

2017 interim update of the 2015 BASHH National Guidelines for the Management of the Viral Hepatitides

This guideline is an interim update of the 2015 guidelines to reflect recent changes in epidemiology, testing and treatment. We have added new advice on hepatitis A testing and vaccination in response to the recent HAV outbreak in MSM, updated the definition of chronic hepatitis B and advice on vaccination of HIV+ patients. We have also updated advice on hepatitis C testing and treatment. This is accompanied by expansion of the relevant background sections in the main text (sections 2-5). Changes to the 2015 guideline are highlighted in yellow.

This update was performed by a small subgroup of the 2015 writing committee but using the same methodology as below.

Introduction and Methodology for the 2015 guideline

This guideline is an update of the guideline published in 2008 and, like its previous version, provides guidance for best practice in the diagnosis, management and prevention of viral hepatitis types A, B and C. It is primarily intended for use in UK Genitourinary Medicine (GUM)/Sexual Health settings, but can be applied or adapted for use in other settings where sexually transmitted infection (STI) assessments are undertaken such as in integrated STI/contraception sexual health services and other specifically commissioned services, including general practice. This guideline is for use by all healthcare professionals (doctors, nurses and health advisers) and for use when dealing with patients who are attending with symptoms that may be attributed to a STI, with concern about STIs or are requesting screening for STIs. It will also be useful to managers and commissioners of sexual health services in understanding service needs.

The purpose of the guideline is to help improve the sexual health of individuals attending sexual health clinics by encouraging high standards of care. The guideline offers recommendations on best practice regarding viral hepatitis for both men and women, including adolescents.

The guideline is predominantly based on what a broad range of clinicians believe constitutes reasonable practice, based on best evidence. Evidence is sometimes cited from non-UK sexual health settings and from other settings outside sexual health care where necessary. The recommendations/evidence are graded using the GRADE system (appendix).

Search Strategy

This document was produced in accordance with the guidance set out in the Clinical Effectiveness Group's (CEG) document "Framework for guideline development and assessment" at <http://www.bashh.org/guidelines>. The 2015

guideline updates the previous guideline by searching Medline 2008-2014 for 'hepatitis A', 'hepatitis B', 'hepatitis C', 'Hepatitis D' and 'Delta virus' and limited to "human" and "English".

The Cochrane database was searched for 'hepatitis A', 'hepatitis B', 'hepatitis C', 'Hepatitis D' and 'Delta virus'. The 2010 European (IUSTI/WHO) guideline on the management of viral hepatitis, the 2017 European Association for the Study of the liver (EASL) guidelines for the management hepatitis B and the 2014 European Association for the Study of the liver (EASL) guidelines for the management hepatitis C, the 2014 British HIV Association (BHIVA) guidelines for the management hepatitis viruses and the 2014 American Association for the Study of Liver Disease (AASLD) Recommendations for Testing, Managing, and Treating Hepatitis C were reviewed. In addition, sections on hepatitis in relevant BASHH and other guidelines were reviewed for other references. Forward and backward searching from key references was also conducted.

Piloting and Feedback

The writing committee includes clinicians from the specialties of GUM, hepatology, infectious diseases, microbiology, nursing and sexual health advising. Prior to publication, the final draft of the guideline was placed on the British Association for Sexual Health and HIV (BASHH) website for a two month consultation period and copies were circulated to the Genitourinary Nurses Association (GUNA) and the Society of Sexual Health Advisers (SSHA) chairs for comment and peer review. It was also reviewed by the BASHH Public Panel. The guideline was piloted before it was finally ratified.

Abbreviations used in these guidelines

ALF: Acute liver failure	HBIG: Hepatitis B Immunoglobulin
ALT: Alanine transaminase	HBV: Hepatitis B virus
ALP: Alkaline phosphatase	HBV-DNA: Hepatitis B virus deoxyribose nucleic acid
APRI: AST to platelet ratio	HCC: Hepatocellular carcinoma
ART: Antiretroviral therapy	HCV: Hepatitis C virus
AST: Aspartate transaminase	HCV-RNA: Hepatitis C virus ribose nucleic acid
Anti-HBc: antibody against hepatitis B core antigen	HDV: Hepatitis D virus
Anti-HBe: antibody against hepatitis B 'e' antigen	HEV: Hepatitis E virus
Anti-HBs: antibody against hepatitis B surface antigen	HNIG: Human normal Immunoglobulin
DAA: Direct acting antiviral agents	IgG: Immunoglobulin type G
EASL-CPG: European Association for the Study of the Liver clinical practice guideline	IgM: Immunoglobulin type M
ELF: Enhanced liver fibrosis score	LFT: Liver function test
FIB-4: Fibrosis 4 score	MSM: Men who have sex with men
HAV: Hepatitis A virus	NEAT: European AIDS Treatment Network
HBsAg: Hepatitis B surface antigen	PCR: Polymerase chain reaction
HBeAg: Hepatitis B 'e' antigen	PT: Prothrombin time
	PWID: People who inject drugs
	STI: Sexually transmitted infection

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1 Key Recommendations

1.0 Acute Hepatitis

What to do if a patient presents with symptoms suggestive of acute viral hepatitis.

- Clinically assess the patient and if necessary refer for hospital admission(1A) *section 2.8.4.*
- Perform tests to assess the severity of the hepatitis including LFT, clotting, and hepatitis serology (including HAV IgM, HBsAg, HCV antibodies/antigen/RNA and HEV serology/PCR) (1B) *section 2.7.2.*
- Inform the appropriate public health authority, for contact tracing (1C) *section 2.8.1*

1.1 Hepatitis A

1.1.1 Which asymptomatic patients should be screened for evidence of past HAV infection in the sexual health setting?

- In the sexual health setting, the hepatitis A virus total antibody test can be offered to at-risk patients whose immune status is unknown and who do not have a definite history of a completed HAV vaccination course, depending on local funding arrangements and risk of patient not returning for vaccination. (2B) *section 2.9.*
- In an outbreak situation or if the patient may not return, antibody testing should not prevent the administration of the first vaccine dose on the same day as testing.
- The patients to be targeted are: MSM, PWID, HBV+, HCV+ and HIV+ patients (1B) *section 2.9.*
- HAV screening should not be offered to patients who are known to be immune or fully vaccinated (1B) *section 2.9.*

1.1.2 What to do if the HAV total antibody test is negative or the antibody test is not done in the asymptomatic patient.

- In at-risk patients (all MSM attending a sexual health clinic, PWID, HBV+, HCV+ and HIV+ patients) offer a course of Hepatitis A vaccination with either the mono-dose vaccine (or the combined Hepatitis A and B vaccine if non-immune to both infections) and no documented evidence of previous hepatitis A vaccination (1B) *section 2.9.*
- Discuss safer sex and how to reduce risk of catching this infection (1D) *section 2.9*

1.1.3 What if the patient is found to have acute hepatitis A?

- Partner notification should be performed for at-risk MSM contacts (oro/anal, digital/rectal and penetrative anal sex) within the period two weeks before, to one week after, the onset of jaundice. (1C) *section 2.8.5.*
- Employment history should be obtained so patient can be advised appropriately and patients should be advised to avoid food handling and unprotected sexual intercourse until they have become non-infectious (1B) *section 2.8.1.*
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information (1B) *section 2.8.1.*
- Pregnant women should be advised of the increased risk of miscarriage/premature labour and the need to seek medical advice if symptoms develop (1B) *section 2.8.4.*
- The risk from breast feeding is uncertain. Therefore the balance of risks between infection and stopping breast feeding should be considered on an individual basis (2C) *section 2.8.4.*

1.1.4 What to do if a patient presents as a contact of a patient with acute hepatitis A.

- Screen for evidence of HAV infection or immunity (1B) *section 2.9.*
- For known sexual contacts e.g. MSM with oro/anal, digital/rectal and penetrative anal sex within the period two weeks before to one week after the onset of jaundice, offer post exposure prophylaxis with HAV vaccine if not known to be immune/fully vaccinated previously (1A) *section 2.8.5.*
- Human normal immunoglobulin (HNIG) 250-500 mg. intramuscularly should also be considered in addition to the vaccine for patients at higher risk of complications (concurrent chronic hepatitis B or C, chronic liver disease, HIV+ or age >50 yo) (IA) *section 2.8.5*
- If the type of hepatitis of the index case is not known, also offer post-exposure prophylaxis against hepatitis B (1A) *section 2.8.5 and section 3.8.6.*
- Give advice on action to take if symptoms suggestive of hepatitis subsequently occur (1D) *section 2.8.5 .*

1.1.5 What to do if there is a hepatitis A outbreak in MSM.

- Offer hepatitis A vaccine to all MSM attending a sexual health clinic at the first visit unless there is confirmed evidence of prior vaccination/immunity. Do not wait for the results of a hepatitis A antibody test. *section 2.9.*
- If there is a shortage of vaccine hepatitis A monodose or combined A+B vaccines, alternatives to use in an emergency are the paediatric monodose vaccine or the combined typhoid/Hepatitis A vaccine. *section 2.9.*

1.2 Hepatitis B

1.2.1 Which asymptomatic patients should be screened for evidence of past /current hepatitis B infection in the sexual health setting?

