. Has this patient been recently immunised? The HBsAg in vaccine can be detectable for about one week after vaccination¹.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Indicates early acute infection with hepatitis B. Please repeat immediately and if confirmed test again in three months⁹.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Indicates recent infection with hepatitis Bg. Immediate repeat and send another sample in three months to check for resolution.</td>
<td></td>
</tr>
</tbody>
</table>

* Please consult the footnotes for further information and actions.
Hepatitis B Diagnostic Serology in the Immunocompetent (including Hepatitis B in Pregnancy)

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Positive</th>
<th>Positive or Negative</th>
<th>Negative or Positive</th>
<th>Positive</th>
<th>Suggests a flare of chronic hepatitis B virus infection, but acute infection cannot be excluded. Immediate repeat and send another sample in three months to check for resolution.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive or Negative</td>
<td>Negative or Positive</td>
<td>Positive</td>
<td>可爱</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Positive</th>
<th>Negative</th>
<th>Positive</th>
<th>Negative or Low Positive</th>
<th>Positive</th>
<th>Consistent with chronic HBeAg positive hepatitis B. Immediate repeat and send another sample in 3-6 months to confirm chronic infection.</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative or Low Positive</td>
<td>Positive</td>
<td>属于</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Positive</th>
<th>Negative</th>
<th>Positive</th>
<th>Negative or Low Positive</th>
<th>Positive</th>
<th>Consistent with anti-HBe positive chronic hepatitis B. Please send another sample in three to six months to confirm chronic infection.</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative or Low Positive</td>
<td>Positive</td>
<td>可爱</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Positive</th>
<th>Negative</th>
<th>Negative</th>
<th>Positive or Low Positive</th>
<th>Positive</th>
<th>Indicates chronic hepatitis B, at present without detectable HBe markers. Please send another sample in six months to confirm chronic infection.</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative or Low Positive</td>
<td>Positive</td>
<td>可爱</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Positive</th>
<th>Positive</th>
<th>Negative or Low Positive</th>
<th>Positive</th>
<th>Evidence of hepatitis B infection though not of recent onset. The HBe marker pattern is unusual. Regard as HBeAg positive at present, but please send a repeat sample in three months to look for changing HBe status.</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative or Low Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

*There are other combinations of results (e.g., equivocal HBsAg reactive HBeAg is one) which have not been tabled but which do occur and require individual comments based upon profile and clinical setting, along with a further sample.

**Repeat testing for hepatitis B should not be necessary unless the patient becomes immunocompromised.
Notes Relating to the Table

Acute infectious hepatitis is a notifiable disease. All HBsAg positive patients should be reported promptly: see Notification and Referral section.

The testing algorithm wording of reports assumes this is the first sample received from this patient. Later samples will require modified report comments.

Anti-HBc IgM may be detectable in recent acute hepatitis B or during a flare of viral replication, and may be seen in chronic infection with hepatitis B. In determining whether a case is likely to be acute hepatitis B the clinical details as well as any earlier results on record and the level of anti-HBc IgM are useful. Acute cases are more likely to have levels over 200 Paul Ehrlich Units/ml. Levels between 50 and 200 are probably acute, levels below 50 are probably a flare of chronic infection, but may be due to late acute infection.

Note: interpretative comments should be provided on reports: see CPA Standards for the Medical Laboratory (2007) Standard G5. Patients considered to be at an increased risk of HBV exposure, or having chronic liver disease, should be tested for anti-HBc when found to be HBsAg negative.

Hepatitis B may reactivate in patients who are immunocompromised

a) It is advisable to confirm isolated anti-HBc positive results with a second assay, as isolated anti-HBc sometimes represents false reactivity.

b) In clinical scenario of recent acute liver failure (fulminant hepatitis) HBsAg may be negative due to the pronounced immune response and rapid viral clearance of HBV; total anti-HBc and anti-HBc IgM may then be the only positive serological markers.

c) The detection of HBsAg without evidence of anti-HBc and anti-HBc IgM is associated with early acute infection before antibody production. HBV DNA testing is essential to confirm this. Request repeat sample to confirm identity of patient and to check for confirmation of acute Hepatitis B virus infection by development of other markers, these can take many weeks to evolve and may not be accompanied by symptoms of acute hepatitis.

d) HBeAg positive samples are strongly associated with high infectivity unless HBV replication is being suppressed by antiviral therapy.

e) Anti-HBe positive patients often have low infectivity, but a proportion have precore mutant virus infection with high HBV DNA levels.

f) HBV DNA PCR is widely available in virology specialist centres and can be used to evaluate the viral load. This has been shown to have prognostic value, independent of HBe status in the evaluation risk of cirrhosis, and development of hepatocellular carcinoma in patients with chronic infection. It is also used to monitor antiviral therapy.

g) Please screen and immunise sexual household contact.

In pregnant patients testing HBsAg positive, additional comments should be added to guide immunisation and follow-up of the baby after birth. See below for further details.
Hepatitis B in Pregnancy

- The general testing strategies, reporting and notification patterns for pregnant women infected with hepatitis B are identical to those for other individuals.

- Additional reporting to specialist midwives, or similar healthcare workers, responsible for the care of pregnant women and their babies should be in place locally.

- Vertical transmission of hepatitis B to the neonate is a substantial risk and prophylaxis for the neonate should be arranged well before delivery wherever possible. Local arrangements may vary.

- The guidance promulgated by the DH in Chapter 18 of ‘Immunisation against Infectious Disease’ should be followed taking particular note of online Chapter updates.

- Reference should also be made to DH Guidance ‘Screening for infectious diseases in pregnancy: Standards to support the UK antenatal screening programme’.

All children born to mothers infected with HBV should be followed up to ensure completion of immunisation in accordance with national guidance. Testing for HBsAg at one year is currently recommended.
Notification to PHE\textsuperscript{2,3} or Equivalent in the Devolved Administrations\textsuperscript{4-7}

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.

\textbf{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’.

\url{http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/HealthProtectionRegulations/}

Other arrangements exist in \textit{Scotland}\textsuperscript{4,5}, \textit{Wales}\textsuperscript{6} and \textit{Northern Ireland}\textsuperscript{7}. 