- Hepatitis B testing in asymptomatic patients should be recommended in MSM, sex workers (of either sex), people who inject drugs (PWID), HIV-positive patients, sexual assault victims, people from countries where hepatitis B is endemic (outside of Western Europe, North America and Australasia), needlestick victims and sexual partners of positive or high-risk patients (1A) *section 3.9.1.*
- The screening tests of choice are anti-HBcore antibody and/or the hepatitis B surface antigen (HBsAg) test with further serology to assess the stage of infection and infectivity as appropriate (1B). Measure anti-HBs in those who have been vaccinated (1B) *section 3.9.1.*

1.2.2 What if the asymptomatic patient is not immune to hepatitis B?

- In at-risk patients, consider vaccination with the monovalent hepatitis B vaccine or the combined hepatitis A and B vaccine if non-immune to both. In most cases the ultra-rapid 0,1,3 week, 12 month vaccination course is recommended (1B) *section 3.9.4.*
- Discuss safer sex and how to reduce risk of becoming infected (1D) *section 3.9.4*
- The ultra-rapid vaccination schedule (0,1,3 weeks) leads to an anti-HBs antibody response in only 80% of recipients 4-12 weeks after the third dose. This rises to 95% just prior to the 12 month booster dose. Consider offering booster vaccinations of up to three further doses to the 20% without detectable antibodies 4-12 weeks after the primary course even though most would have eventually developed an antibody response (1C) *sections 3.8.6, 3.9.4.*
- Protection provided by monovalent vaccination is believed to persist for >20 years once immunity has been confirmed (1B) *section 3.8.6.*
- HIV positive patients show a reduced response rate to HBV vaccine and become anti-HBs negative more quickly, although double dose vaccine increases the response by 13% (1B).
 - Response correlates with CD4 count if not on antiretroviral therapy (ART) but also with viral load and ART use. Vaccine response improves if the CD4 count rises and the viral load is undetectable on ART.
- BHIVA recommends high dose vaccination (40µg Engerix or HBvaxPro) or Fendrix 20mcg at 0,1,2,6 months. Only to use a single dose 0,1,3 week ultra rapid course if CD4 >500 and a rapid course is essential
- Hep BsAb levels should be measured 4-8 weeks after completion of the primary course. If <10 three further vaccine doses should be given at monthly intervals. Individuals with a HepBsAb level of >10 <100 after the primary course should be given a booster dose (1B) *sections 3.8.6, 3.9.4.*

1.2.3 What if the patient is found to have acute hepatitis B?

- See section 1.0
- There is evidence that anti-viral agents can prevent acute liver failure (ALF), improve morbidity and mortality in patients with severe acute infection (1A) *section 3.8.3*
- Clinically assess the patient and if necessary refer for hospital admission (1A) *section 2.8.4.*

- Patients should be advised to avoid unprotected sexual intercourse, including oro-anal and oro-genital contact until they have become non-infectious (HBsAg negative) or their partners have been successfully vaccinated (1D) *section 3.8.1.*
- Partner notification should be performed and documented and the outcome documented at subsequent follow up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex or oro/anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious. The infectious period is from two weeks before the onset of jaundice until the patient becomes surface antigen negative (1D) *section 3.8.6.*
- Patients should be advised not to donate organs/semen/blood until non-infectious (loss of HBsAg) (1B) *section 3.8.1.*
- Patients who are HBsAg+ve should be given a detailed explanation of their condition with particular emphasis on the implications for the health of themselves and their partner(s) and routes of transmission of infection (1C) *section 3.8.1..*
- Hepatitis B should be notified to the public health authorities (the route of which depends on the country) (1D)*section 3.8.1.*

1.2.4 *What if the patient is found to have chronic hepatitis B?*

- Arrange referral to a hepatologist or other suitable specialist for disease monitoring, liver cancer screening and possible therapy (1D) *section 3.8.4.*
- Arrange screening for hepatitis C, hepatitis D and hepatitis A immunity (1D) *section 3.8.4*
- Vaccinate against hepatitis A if non-immune (1D)*section 3.8.4.*
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information (1C) *section 3.8.1.*
- Partner notification should be performed and documented and the outcome documented at subsequent follow up. Trace contacts as far back as any episode of jaundice or to the time when the infection is thought to have been acquired although this may be impractical for periods of longer than two or three years (1D) *section 3.8.6.*
- They should be advised of the need to disclose to new sexual partners, and partners encouraged to be vaccinated (1D)*section 3.8.1.*
- Arrange screening for hepatitis B of children who have been born to infectious women if the child was not vaccinated at birth (1C) *section 3.8.6.*
- For screening of other nonsexual partners who may be at risk, discuss with the public health doctors (1C) *section 3.8.6.*
- If pregnant, inform the woman about the risk of vertical (mother to infant) infection transmission and the need for monitoring and intervention to prevent this (1C) *section 3.8.6.*
- Advice for MSM and HIV+ MSM should include use of condoms, gloves for fisting, single person only sex toys/condoms on sex toys and changed between partners. Also not to share lube and avoid group sex situations such as 'chem-sex' parties (1D) *section 4.8.6. & 4.9*

1.2.5 *What to do if a patient presents as a contact of a patient with hepatitis B.*

- Screen for evidence of HBV infection or immunity (1A) *section 3.8.6.*
- Specific hepatitis B immunoglobulin 500 i.u. intramuscularly (HBIG) may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure/needlestick injury if the donor is known to be infectious. This works best within 12 hours, ideally should be given within 48 hours and is of no use after more than seven days (1A) *section 3.8.6.*
- An accelerated course of hepatitis B vaccine (at 0, 1, 3 weeks or 0,1, 2 months with a booster at 12 months in either course) should be offered to all non-immune sexual and household contacts, including to those given HBIG. Vaccination theoretically will provide some protection from disease when started up to six weeks after exposure (1A) *section 3.8.6.*
- Contacts who have previously been vaccinated and achieved immunity can have a single booster dose, with no HBIG (1A) *section 3.8.6.*
- Avoid sexual contact, especially unprotected penetrative sex, until vaccination has been successful (anti-HBs titres >10I.U./l.)(1D) *section 3.8.6.*

1.3 Hepatitis C

1.3.1 *Which asymptomatic patients should be screened in the sexual health setting?*

- Offer testing for hepatitis C to PWID, HIV-positive individuals, MSM eligible for three monthly HIV testing and those taking or eligible for PrEP (see BASHH MSM guidelines 2017), people with haemophilia or other patients who received blood or blood products pre1990 who are previously unscreened and in people sustaining a needlestick injury if the donor HCV status is positive or unknown (1A) *section 4.9.*
- Other groups to be tested are sexual partners of HCV positive individuals, sex workers, tattoo recipients, migrants from high endemic countries, alcoholics and ex-prisoners. (1A) *section 4.9.*
- Screen with anti-HCV antibody or the combined antibody/antigen test. It may take three months or more for the anti-HCV test to become positive after exposure, although the antigen test has a much shorter window period. Alternatively use HCV-RNA PCR if the above tests are negative and a more recent exposure is suspected (1A) *sections 4.7.1 and section 4.9.*

1.3.2 *What to do if the at-risk patient is HCV non-infected?*

- Discuss the low risk of sexual transmission except in HIV+ MSM, safer sex and how and how to reduce any risk of catching this infection (1D) *section 4.9.*
- Offer the test at least annually to MSM eligible for three monthly HIV testing and those taking or eligible for PrEP (see BASHH MSM guidelines 2017)
- Discuss safer injecting practices, including not sharing any of the paraphernalia, and access to needle exchange schemes for current PWID (1D) *section 4.9.*
- All HIV+ individuals should be screened for HCV at HIV diagnosis and every year thereafter. Patients with HCV Ab+ who have self-cleared or have been successfully treated should have annual an HCV RNA test (1D) *section 4.9.*

1.3.3 *What if the patient is found to have acute hepatitis C?*

- See section 1.0 and 4.7.1
- Patients should be referred to a specialist centre for assessment, monitoring and treatment and access to clinical trials (1A) *section 4.8.3.*
- Patients with acute HCV should be followed with four-weekly HCV RNA quantitation; those who fail to show a viral load reduction by at least 2 log₁₀ at week 4 or those who remain positive at week 12 should be considered for treatment (1A) *section 4.8.3.*
- Patients should be advised to avoid unprotected sexual intercourse (1D) *section 4.8.6.*
- Partner notification should be performed and documented and the outcome documented at subsequent follow up. Contact tracing of sexual contacts to take place if the index patient or partner are HIV+ (vaginal, anal or oro/anal sex) or for needle sharing partners during the period in which the index case is thought to have been infectious (1D) *section 4.8.6.*

1.3.4 *What if the patient is found to have chronic hepatitis C?*

- Arrange referral to a hepatologist or other suitable specialist for disease monitoring, liver cancer screening and possible therapy (1A) *section 4.8.3.*
- The need for treatment should be managed in a specialist clinic with access to Directly Acting Antivirals (DAAs) based therapy and clinical trials. (1A) *section 4.8.3.*
- In the era of DAAs, HIV positive patients respond to treatment as well as HIV-negative patients, and should be considered for therapy, bearing in mind important drug-drug interactions between the DAAs and antiretroviral therapy regimens (1A) *section 4.8.3.*
- Trace contacts back to the time when the infection is thought to have been acquired although this may be impractical for periods of longer than two or three years Contact tracing of sexual contacts to take place if the index patient or partner are HIV+ (vaginal, anal or oro/anal sex) or for needle sharing partners during the period in which the index case is thought to have been infectious. (1D) *section 4.8.6.*
- Patients should be advised of the need to disclose to new sexual partners (1D) *section 4.8.6.*
- Arrange screening for hepatitis C of children who have been born to HCV+ women if the child was not tested previously (1A) *section 4.8.6.*
- In patients with chronic infection, sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided, but given the very low rates of transmission outside of HIV co-infection, monogamous partners may choose not to use them. Sexual contacts with HIV should be advised of the risk of sexual transmission, with regular testing and condom use encouraged. (1D) *section 4.8.6.*
- Advice for MSM and HIV+ MSM should include use of condoms, gloves for fisting, single person only sex toys/condoms on sex toys and changed between partners. Also not to share lube and avoid group sex situations (1D) *section 4.8.6.*

- For other non-sexual contacts thought to be at risk, consider contact tracing on a case-by-case basis. (1D) *section 4.8.3*
- Arrange screening for hepatitis A and B. Vaccinate against hepatitis A and B if non-immune (1A) *section 4.8.3*.
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information (1D) *section 4.8.1*.
- Women should be informed of the small potential risk of vertical transmission in pregnancy (1D) *section 4.8.1*.

1.3.5 What to do if a patient presents as a contact of a patient with hepatitis C.

- Screen for evidence of past or current HCV infection (1D) *section 4.8.6*.
- Sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided, but given the very low rates of transmission outside of HIV co-infection, monogamous partners may choose not to use them (1D) *section 4.8.6*.
- Sexual contacts with HIV should be advised of risk of sexual transmission, with regular testing and condom use encouraged (1D) *section 4.8.6*.
- There is currently no available vaccine or immunoglobulin preparation that will prevent transmission. *section 4.8.6*.

Main Text

2. Hepatitis A virus infection

2.1 Aetiology

Hepatitis A is a picorna (RNA) virus. It is particularly common in areas of the world where sanitation is poor (developing countries), where it mainly affects children. In the developed world it is less common (352 cases reported in England and Wales, 2009) and causes disease in all age groups [1].

2.2 Transmission:

- Faeco-oral (via food, water, close personal contact) [2-7].
- Outbreaks have previously been reported in MSM, linked to oro-anal or digital-rectal contact, multiple sexual partners, anonymous partners, sex in public places and group sex [8-14]. Seroprevalence studies in the UK, Spain, USA and Italy show a similar rate of hepatitis A (IgG) antibodies in homosexual and heterosexual men who attend sexual health clinics [15,16].
- HIV-positive patients are not at increased risk but may be more infectious [17,18].
- Outbreaks have also been reported amongst PWID [1,19], in institutions for people with learning difficulties, and in contaminated batches of factor VIII [20-22].
- Patients are infectious for approximately two weeks before and one week after the period of jaundice by the non-parenteral routes but virus can be found in blood and stool until after the serum amino-transferase levels have

peaked [23]. In HIV positive patients, HAV viraemia may continue for over 90 days [17,18].

2.2.1 Hepatitis A Outbreak in the UK and Europe 2016-17

The European Centre for Disease Prevention and Control (ECDC) reported that between June 2016 and June 2017, 1,500 confirmed hepatitis A (HAV) cases and 2,660 probable or suspected cases have been reported in the EU, predominantly among adult men who have sex with men (MSM). The viruses identified belonging to three separate clusters based on genetic sequencing of HAV

Event 1 – Cluster VRD_521_2016 ('Spanish Strain') initially linked to travel to Spain.

Event 2 – Cluster RIVM-HAV16-090 ('Europride Strain') initially linked to MSM who participated in the EuroPride festival in Amsterdam (23 July to 7 August 2016)

Event 3 – Cluster V16-25801 ('Berlin Strain') initially reported in Berlin in November and December 2016. (23a)

In May 2017 Public Health England reported that 'between July 2016 and 2 April 2017, 266 cases associated with the outbreak had been identified in England. At least 74% of these were among MSM, and 63% of cases were in London. There is evidence that there have been some cases in the wider population linked to the outbreak.

A high proportion of cases likely acquired the infection abroad at the beginning of the outbreak, but transmission now mainly occurs in England'. (23b)

The number of cases have continued to rise subsequently.

2.3 Incubation Period:

15-45 days (average 28 days) [2,3,24,25]

2.4 Symptoms [24,25]

Most children and up to half of adults are asymptomatic or have mild non-specific symptoms with little or no jaundice.

In the more 'typical' case there are two phases of symptoms -

- *The prodromal illness:* flu-like symptoms (malaise, myalgia, fatigue), often with right upper abdominal pain. This phase lasts for 3-10 days and is followed by -
- *The icteric illness:* jaundice (mixed hepatic and cholestatic) associated with anorexia, nausea and fatigue which usually lasts for 1-3 weeks. It can persist for 12 or more weeks in a minority of patients who have cholestatic symptoms (itching and deep jaundice) [25]. Fever is rare in this phase.

2.5 Signs [16,24,25]

- Non-specific in the prodromal phase.
- Icteric phase - jaundice with pale stools and dark urine. Liver enlargement/tenderness and signs of dehydration are also common.

2.6 Complications

- Acute liver failure (ALF) complicates approximately 0.4% of cases, although 15% of patients with acute infection may require hospital care, of whom a quarter will have severe hepatitis (Prothrombin time P.T.> 3 seconds

prolonged or bilirubin $>170\mu\text{moles/l}$ [26,27]. ALF due to hepatitis A is more common in patients already infected with chronic hepatitis B or C, although studies differ widely in measured rates [26,28].

- Chronic infection (>6 months) has only been reported in a small number of case-reports [29].
- The overall mortality is $< 0.1\%$ although rises to 40% in those with ALF. Patients with ALF should be considered for liver transplantation [26,27].
- Pregnancy - The infection does not have any teratogenic effects but there is an increased rate of miscarriage and premature labour, proportional to the severity of the illness [30,31]. There have been case reports of possible vertical transmission [30,32,33].

2.7 Diagnosis (See also: BASHH CEG 2014 summary guidance on tests for STI) (www.BASSH.org)

2.7.1 Serology

- Confirmed by a positive serum Hepatitis A virus - specific IgM (HAV-IgM) which usually remains positive for 45-60 days although can be positive for six months or more [34,35]. HAV-IgG does not distinguish between current or past infection and may remain positive for life [34].
- For all patients with an undiagnosed type of acute hepatitis also test for HBV, HCV (see sections 3.7 and 4.7.1) and Hepatitis E (HEV). HEV in the UK is as common as HAV and most cases arise from eating processed pork products [36]

2.7.2 Other tests

- Typically the serum/plasma amino-transferases (AST/ALT) is in the range 500-10,000 i.u./l, the bilirubin up to 500 $\mu\text{moles/l}$, alkaline phosphatase levels $< 2x$ the upper limit of normal, but higher if there is cholestasis [24,26-28].
- Prothrombin time (PT) prolongation by more than 5 seconds is a sign of severe infection. ALF is typically associated with PT prolongation by 50 seconds or more [24,26].

2.8 Management

2.8.1 General Advice

- Employment history should be obtained so the patient can be advised appropriately and patients should be advised to avoid food handling and unprotected sexual intercourse until they have become non-infectious (from two weeks before to one week after the onset of jaundice) (1B) [2-14]
- Patients should be given a detailed explanation of their condition with particular emphasis on the implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information (1D). [37]
- Hepatitis A is a notifiable disease for public health purposes in England, Wales and Northern Ireland.[38]

2.8.2 Further Investigations

Screen for other sexually transmitted infections in cases of sexually-acquired hepatitis or if otherwise appropriate (1B)[8].

2.8.3 Acute icteric hepatitis

- Mild/moderate (80% of all infected patients) - manage as an outpatient emphasising rest and oral hydration (1B) [24].
- Severe attack with vomiting, dehydration or signs of hepatic decompensation (change in conscious level or personality) - admit to hospital (1A) [26,27].

2.8.4 Pregnancy and Breast Feeding

- Pregnant women should be advised of the increased risk of miscarriage/premature labour and the need to seek medical advice if this happens (1B) [30, 31].
- The risk from breast feeding is uncertain although there are no reported cases of transmission from breast milk. Even if the infant is infected, the disease is normally mild or asymptomatic [39]. Therefore the balance of risks between infection and stopping breast feeding should be considered on an individual basis(2C).

2.8.5 Sexual and Other Contacts

- Partner notification should be performed for at-risk MSM contacts (oro/anal, digital/rectal and penetrative anal sex) within the period two weeks before to one week after the onset of jaundice (1D). This to be documented and the outcome documented at subsequent follow-up. Other people thought to be at risk (household contacts, those at risk from food/water contamination) should be contacted via the public health authorities (1D).[40]
- Hepatitis A vaccine may be given up to 14 days after exposure providing exposure was within the infectious period of the source case (during the prodromal illness or first week of jaundice) (IA) [41,42].
- Human normal immunoglobulin (HNIG) 250-500 mg. intramuscularly should also be considered in addition to the vaccine for patients at higher risk of complications (concurrent chronic hepatitis B or C, chronic liver disease, HIV+ or age >50 yo) (IA) [41]. HNIG that is effective against HAV is in short supply in the UK and can only be obtained from Public Health England, (England and Wales), Health Protection Scotland or the Northern Ireland Public Health Laboratory Belfast [41].
- HNIG works best if given in the first few days after first contact with an efficacy of 90% and is unlikely to give any protection if given more than two weeks after first exposure, but may reduce disease severity if given up to 28days after exposure [41].
- Patients are most infectious for two weeks before the jaundice (i.e. before the illness is recognised) [41,42].
- Hepatitis A vaccine schedule: doses at 0 and 6-12 months; 95% protection for at least ten years (1A)[41-45]. Current advice is to revaccinate after ten years (1B) [41-46], however there is increasing evidence that vaccine-induced immunity may be ≥ 20 years and possibly lifelong, so no further booster doses may be needed after the primary course in immunocompetent patients (1B)[43-44].

- HIV-positive patients respond (as demonstrated by antibody production) in 46-88% but titres are lower than in HIV-negative individuals, and correlate with CD4 count [45,46].
- If patients with a low CD4 count (<300 cells/mm³) are vaccinated, they should be revaccinated if the CD4 count rises above 500/mm³ as a result of effective HIV treatment if the HAV IgG remains negative on retesting (1C) [45-47].
- The combined Hepatitis A+B vaccine is given on the same schedule as the hepatitis B vaccine and has similar efficacy to the individual vaccines although early immunity to hepatitis B may be impaired (1 B) [48,49].
- If an outbreak is suspected or if the index case is a food handler, notify the local CCDC/health protection team by telephone (1C)[38,39].

2.8.6 Follow-Up

- See at one or two weekly intervals until amino-transferase levels are normal (usually 4 -12 weeks) (1B).
- Immunity is usually lifelong (1B). [34,36]

2.9 Screening and Primary Prevention

- Since the outbreak of hepatitis A in 2016-17 PHE and BASHH now recommend that 'All MSM attending GUM and HIV clinics should be opportunistically offered a single dose of adult monovalent hepatitis A vaccine, where available, unless they have documented evidence of two doses of hepatitis A vaccine or of previous hepatitis A illness'. [49b](1B)
- An international shortage of hepatitis A vaccine led to above guidance regarding using a single dose. Once vaccine supplies are restored it is recommended that all unvaccinated/non-immune MSM attending GUM and HIV clinics should be offered full vaccination, even after the outbreak ceases (1B) (see section 2.8.5)
- Screening for pre-existing hepatitis A exposure before vaccination has been found to be cost-effective in one study and therefore may be performed, depending on other factors such as funding and clinic access. (2B) [51].
- If a hepatitis A antibody test is performed, during the outbreak situation, or if it is likely that the MSM will not return, the first dose of vaccine should be given at the same time (1B). The antibody result will aid decision making regarding further doses. [51a]
- To prevent sustained outbreaks, it is estimated that at least 70% of MSM should be immune. [51b]
- If monovalent hepatitis A or combined A+B vaccines are not available, alternative vaccines to be used in an emergency include the paediatric formulation of the hepatitis A monovalent vaccine at single or double dose (for HIV patients with CD4 <500) or the combined Hepatitis A/typhoid can be used (2D)
- PWID and people with chronic hepatitis B and C infection should also be vaccinated (1B) [41,42].

- Vaccination is also recommended via primary care for travellers to developing countries, people with chronic liver disease, those with occupational exposure risk (who should be directed to their occupation health department) and for people at risk in an outbreak (1A) [41,42].
- Health/sex education should stress the routes of transmission and the higher incidence in developing countries (1D) [41,42].

3. Hepatitis B virus infection

3.1 Aetiology

Hepatitis B is an hepadna (DNA) virus. It is endemic worldwide, apart from isolated communities, with very high carriage rates (up to 20%) particularly in South and East Asia, but also in Southern Europe, Central and South America, Africa and Eastern Europe. In the UK, HBV sero-prevalence varies from 0.01-0.04% in blood donors and to >1% in PWID and MSM. In 2015 5090 HBV cases were notified in England and Wales of which 457 were acute infections[52a]. There are 8 distinct genotypes (A-H) which vary in geographical distribution, pathogenicity and treatment susceptibility [53].

3.2 Transmission

- Sexual transmission occurs in unvaccinated/non-immune MSM and is associated with multiple partners, unprotected anal sex and oro-anal sex (“rimming”) [53, 54]. Transmission also occurs with heterosexual contact e.g. 18% infection rates for regular partners of patients with acute hepatitis B [52-56]. Sex workers are also at higher risk [57,58].
- Other routes are: vertical (infected mother to infant), parenteral (unscreened blood and blood products, injecting drug users sharing needles, syringes and other ‘works’, occupational needlestick injuries, non-sterile acupuncture and tattoo needles) [52-53, 59-62].
- Sporadic infection occurs in people without apparent risk factors, in institutions for learning difficulties and also in children in countries of high background prevalence; in these cases the mode of transmission is poorly understood [63,64].

3.3 Incubation period.

40-160 days [59]

3.4 Symptoms

- Virtually all infants and children have asymptomatic acute infection. Acute infection is also asymptomatic in 10-50% of adults and is especially likely in those with HIV co-infection[24, 65-67].
- Chronic carriers are usually asymptomatic but may have fatigue or loss of appetite [66].
- The prodromal and icteric phases are very similar to hepatitis A, but may be more severe and prolonged [24].

3.5 Signs

- As for hepatitis A in the acute phase.
- If chronic infection occurs there are often no physical signs. After many years of infection, depending on the severity and duration, there may be signs of chronic liver disease including spider naevi, finger clubbing, jaundice and hepato-splenomegaly, and in severe cases thin skin, bruising, ascites, liver flap and encephalopathy [68-70].

3.6 Complications

Acute Infection

- ALF occurs in less than 1% of symptomatic cases but carries a worse prognosis than that caused by hepatitis A [26,27].
- Pregnancy – there is an increased rate of miscarriage/premature labour in acute infection [31]. There is a risk of vertical transmission (see above) [53,59]
- Mortality is less than 1% for acute cases [26].

Chronic infection

- Chronic infection (>6 months) occurs in 5-10% of symptomatic cases but the rate is higher in immunocompromised patients with HIV infection, chronic renal failure or those receiving immunosuppressive drugs [52, 68, 69, 71, 72].

Profound immunosuppression, for example in advanced HIV infection or in patients taking immunosuppressive treatment can also reactivate hepatitis B [74]. A higher rate of chronic infection is also found in patients at institutions for learning disabilities [63]. Almost all (>90%) of infants born to infectious (HBeAg +ve) mothers will become chronic carriers unless immunised immediately at birth [59].

- There are five phases of chronic infection or carriage ::

1. HBeAg-positive chronic HBV infection, previously known as Immune Tolerant (hepatitis B e antigen positive, high levels of HBV DNA, normal aminotransferase levels, little or no necro-inflammation on liver biopsy),

2. HBeAg-positive chronic hepatitis B previously known as Immune Active, HBeAg-positive phase (hepatitis B e antigen positive, high but falling levels of HBV DNA, raised aminotransferases, significant necro-inflammation and progressive fibrosis),

3. HBeAg-negative chronic HBV infection, previously known as Inactive hepatitis B carrier (typically HBeAg-negative, low levels of HBV DNA and normal aminotransferases) and

4. HBeAg negative chronic active hepatitis (HBeAg -ve, detectable and fluctuating HBV DNA, inflammation and progressive fibrosis, genetic sequencing might detect mutations in the precore or core promotor mutations regions of the viral genome,).

5. HBsAg-negative phase also known as occult HBV infection (negative Hep BsAg and positive anti-HBc +/- anti-HBs, normal ALT, undetectable serum HBV DNA but HBV DNA (cccDNA) can be detected in the liver)

Immunosuppression can lead to reactivation in these patients.[79b]

Progression to cirrhosis may occur during phases 2 and 4 [67,68]. Primary liver cancer may complicate chronic HBV infection at any stage, but most commonly after development of cirrhosis.

- Concurrent hepatitis C infection can be associated with more aggressive chronic hepatitis with greater risk of cirrhosis and liver cancer [73-75].
- Concurrent HIV infection increases the risk of progression to cirrhosis and death [72, 76].
- Acute Hepatitis A co-infection can be severe in patients with HBV [77]
- Concurrent delta virus infection, or delta virus superinfection is typically associated with acute hepatitis and chronic hepatitis of increased severity, and may be associated with more rapidly progressive fibrosis, cirrhosis and end-stage liver disease.
- Between ten and fifty percent of chronic carriers will develop cirrhosis leading to premature death in approximately 50% [68-70, 75]. 10% or more of cirrhotic patients will progress to liver cancer. [68-70, 75].

3.7 Diagnosis (see also Sexually Transmitted Infection Screening and Testing Guidelines Hepatitis A, B and C)

3.7.1 Table: Hepatitis B serology [34, 67-70]

Stage of infection	Surface antigen (HBsAg)	'e' antigen (HBeAg)	IgM anti-core antibody	IgG anti-core antibody	Hepatitis B virus DNA	Anti-HBe	Anti-HBs	ALT
Acute (early)	+	+	+*	+	+	-	-	↑↑↑
Acute (resolving)	+	-	+	+	-	+/-	-	↑↑
Chronic (immune tolerant)	+	+	-	+	++	-	-	N**
Chronic (immune active)	+	+	-	+	+	-	-	↑
Chronic (eAg Neg.)	+	-	-	+	+	+/-	-	↑
Chronic (inactive carrier)	+	-	-	+	-	+	-	N
Resolved (immune)	-	-	-	+	-	+/-	+/-	N
Successful vaccination	-	-	-	-	-	-	+	N

*in very early infection the IgM and IgG anti-core can be negative

** N=normal

3.7.2 Biochemistry

- Acute infection: see hepatitis A (2.7.2)
- Chronic infection - in most cases the only abnormality will be mildly elevated serum aminotransferase levels; in many the liver enzymes will be normal.

3.8 Management

3.8.1 General Advice

- Patients should be advised to avoid unprotected sexual intercourse, including oro-anal and oro-genital contact until they have become non-infectious (loss of HBsAg) or their partners have been successfully vaccinated (see below) (1D) [52,54,59].
- Patients should be advised not to donate organs/semen/blood until non-infectious (loss of HBsAg) (1B)[52,54,59].
- Patients who are HBsAg+ve should be given a detailed explanation of their condition with particular emphasis on the implications for the health of themselves and their partner(s), routes of transmission of infection (see below) (1C) [52-63].
- Hepatitis B should be notified to the public health authorities (the route of which depends on the country) (1D) [59]

3.8.2 Further Investigations

- Screen for other STI in cases thought to have been sexually acquired (1D)[54,55, 59].
- In chronic infection, a liver imaging ultrasound should be performed and in addition liver fibrosis should be assessed by either a non-invasive technique (such as fibroscan) or with liver biopsy in selected patients. (1B)[78,79].

3.8.3 Acute icteric hepatitis

- As for hepatitis A.
- There is evidence that anti-viral agents can prevent ALF, improve morbidity and mortality in patients with severe acute infection (1A) [80,81].

3.8.4 Treatment of Chronic Infection

- Arrange screening for hepatitis C, hepatitis D and hepatitis A immunity (1D).
- Vaccinate against hepatitis A if non-immune (1D) [78,79]
- Refer all HBsAg+ve patients to a specialist experienced in the management of viral hepatitis (1D) [78,79]
- The decision to treat depends on pattern of disease, HBV DNA level, and presence or absence of significant necro-inflammation and hepatic fibrosis. Treatment is usually given to adults with an HBV DNA >2000 IU/ml with evidence of necro-inflammation and/or fibrosis [78,79].
- Treatment options are Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), entecavir or pegylated interferon (1A)[78,79, 79b]. Treatment responders have long-term benefits in terms of reduced liver damage and decreased risk of liver cancer [82,83].
- All patients should have an HIV test prior to starting HBV therapy because of the similar risks of acquisition, the different treatment strategies required in HIV co-infection and the significant risk of anti-retroviral resistant HIV developing if lamivudine, TDF, TAF or entecavir are used as monotherapy (1A) [78,79, 79b].
- Lamivudine, Emtricitabine, TDF and TAF will suppress hepatitis B viral replication during therapy of HIV [47, 87-90], and will prevent HBV-associated liver damage if given as part of triple antiretroviral therapy. (1B)[47, 87-90].

- Lamivudine and emtricitabine should only be given to HIV+ patients in combination with TDF or TAF as part of HAART because of the rapid high rate of resistance that occurs to these drugs if given as the only HBV-active agent (1A) [87-90]. Entecavir should not be used in HIV+ patients without adequately suppressed HIV as it causes the M184V (lamivudine/emtricitabine) resistant mutation (47).
- Active surveillance by a hepatologist of patients with significant fibrosis/cirrhosis for hepatocellular carcinoma(HCC) with ultrasound and alpha-feto protein is recommended 6-12 monthly (1B) [78,91].
- In the context of HBV, there is a high risk of HCC development in some groups of non-cirrhotic patients. This includes African patients over the age of 20, Asian males over 40, Asian females over 50, and patients with a family history of HCC. HBV-infected patients meeting these criteria should be offered HCC screening in the hepatology clinic [91].

3.8.5 Pregnancy and Breastfeeding

- In the absence of intervention, vertical transmission occurs in 90% of pregnancies where the mother is hepatitis B e antigen positive and in about 10% of surface antigen positive, e antigen negative mothers. Most (>90%) infected infants become chronic carriers [92].
- Infants born to infectious mothers are vaccinated from birth. Hepatitis B specific Immunoglobulin 200 i.u. IM is also given in certain situations where the mother is highly infectious (1A) [59,78,92]. This reduces vertical transmission by 90%.
- Consider Tenofovir monotherapy for pregnant women with HBV DNA >10⁷ IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby (1A) [78]
- Hepatitis B activity may increase immediately following pregnancy, but is seldom associated with clinical consequences [78,93]

3.8.6 Sexual and Other Contacts

- Partner notification should be performed and documented and the outcome documented at subsequent followup. Contact tracing to include any sexual contact (penetrative vaginal or anal sex or oro/anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious (1D) [37,40].
- The infectious period is from 2 weeks before the onset of jaundice until the patient becomes surface antigen negative.
- In cases of chronic infection, trace contacts as far back as any episode of jaundice or to the time when the infection is thought to have been acquired although this may be impractical for periods of longer than 3 years [40] (1D)
- Arrange screening for hepatitis B of children who have been born to infectious women if the child was not vaccinated at birth (1C)[59,78].
- For screening of other nonsexual partners who may be at risk, discuss with the public health authorities (1C) [59,78].
- Specific hepatitis B immunoglobulin 500 i.u. intramuscularly (HBIG) may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure/needlestick injury if the donor is known to

be infectious. This works best within 12 and ideally within 48 hours and is of no use after seven days (1A) [59,78, 94, 95].

HBIG that is effective against HBV is in limited supply in the UK and can only be obtained from Public Health England (England), NPHS Microbiology Cardiff (Wales), Blood Transfusion Service (Scotland) or the Northern Ireland Public Health Laboratory Belfast [59].

- An accelerated course of recombinant vaccine should be offered to those given HBIG plus all sexual and household contacts (at 0, 7 and 21 days or 0,1, 2 months with a booster at 12 months in either course) (1A) [59,61, 96-101].

Vaccination theoretically will provide some protection when started within six weeks after the contacts first exposure (1B) [59].

- Contacts who have previously been vaccinated and achieved immunity can have a single booster dose, with no HBIG (1B)[95].

- Contacts should themselves avoid sexual contact, especially unprotected penetrative sex, until it is shown that infection has not been acquired and it has been shown that vaccination has been successful (anti-HBs titres >10i.u./l.) (1D) [59,61, 96-101].

- The ultra-rapid vaccination schedule (0,1,3 weeks) leads to an anti-HBs antibody response in only 80% of recipients 4-12weeks after the third dose [96-101].

This rises to 95% just prior to the 12 month booster dose. It would be prudent to offer booster vaccinations of up to three further doses to the 20% of sexual or household contacts without detectable antibodies 4-12 weeks after the primary course (1C), even though most would have eventually developed an antibody response.

- Protection from monovalent vaccines is believed to persist for >20 years once immunity has been confirmed (1B)[102].

- Patients with a chronic infection should be advised of the need to disclose to new sexual partners, and partners encouraged to be vaccinated (1D).

3.8.7 Follow-up.

- Acute infection: as for hepatitis A. In view of the possibility of chronic infection, serology should be repeated after 6 months even if the LFTs are normal [69,78].

- Chronic infection: If untreated, patients should be regularly reviewed at intervals of one year or less, ideally by a physician with expertise in this disease (1B) [69,78].

- Immunity after recovery from infection (surface antigen negative) is life-long in over 90%(1B) [69,78].

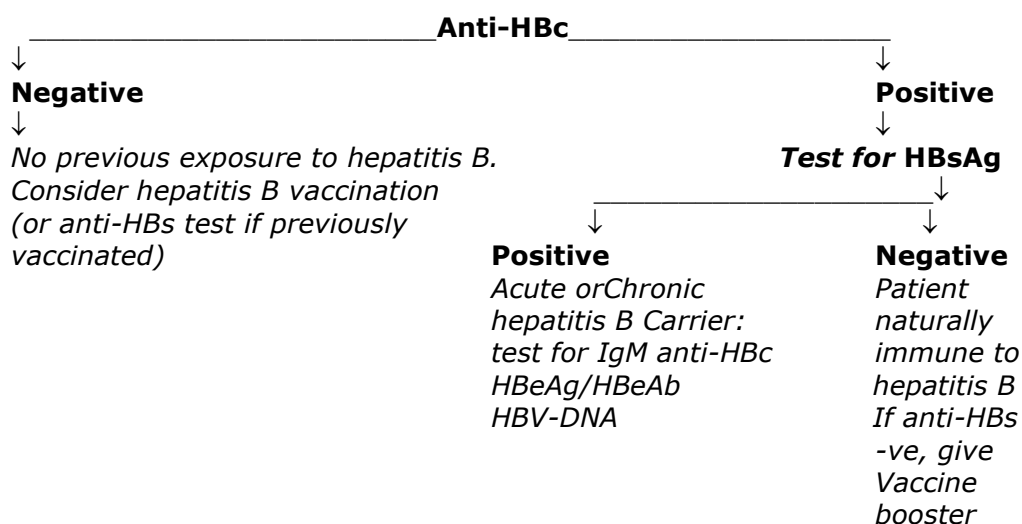
3.9 Screening and Primary Prevention (see also [107])

3.9.1 Screening

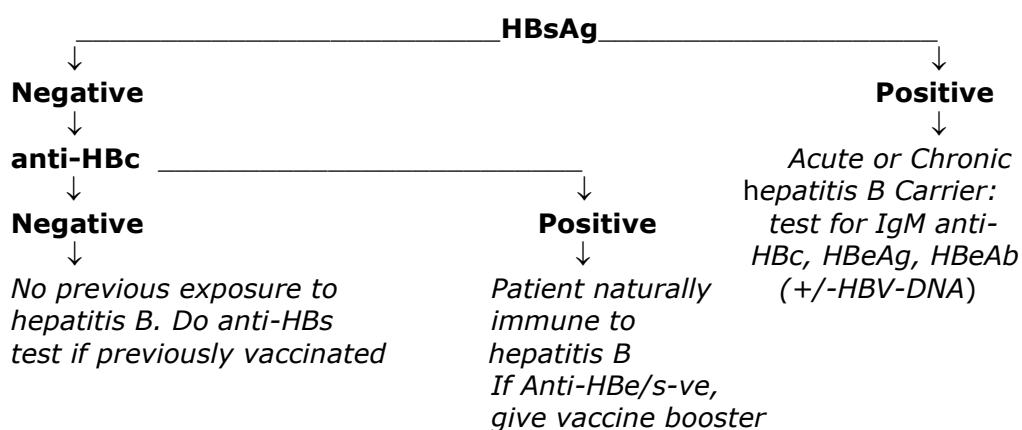
- Hepatitis B testing in asymptomatic patients should be recommended in MSM, sex workers (of either sex), PWID (including people who inject steroids and 'recreational' drugs ('slamming')), HIV-positive patients, sexual assault victims, people from countries where hepatitis B is endemic (outside of Western Europe, North America and Australasia), needlestick victims, heterosexuals with a large number (≥ 10 /year) of partners and sexual partners of positive or high-risk patients (1A) [52-62]. For needlestick injury follow PHE guidelines [59].

- If non-immune, consider vaccination (see below) (1A) [96-102]. If found to be a chronic carrier, refer the patient to an expert in hepatitis for long-term surveillance and to consider therapy (1A) [72,73, 78-86].
- The screening tests of choice are anti-HBc antibody and/or the hepatitis B surface antigen (HBsAg) test with further serology to assess the stage of infection and infectivity as appropriate (1B); measure anti-HBs in those who have been vaccinated (1B)[97-102,108,109].
- In those who are anti-HBc + and HBsAg -ve measure anti-HBs and anti-HBe. If both are negative the anti-HBc may be a false positive. In this case a single hepatitis B vaccine dose will induce anti-HBs if there has been past natural HBV exposure (anamnestic response, measured 4 weeks after single dose of HBV vaccine). If anti-HBs is still negative after a single booster, regard as non-immune and give a full course of vaccine (1C).[110]

3.9.2. Figure: Flow chart for hepatitis B screening using serum anti-HBc



3.9.3 Flow chart for hepatitis B screening using serum HBsAg



3.9.4 Primary prevention

- Discuss safer sex and how to reduce the risk of catching this infection (1C)
- Vaccination should be offered to non-immune patients in the above groups (1A) [59, 97-102,108,109] except those people born in countries of high endemicity but not at continuing risk who are being screened primarily to detect chronic carriage (1B)[78].
- The vaccination schedule for both the monovalent and the combined hepatitis A+B vaccines is outlined in Table 2. The ultra-rapid 0, 1,3 week regimen offers the advantage of a higher completion rates and more rapid development of early immunity. Test for response (anti-HBs >10i.u./l, ideally >100i.u./l) 4-12 weeks after the last dose (1A)[59, 97-102,108,109]. Only 80% of ultra-rapid vaccine recipients will have detectable anti-HBs antibodies at this stage (see 'Sexual and other contacts' above). If someone is at high risk of acquiring infection, and are in the 20% without an early antibody response, consider further booster doses (1C). This should be as a repeat course (1C) with response rates up to 100% [109-110]. Alternatively, for those at lower risk, offer a booster at 12 months by which time 95% would be anti-HBs positive [59, 97-102,108,109].
- Vaccines with novel adjuvants (e.g. Fendrix ®) are effective for haemodialysis patients and others who haven't responded to conventional vaccine (1A)[112-115].

HIV positive individuals

- HIV positive patients show a reduced response rate to HBV vaccine and become anti-HBs negative more quickly, although double dose vaccine increases the response by 13% (1B)[47, 103-106, 111].
 - Response correlates with CD4 count if not on antiretroviral therapy (ART) but also with viral load and ART use. [103-106] Vaccine response improves if the CD4 count rises and the viral load is undetectable on ART.
- BHIVA recommends high dose vaccination (40µg Engerix or HBvaxPro) or Fendrix 20mcg at 0,1,2,6 months. Only to use a single dose 0,1,3 week ultra rapid course if CD4 >500 and a rapid course is essential
- Hep BsAb levels should be measured 4-8 weeks after completion of the primary course. If <10 three further vaccine doses should be given at monthly intervals. Individuals with a HepBsAb level of >10 <100 after the primary course should be given a booster dose [115a]

3.9.5 Table: Vaccination Schedules for Hepatitis B using monovalent vaccine or combined A+B vaccine [41-43, 59, 96-106].

Vaccine Schedule	Advantages	Disadvantages
Ultra rapid 0,1,3 weeks, 12 months	<ul style="list-style-type: none"> - Rapid immunity, - Short duration, - High antibody titres at 12 and 13 months - Better uptake 	<ul style="list-style-type: none"> - Less evidence on HIV or other immune-compromised patients - Low antibody titres in the first year (but current evidence suggests that protection is still adequate in the immune-competent)

Rapid 0,1,2,12 months	- Shorter time to early immunity than the 0,1,6 course - High antibody titres at 12 and 13 months	- Antibody titres lower than the 0,1,6 regimen in the first year
Standard 0,1,6 months	- Higher antibody titres at 7 months than the other two regimens although this may not be clinically important - Long established regimen - Most researched in HIV	- Poor uptake of the 6 month dose in the clinical setting

- It is probable that booster doses of vaccine are not required for at least fifteen years in immunocompetent children and adults who have responded to an initial vaccine course (1B) [102, 116-119] although in those vaccinated in infancy 10% will be non-immune and show no immunological memory after 18 years [119]. HIV-positive and other immunocompromised patients will still need to be monitored and given boosters when anti-HBs levels fall below 100 IU/L (1C) [87, 103-106,119].
- Evidence suggests that if vaccine courses are not completed in immunocompetent patients, the outstanding doses can be given 4 or more years later without the need to restart a 3 dose course (1B) [120]. One or 2 doses of vaccine may provide immunity in 40% and over 90% of immunocompetent patients respectively [120, 121].

3.10 Hepatitis D (Delta virus infection, HDV)

This is a small incomplete RNA virus that can only infect individuals who have HBV. It is only found in patients with hepatitis B (HBsAg+ve) infection. The main risk groups are: people who have acquired the infection abroad, PWID and their sexual partners, sex workers and sporadically in other groups [122]. Suspect HDV in an individual with hepatitis B infection if the acute hepatitis is severe, if chronic hepatitis B carriers experience a further attack of acute hepatitis or if the liver disease in chronic HBV is rapidly progressive [24,26, 54, 69]. It is associated with a high rate of fulminant hepatitis and progression to cirrhosis [24, 26, 73]. All hepatitis B positive patients should have an anti-HDV test. Diagnosis is confirmed by a positive anti-HDV antibody and HDVRNA test [34, 108]. Response to antiviral therapy is poor [123, 124]. Refer to physician with experience in managing HBV/HDV co-infections for assessment and treatment (IV,C).

4. Hepatitis C virus (HCV) infection

4.1 Aetiology

Hepatitis C is a RNA virus in the flaviviridae family. It is endemic worldwide

an estimated 185 million individuals infected and with prevalence rates varying from 1% in Europe to as high as 4% in North Africa/Middle East[125]. Recent national estimates suggest approximately 215000 individuals are chronically infected with HCV in the UK, **but most are unaware of their infection**. Most (90%) is due to infection with genotypes 1 and 3 [126].

4.2 Transmission in the UK

- Parenteral spread accounts for the majority of cases through shared needles/syringes in PWID (including the practice of ‘slamming’ recreational drugs – see 4.9 below), transfusion of blood or blood products (pre1990s), re-use of needles in healthcare, renal dialysis, needlestick injury, sharing a razor with an infected individual and sharing of straws and notes for snorting recreational drugs. [125-135].
- Sexual transmission is extremely unlikely in heterosexual relationships (<0.1% /10years) but the rate increases if the index patient is also HIV infected [136-142]. There has been a steadily rising incidence of acute HCV in MSM in the South of England since the year 2000 which is largely linked to HIV co-infection [126, 138, 140]. Associated factors include the presence of other STIs including syphilis and LGV, traumatic anal sex, fisting, sharing sex toys, communal lubricant, group sex, sero-sorting and use of recreational drugs [138-140]. More recent data from enhanced surveillance suggests ongoing but perhaps a levelling off of rates of sexual transmission of HCV among HIV-positive MSM. [140]
- There is also evidence of increased rates of infection in sex workers [143].
- Other risk groups include former prisoners, people from highly endemic countries, tattoo recipients, people who inject steroids and recreational drugs, people who snort cocaine and alcoholics [144-147].
- Vertical (mother to infant) spread also occurs at a low rate (about 5%), but higher rates (7% or more) are seen if the woman is co-infected with HIV [148-152]. In all groups transmission risk correlates with the quantity of detectable HCV RNA in the mother’s blood [148- 152].
- Amongst blood donors, 25% of those with HCV infection do not admit to having risk factors [153].

4.3 Incubation period

- The incubation period is 4 to 20 weeks. HCV serology is positive three months after exposure in 90%, but can take as long as nine months. Occasional cases of infection proven by HCV RNA detection (see “diagnosis”) do not result in positive antibody tests [154].
- In the context of HIV-infection, the appearance of HCV antibodies may be significantly delayed [155,156]

4.4 Symptoms [131, 132]

- The majority of patients (>60%) have asymptomatic infection.
- The uncommon cases of acute icteric hepatitis are similar to hepatitis A.

4.5 Signs

- Acute icteric hepatitis see hepatitis A (Section 2.4).
- Chronic hepatitis see hepatitis B (Section 3.4)

4.6 Complications

Acute hepatitis C

- Acute fulminant hepatitis is rare ($\leq 1\%$ of all hepatitis C infections). Hepatitis A super-infection of chronic hepatitis C carriers [28, 131, 132, 157] may cause a very severe hepatitis. However, acute hepatitis A can reduce HCV replication [158].
- Approximately 50-85% of infected patients become chronic carriers; a state which is usually asymptomatic but may cause nonspecific ill health [153,159,160]. Patients with favourable polymorphisms around the IL28B gene are more likely to clear virus spontaneously [161]
- Pregnancy: complications of acute icteric hepatitis: as for hepatitis A [21].

Chronic hepatitis C

Once established (infected > 6 months), the chronic carrier state rarely resolves spontaneously (0.02%/year)[131-2]. Symptoms/signs are worse if there is a high alcohol intake or other liver disease [162,163]. Significant liver disease can be present in the 35% of carriers who have normal serum aminotransferase levels, [131, 132, 164,165].

- Up to 30% of chronic carriers will progress to severe liver disease after 14-30 years infection, with an increased risk of liver cancer (approximately 14% of all patients and up to 33% of those with cirrhosis) [68, 69, 81, 131, 132, 164, 165, 166-168].
- HIV co-infection worsens the prognosis although this may be ameliorated to some degree by ART [169-171]. Recent data suggests a deleterious effect of HCV on both overall and HIV/AIDS related-morbidity/mortality [172]

4.7 Diagnosis (see also Sexually Transmitted Infection Screening and Testing Guidelines Hepatitis A, B and C)

4.7.1 Serology

Acute infection

- This is defined as recent exposure to HCV following which the patient is HCV-RNA positive but anti-HCV negative or seroconverts from anti-HCV negative to positive. An antibody test may not become positive for several months after acute infection but a test for HCV-RNA will usually be positive after two weeks [154-156, 173].

HCV core antigen is a surrogate marker of HCV replication. HCV core antigen detection can be used instead of HCV RNA detection to diagnose acute or chronic HCV infection. HCV core antigen assays are less sensitive than HCV RNA assays (lower limit of detection equivalent to approximately 500 to 3000 HCV RNA IU/ml, depending on the HCV genotype [154 a, 154 b])

Chronic Infection

- A screening antibody or antibody/antigen test such as an Enzyme immunoassay (EIA) or other immunoassay is initially performed and RNA detection confirms active infection [154-156,173,174]. (1A)

- In HIV+ patients with a low CD4 count (<200 cells/mm³) the EIA may be negative and HCV RNA detection may be needed for diagnosis (175).
- Chronic infection is confirmed if an HCV RNA assay is positive six months after the first positive test [154-156,173,174]. .
- All patients should have a viral RNA test to confirm viraemia and the HCV genotype should also be identified [129, 163,176]. (1A)

4.7.2 Other tests

- Acute infection - as for hepatitis A (2.7.2).
- Chronic infection - as for hepatitis B (3.7.2).

4.8 Management

4.8.1 General Advice

- Patients should be reassured that hepatitis C is curable (1A) [127].
- Patients should be told not to donate blood, semen or organs and given advice on other routes of transmission (see below) (1D) [126,153].
- Patients should be given a detailed explanation of their condition with particular emphasis on the longterm implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information. (1D)
- Acute hepatitis is a notifiable infection in England, Wales and Northern Ireland [59,126].
- Refer all HCV RNA+ve patients to a specialist for further management (1A)[127].

4.8.2 Further Investigations

- Screen for other STIs in cases thought to have been sexually acquired (1C)[136,137]
- Non-invasive methods of assessing liver fibrosis such as Hepatic elastography (e.g. fibroScan) and/or serum markers (e.g. FibroTest, APRI, FIB-4, ELF) are the investigation of choice for disease staging [177] although the liver biopsy remains the investigation of choice for selected patients [178,179].
- A liver imaging ultrasound should also be performed (1B)[180].

4.8.3 Treatment

The goal of treatment is to cure HCV infection and to reduce the progression of liver fibrosis, decompensation of cirrhosis, hepatocellular carcinoma and extrahepatic manifestations.

HCV cure is defined by negative HCV RNA in blood 12 weeks after completion of HCV treatment.

Acute infection:

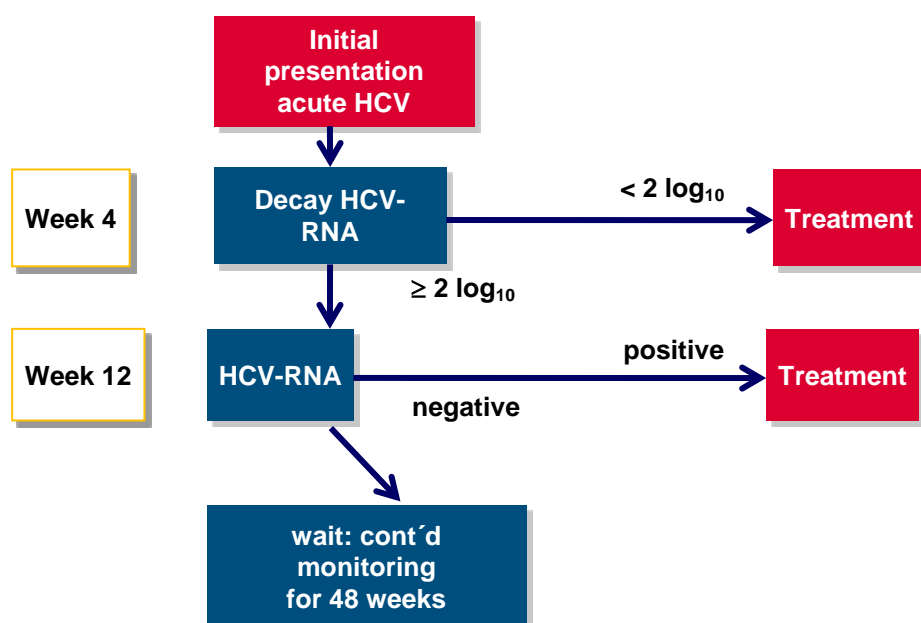
Most patients with acute hepatitis C are asymptomatic

- There is clear evidence that treatment given during the acute phase reduces progression and will reduce the rate of chronicity (1A) [181,182]. Spontaneous resolution of acute hepatitis C is defined as loss of HCV RNA within the first six months. Patients with acute HCV should be followed with four-weekly HCV RNA quantitation; if there is less than a 2 log₁₀ decline in HCV RNA

at week 4 or the HCV RNA remains positive at week 12, they should be considered for treatment in the acute phase. Treatment in the acute phase generally has significantly higher success rates than treatment in the chronic phase. (1A) [183,184]

• Patients should be referred to a specialist centre for monitoring and treatment and access to clinical trials (1A) [183, 184]. See algorithm below for the management of Acute HCV (NEAT algorithm) (1A) [184].

4.8.4 Figure: Summary of NEAT Algorithm for the management of Acute HCV[183]



Chronic infection

We recommend all patients with HCV should be assessed for treatment with direct-acting antiviral agents (DAAs).

The DAAs target HCV non-structural proteins to prevent viral replication.

- Currently used DAAs target NS3/4A protease inhibitors (simiprevir, ritonavir boosted ombitasvir, grazoprevir, glecaprevir),
- NS5A (ledipasvir, daclatasvir, ombitasvir, velpatasvir, elbasvir, pibrentasvir)
- NS5B inhibitors (sofosbuvir, dasabuvir).

With the advent of Directly Acting Antivirals (DAAs) the treatment paradigm for chronic HCV is rapidly evolving ([185]. The need for treatment should be

managed in a specialist clinic with access to DAA-based therapy and clinical trials (1A).

- In the era of DAAs, HIV positive patients respond to treatment as well as HIV-negative patients, and should be considered for therapy, bearing in mind important drug-drug interactions between the DAAs and antiretroviral therapy regimens (1A) [47,186].
- Patient selection for therapy and specific-therapy will depend on HCV genotype and viral load, liver disease stage, **prior HCV treatment history** and co-morbidities [177,186].
- **HCV resistance to NS5A inhibitors can be used to guide certain treatment options. Duration of treatment and addition of ribavirin can be considered based on the presence of resistance-associated substitutions (RASs)** 79b
- Given the potential for fulminant hepatitis in co-infection with hepatitis A and C and the worse prognosis of hepatitis B and C co-infection, patients with hepatitis C should be vaccinated against both hepatitis A and B (1A) [28, 131, 132, 157,187].

4.8.5 Pregnancy and Breast feeding

- At present there is no clearly demonstrated intervention to reduce HCV transmission from mother-to-child [149]
- Ribavirin is teratogenic. Treatment of HCV in pregnancy is not recommended (1D)
- Women should be informed of the small potential risk of transmission in pregnancy (see transmission) (1D) [148-152].
- Breast feeding: there is no firm evidence of additional risk of transmission(1B)[148-152].

4.8.6 Sexual and Other Contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual contact if the index patient or partner are HIV+ (penetrative vaginal or anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious (1D) [37]. If there is no acute infection trace back to the likely time of infection (e.g. blood transfusion, first needle sharing) although this may be impractical for periods longer than two or three years. (1D)
- Screen contacts for evidence of past or current HCV infection (1D).
- Test children born to viraemic women (1A) [148-152].
- For other non-sexual contacts thought to be at risk, consider on a case-by-case basis. (1D)
- There is currently no available vaccine or immunoglobulin preparation that will prevent transmission. Spontaneous resolution of infection and previous successful treatment do not provide protection if further HCV exposure occurs.
- In acute infection, patients should be advised to avoid unprotected sexual intercourse (1D)
- In patients with chronic infection, sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided, but given the very low rates of transmission outside of HIV co-

infection [136-142] (see above), monogamous partners may choose not to use them. Sexual contacts with HIV should be advised of the risk of sexual transmission, with regular testing and condom use encouraged (1D)[136-142].

- Advice for MSM and HIV+ MSM should include use of condoms, gloves for fisting, single person only sex toys/condoms on sex toys and changed between partners. Also not to share lube and avoid group sex situations (1D).

4.8.7 Follow-up

- Patients with chronic untreated HCV should have liver fibrosis assessments 6-12 monthly (1A)[177,178].
 - Patients with advanced fibrosis/cirrhosis should have 6 monthly HCC screening with ultrasound and alpha-feto protein (1A) [179].
- Previous exposure to HCV does not confer immunity and risk of re-infection and dual/super infection is well documented [188,189].

4.9 Screening and Primary Prevention.

- It may take three months or more for the anti-HCV test to become positive after exposure (see “incubation period”). (1A)
- Offer testing for hepatitis C in all PWID, including people who inject steroids and ‘recreational’ drugs, all HIV-positive patients, people with haemophilia or other patients who received blood or blood products pre1990 and remain untested, (1A) [124-130, 138-140,188,189]. For needlestick injury follow PHE guidelines.
- Offer the test at least annually to MSM eligible for three monthly HIV testing and those taking or eligible for PrEP (see BASHH MSM guidelines 2017)
- In the last few years, ‘chem-sex parties’, largely attended by MSM and involving multiple sexual partners and the use of ‘recreational drugs’ such as gamma-hydroxybutyric acid/gamma-butyrolactone (GHB/GBL), mephedrone and crystal methamphetamine have been described [190]. The drugs are frequently injected (‘slamming’), leading to high risk of BBVs including HCV and HIV. They also lead to a loss of attention to safer sex. MSM with such risks should be screened for HCV and other BBVs and the risks/prevention discussed (2D).
- Other groups to be tested include: the sexual partners of HCV positive individuals, sex workers, tattoo recipients, migrants from highly endemic countries, alcoholics, people who snort cocaine and ex-prisoners (1B) [136,137,141-143,145,146]
- Currently there is no evidence that HIV-negative MSM without other risk factors should be routinely screened (1B) [191].
- All HIV+ patients should be screened for HCV at HIV diagnosis and every year thereafter. Patients with previous infection who have cleared the infection (either spontaneously or through treatment) should have annual HCV PCR (1D). [192]
- Offer additional HCV testing in HIV+ MSM if other STIs have been diagnosed including syphilis and LGV or in situations of traumatic anal sex, fisting and sharing of sex toys [138-140].
- Since September 1991 all donated blood in the UK has been screened for HCV [193].
- Needle and syringe exchange schemes have led to a fall in parenterally

transmitted infections including HCV, HBV and HIV, although not consistently, as this infection can be transmitted through sharing other drug paraphernalia such as shared spoons, filters and water.[127,194-196].

- Non-sterile needle use in the healthcare setting remains an important cause of HCV transmission in **developing countries**[128].
- Discuss how to reduce any risk of catching this infection where appropriate (1D)

5. Resource implications

The major costs that arise from these guidelines are the additional costs of testing and vaccination. Testing costs will vary from laboratory to laboratory but screening tests for hepatitis (e.g. anti-HBc, anti-HCV, anti-HAV) cost £10-20 each, with similar costs for each additional blood test done on patients testing positive. NAATs (e.g. HBV-DNA, HCV-RNA) when performed, cost in the range £30-40 per test, with genotyping costing about £50. Vaccination costs are in the range £10-20 per dose for monodose vaccines and more for multiple-component vaccines. Additional clinic visits will also incur resources costs.

6 Qualifying statement

“The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.”

“All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.”

Planned review date: 2019

7. Auditable Outcomes

Acute hepatitis (A, B or C)

- * Patients with acute hepatitis infection should have blood samples taken for liver function tests at the first attendance after the diagnosis is known (target >90%)
- * A clear immediate management plan should be recorded within two months of the diagnosis being made (target 97%)
- * Services should have easily accessible, local written guidance for the provision of partner notification for all cases of acute hepatitis
- * A clear follow-up plan should be recorded (target 97%)
- * Partner notification should be recorded as resolved in accordance with the BASHH Statement on Partner notification for Sexually Transmissible Infections: [http://www.bashh.org/documents/2012%20Partner%20Notification%20State ment.pdf](http://www.bashh.org/documents/2012%20Partner%20Notification%20Statement.pdf) (target 97%)

Hepatitis A

* Provide written information on transmission and outcome of hepatitis A to infected patients (target >95%)

Hepatitis B

* Test patients in known at-risk groups for infection/immunity (target >90%). This could be risk-specific e.g. MSM or CSW.

* Offer vaccination to all nonimmune patients at continuing risk (target >90%) * In those offered vaccination, give a full course of 3 doses (target >65%) * Provide written information on transmission and outcome of hepatitis B to infected patients (target >95%)

Hepatitis C

* Screen all patients with HCV for HAV (target >95%) and for HBV (target >95%)

* Provide written information on transmission and outcome of hepatitis C to infected patients (target >95%)

* Refer all confirmed HCV viraemic patients to a specialist clinic for assessment and consideration for treatment (target >95%)

8. Conflicts of interest (2015 authors)

Gary Brook: None

Sanjay Bhagani: has received honoraria for speaking engagements, served on advisory boards and has received support for conference attendance from Abbvie, BMS, Gilead, Janssen and MSD.

Ranjababu Kulasegaram: received honoraria for speaking engagements, served on advisory boards and has received support for conference attendance from Abbvie, BMS, ViiV, Janssen and MSD

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Emma Devitt: None declared

Ann K Sullivan

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Appendix

Levels of evidence and grading of recommendations. The GRADE System

A **Grade 1** recommendation is a strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording 'We recommend'.

A **Grade 2** recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording 'We suggest'. The strength of a recommendation is determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and preferences, and where appropriate resource use. Each recommendation concerns a defined target population and is actionable.

The quality of evidence is graded from A to D and is defined as follows:

Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials (RCTs), or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect.

Grade B evidence means moderate-quality evidence from randomised trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias.

Grade C evidence is low-quality evidence from controlled trials with several serious limitations, or observational studies with limited evidence on effects and exclusion of most potential sources of bias.

Grade D evidence is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate.